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SYSTEMATIC REVIEW

Annual review of selected scientific literature: A report of the Committee on Scientific Investigation of the American Academy of Restorative Dentistry

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ABSTRACT

The Scientific Investigation Committee of the American Academy of Restorative Dentistry offers this review of the 2020 professional literature in restorative dentistry to inform busy dentists regarding noteworthy scientific and clinical progress over the past year. Each member of the committee brings discipline-specific expertise to this work to cover this broad topic. Specific subject areas addressed include prosthodontics; periodontics, alveolar bone, and peri-implant tissues; implant dentistry; dental materials and therapeutics; occlusion and temporomandibular disorders (TMDs); sleep-related breathing disorders; oral medicine and oral and maxillofacial surgery; and dental caries and cariology. The authors focused their efforts on reporting information likely to influence day-to-day dental treatment decisions with a keen eye on future trends in the profession. With the tremendous volume of dentistry and related literature being published today, this review cannot possibly be comprehensive. The purpose is to update interested readers and provide important resource material for those interested in pursuing greater detail. It remains our intent to assist colleagues in navigating the extensive volume of important information being published annually. It is our hope that readers find this work useful in successfully managing the dental patients they encounter. (J Prosthet Dent 2021;126:276-359)

PROSTHODONTICS

The 2020 professional literature pertinent to the clinical practice of prosthodontics was again substantial. Critically selected articles from well over 50 professional journals were included in this prosthodontics review to update readers in this increasingly broad area of restorative dentistry. For convenience, this extensive subject has been divided into 8 specific topics: general prosthodontic considerations, conventional complete dentures, conventional removable partial dentures, conventional fixed prosthodontics, general implant prosthodontic considerations, implant removable prosthodontics, implant fixed prosthodontics, and prosthodontic materials.

There were 3 interesting and important publications that will be mentioned, but not extensively reviewed here because they lie beyond the scope of this work. However, their consideration is strongly recommended for interested readers.

The first of these publications was the updated version of the Parameters of Care for the Specialty of Prosthodontics.[1] Authored by several key committees of the American College of Prosthodontists, this lengthy and highly referenced work is intended to help improve clinical care; establish prosthodontic consensus; and

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inform risk management, education, testing and the appropriateness of third-party involvement in clinical care. These parameters provide both a foundation of information and then a broad framework to guide predictable and favorable treatment outcomes.

In the second important publication, Praveen et al[2] reported on a bibliometric study that aimed to determine the characteristics of the 100 most cited articles in prosthodontic journals between 1951 and 2019. The top 5 most cited articles in prosthodontic journal over this time period were written by Brånemark[3] (2368 citations), Humphrey and Williamson[4] (1444 citations), Eriksson and Albrektsson[5] (1297 citations), Tallgren[6] (1228 citations), and Goodacre et al[7] (1054 citations). Majority of the articles cited were originally published in the *Journal of Prosthetic Dentistry* (72 articles), *International Journal of Prosthodontics* (25 articles), *Journal of Prosthodontics* (2 articles), and *Journal of Prosthodontic Research* (1 article). The decade in which most articles were published was the 1990s (33 articles). Many of the authors of the most cited articles were from the United States (55 articles) or Sweden (12 articles), with T. Albrektsson (7 articles) and G.A. Zarb (6 articles) listed most often. The top 100 articles tended to be reviews (35 articles) or experimental studies (34 articles), most commonly addressing dental implants (27 articles) or composite resins and ceramics (21 articles).

The authors concluded that although the article listing described is not a direct measure of quality or importance, it may shed light on a quantitative evaluation of scientific impact. Additionally, the 100 most cited articles in prosthodontics may provide insights into advances, areas of intense research, and future objectives in the field.

While spin in pop journalism is routine, even expected, one might believe that spin should have no place in scientific and/or clinical publications. Not so says Roszhart et al[8] who assessed the prevalence of spin in abstracts from published randomized controlled trials (RCTs) and explored potential influences.

A systematic search of 2015 publications in top 10 dental journals (based on 2016 Eigenfactor score) was conducted to select RCTs that resulted in statistically nonsignificant primary outcomes. Seventy-five articles were identified. The disciplines involved included general dentistry, dental research, implant dentistry, endodontics, oral surgery, periodontics, and oral oncology. Within the published abstracts, there were 3 different categories of spin and factors that could influence its presence. The 3 spin categories included (1) concluding clinical significance in spite of statistical nonsignificance; (2) interpreting statistically nonsignificant as indicating treatment equivalence or comparable effectiveness; and (3) emphasizing statistically significant secondary outcomes and omitting primary outcomes.

Based on the 75 RCTs identified, the authors concluded that 48% had a statistically nonsignificant result for the primary outcome with some form of spin in at least 31% of the accompanying published abstracts. No significant associations were found between spin parameters and journal impact factor, funding type, number of treatment arms, or presence of international collaborations. The authors emphasized the importance of careful appraisal of both the abstract and full text of the publication before adoption of recommendations into clinical practice. While readers should certainly practice caution in this manner, journal editorial boards must carefully control their peer review process to prohibit misleading statistical inferences and unfounded conclusions.

In addition to articles selected for detailed review, a sizable number of excellent general reviews, systematic reviews, meta-analyses, and helpful clinical descriptive articles were also published addressing issues important to prosthodontics. Although it is impractical to provide detailed analysis on all these publications, they are listed here, by topic area, for the reader's convenience: anatomy and physiology,[9-14] bone augmentation,[15] bruxism,[16,17] caries,[18-23] conventional complete dentures,[24,25] conventional fixed prosthodontics,[26-30] conventional removable partial dentures,[31,32] COVID-19,[33,34] dental hygiene,[35-37] dental microbiology,[38-44] dental occlusion,[45,46] dental wear,[47] digital dentistry,[48-53] emerging technology,[54-61] endo-restorative dentistry,[62,63] esthetics,[64-68] evidence-based dentistry,[69-74] geriatric dentistry,[75,76] implant complications,[77-80] implant esthetics,[81-84] implant fixed prosthodontics,[85-88] implant removable prosthodontics,[89,90] implant surgery,[91-97] implant treatment planning,[98-102] impressions,[103-106] material science,[107-119] maxillofacial prosthetics,[120] mechanics/biomechanics,[121] operative dentistry,[122,123] orthodontics-restorative dentistry,[124-126] osseointegration,[127-129] pathology and disease,[130-150] pediatric-restorative dentistry,[151-153] peri-implant tissues,[154-162] periodontics-restorative dentistry,[163-167] pharmacology,[168-177] radiology,[178] sleep disordered breathing,[179-181] TMD and orofacial pain,[182-193] trauma and emergency,[194] and miscellaneous topics.[195,196]

General prosthodontic considerations

Many factors impact the selection of treatment rendered by dentists. In fact, it is quite possible that patients with similar dental and oral conditions may receive substantially different prosthodontic therapy when treated by different practitioners. To investigate if formal training in implant dentistry was associated with treatment proposed by practitioners to edentulous patients and the rationale behind the treatment proposed, Assous et al[197] reported on an internet-based survey conducted among a cohort of French dentists.

From July to December 2018, 2000 dental practitioners were provided an internet-based survey intended to assess first-choice treatment proposed to edentulous patients. Questionnaires focused on treatment proposed and why. Demographic data were also collected to determine respondent's personal and professional background information considered applicable to the questions at hand. Three hundred forty-nine surveys were returned (17.4% response rate), of which 39 were excluded because of missing data.

Statistical assessment indicated that for most clinicians, the first-choice treatment for the maxilla in edentulous patients was a complete denture (CD, 59.7%), followed by an implant fixed prosthesis (IFP, 25.5%) and an implant overdenture (IO, 14.6%). The first-choice mandibular treatment for a healthy edentulous patient was an IO (45.6%) followed by an IFP (26.1) and a CD (30%). Clinical conditions were most often cited for these choices. Approximately 30% of practitioners proposed a mandibular CD as the first option. Binary logistic regression analysis indicted that the likelihood of proposing implant therapy in the maxilla was significantly greater for male dentists (OR, 2.041; 95% CI: 1.231-3.385; $P<.05$) and for clinicians who had greater self-perceived skills due to further training in implant dentistry (OR, 2.301; 95% CI: 1.354-3.917; $P<.05$). In the mandible, the likelihood of prescribing implant treatment was significantly greater for clinicians who graduated 10-19 years ago (OR, 5.312; 95% CI: 1.331-21.208; $P<.05$), had greater self-perceived skills due to further training in implant dentistry (OR, 2.246; 95% CI: 1.121-4.500; $P<.05$), had expectations of improved prosthesis comfort and stability (OR, 11.810; 95% CI: 5.289-26.372; $P<.001$), and proposed treatment based on published national and/or international recommendations (OR, 3.252; 95% CI: 1.208-8.755; $P<.05$).

As the article title suggests, training beyond dental school in implant dentistry for the French cohort surveyed appears to be a determining factor for first-choice mandibular treatment for edentulous patients. Treatment also depends on demographic factors, postgraduation clinical experience, and compliance with published therapeutic guidelines. The authors suggested that promoting international consensus recommendations, instruction in implant dentistry, and clinical implant experience among new graduates may increase the proposal of mandibular implant therapy for edentulous patients.

Dentistry faces significant challenges in the diagnosis and treatment of tooth structure failure in our ever-expanding geriatric patient population. While influenced by many factors, irreversible microstructural changes affecting aging dentin is certainly one important factor. The gradual filling of dentin tubule lumens, a process known as dental sclerosis, begins at the root apex, progresses coronally, and is associated with progressive reduction in the resistance of dentin to fracture. In order to characterize the dynamic mechanical behavior of root dentin with respect to donor age, pulp vitality, and histologic location, Yan et al[198] tested intertubular dentin with nanoindentation-based structural analysis (nanoscopic dynamic mechanical analysis or scanning mode nanoDMA).

Human single-rooted, noncarious, and structurally nondefective premolars were obtained. Donor age and sex were recorded. A total of 12 teeth from 8 patients were selected and divided into young (n=4; age<25 years), old (n=4; age>60 years), and old nonvital (n=4; age>60 years) groups. Teeth in the old and old nonvital groups were matched pairs from mirrored locations of the arch from the same donor that included a vital tooth and nonvital tooth with prior root canal therapy (RCT).

The teeth were mounted and sectioned axially (mesial-distal orientation) with subsequent surface finishing soon after acquisition. NanoDMA with scanning probe microscopy (SPM) was performed on intertubular and peritubular dentin of the prepared specimens in a hydrated condition. The loss modulus (damping capacity), storage modulus (elastic behavior), and complex modulus (a combined effect), as well as the tan delta parameter (viscous deformation capacity) were evaluated in apical, middle, and coronal root thirds for teeth with no restorations and those with root canal treatment (nonvital).

Results indicated significant changes in the dynamic moduli of intertubular dentin with age, particularly in the apical third of the root. The storage modulus (elastic resistance to deformation) was significantly greater ($P<.001$) for both old vital and nonvital teeth over the entire root length compared with that for young teeth. However, the tan delta parameter (relative capacity for viscous deformation) was significantly lower in these 2 groups ($P<.005$).

The authors concluded that radicular dentin loses the capacity for viscous deformation with aging, subsequently becoming embrittled, particularly in the apical third. Additionally, this degradation appears to be accelerated by root canal therapy.

The objective decrease in saliva flow rate (hyposalivation) may be associated with several adverse outcomes, for example, halitosis, mucositis, stomatitis, *Candida* infection, poor digestive function, dental caries (because of suboptimal buffering and remineralization), poor comfort and retention of removable dentures, inefficient food bolus formation and transport, difficulty swallowing, altered taste sensation, and problems with phonation. Additionally, saliva plays a role in controlling the composition of the oral microflora by means of antibacterial, antifungal, and antiviral properties. More specifically, hyposalivation has been associated with

aging. Hyposalivation can substantially affect oral health and quality of life. Therefore, its occurrence within the population is of interest. Pina et al[199] systematically reviewed available literature to estimate the prevalence of hyposalivation, calculated with stimulated and unstimulated protocols, in noninstitutionalized older adults aged ≥60 years.

Existing literature on the topic was surveyed up to February 2019. Inclusion and exclusion criteria were applied. Thirteen studies reporting on a total of 3885 (range, 28-800) individuals aged ≥60 years (range, 60-100 years) were included in the review. Methodologies were evaluated for risk of bias, and meta-analyses were performed.

The results indicated an overall hyposalivation prevalence of 33.37% (95% CI: 23.90-43.57; $P<.001$; n=3447) with higher prevalence in women. The prevalence of hyposalivation for unstimulated and stimulated protocols was 33.39% (95% CI: 21.08-46.96; $P<.001$; n=2425) and 30.47% (95% CI: 22.53-39.04; $P<.001$; n=1495), respectively. Most of the studies demonstrated low risk of bias, 2 had moderate risk, and 1 high risk. Statistical association was found between low salivary flow and the intake of 4 or more prescribed drugs. Study limitations were related to the potential risk of bias in observational studies, identifying and dealing with confounding factors, and the use of different criteria to measure saliva flow rate.

The authors concluded that the overall prevalence of hyposalivation in their older population is 33.37%. When considering stimulated methods for assessing salivary flow, the prevalence of hyposalivation was slightly lower (30.47%). The authors suggested that data were derived from noninstitutionalized elderly individuals and that the prevalence of hyposalivation in institutionalized elderly individuals may be higher.

Conventional complete prosthodontics

While adapting to most new dental prostheses can be a challenge, the challenge offered by conventional complete dentures (CDs) can be overwhelming and may require a substantial adaptation period. Control of the dentures during speech, mastication, deglutition, coordinated mandibular movements, excessive salivation, and routine oral animation must be mastered. It is believed that these problems may be lessened by the appropriate use of denture adhesives and perhaps compounded for patient suffering with advanced alveolar ridge atrophy. To investigate these circumstances, Silva et al[200] evaluated the influence of powder-type adhesive on masticatory performance and oral health-related quality of life (OHRQoL) in patients with normal and resorbed mandibular ridges during the adaptation period with new CDs.

New conventional CDs were provided to 42 edentulous patients (12 men and 30 women, aged 49 to 88 years) using a standard clinical and laboratory protocol. Patient selection criteria included no debilitating systemic of TMJ conditions, normal salivary flow, no previous adhesive use, and previous experience with CDs for at least 1 year. Participants were distributed to 4 groups as follows: (1) normal mandibular ridges with adhesive, n=10; (2) normal mandibular ridges without adhesive, n=10; (3) resorbed mandibular ridges with adhesive, n=11; and (4) resorbed mandibular ridges without adhesive, n=11. Participants scheduled to use adhesive were instructed to do so throughout the observational period following manufacturer's instructions.

At 30, 60, and 90 days after CD placement, masticatory performance was evaluated with the sieving method, and OHRQoL was assessed by the Oral Health Impact Profile in Edentulous Adults (OHIP-EDENT) inventory. Data were analyzed with 2-way ANOVA test and generalized estimating equations, $\alpha=.05$.

For patients with normal mandibular ridges, results indicated that the use of adhesive was associated with better masticatory performance at 30 days (35.76 ±12.63% weight) and 60 days (30.06 ±10.54% weight) after CD placement but did not influence OHRQoL. By 90 days, the use of adhesive no longer improved masticatory performance relative to normal ridge/no adhesive counterparts. For patients with resorbed mandibular ridges, the use of adhesive did not appear to influence masticatory performance during adaptation period but had a negative effect on masticatory discomfort/disability subscale OHRQoL in the 30-day period (5.2; range, 3.6-6.8).

Within the limitations of the present clinical investigation, the authors concluded that powder adhesive use may improve CD masticatory performance for normal mandibular ridge CD wearers during the adaptation period (up to 60 days) after prosthesis placement but had no influence on masticatory performance of those with resorbed mandibular ridges. Adhesive use by patient with resorbed mandibular ridges negatively influence OHRQoL (masticatory discomfort/disability subscale) very early in the adaptation period (30 days) but had no influence on normal ridge patients. The results appear to support the use of powder adhesive to ease the new CD adaptation period for patients with normal mandibular ridges, but not for those with resorbed ridges.

With the rise in popularity of computer-based complete denture (CD) manufacturing, initiating the CAD-CAM workflow with an optical scan is thought to be advantageous. With this in mind, Hack et al[201] sought to evaluate the feasibility and accuracy of computerized optical scanning of edentulous jaws in a clinical (in vivo) setting.

Conventional impressions (modeling plastic impression compound border molded custom trays and polyvinyl siloxane impression material) were made for 29 edentulous patients (27 maxillae and 5 mandibles) in a

dental university setting. Prosthodontic faculty members and supervised dental students made all impressions. One faculty member evaluated all conventional impressions for correctness, digitized each 3 times with a laboratory scanner (D700; 3Shape A/S), and cast impressions in stone. Stone casts were then scanned 3 times with the same laboratory scanner.

At least 1 hour after conventional impression procedures, 3 computerized optical scans (Lava COS or True Definition IS; 3M ESPE) of each edentulous arch were made after titanium oxide powder dusting. A cross-ridge, right-to-left, zig-zag scan path was used in the mandible, while maxillae were scanned with a cross-arch, right-to-left, zig-zag scan path.

Resulting data sets (stone cast, conventional impression, and optical scans) were loaded into a 3D evaluation software program, and aligned surface scans were subjected to 3D comparisons. The obtained difference values were then statistically analyzed and visually evaluated to identify relevant deviations. Mean differences between the stone cast scans, conventional impression scans, and optical scans were 336.7 ±105.0 μm (n=32), 363.7 ±143.1 μm (n=24), and 272.1 ±168.5 μm (n=29), respectively. Visual evaluations of aligned surfaces indicated greatest deviations (≥500 μm) in the soft palate (posterior palatal seal zone), sublingual vestibular (lingual seal zone), and buccal vestibular (peripheral seal zone) areas.

Within the limitations of the study, the authors concluded that intraoral scans of the edentulous jaw did not provide the same surface information as obtained from conventional impressions and their resulting stone casts. The intraoral scanners and/or scanning techniques investigated were not able to adequately capture mobile, vestibular, and poorly traceable tissues. Clinical, technical, and software-related improvements appear when necessary. Current scanners and/or scanning techniques appear incapable of adequately replacing conventional impressions for the fabrication of removable complete dentures.

It is common for dentists to remind patients to remove their complete dentures at night to avoid developing denture stomatitis. Dentists go on to instruct that the dentures must be placed in water while out of the mouth, to avoid dehydration and dimensional change. However, are these routine instructions supported by valid evidence? Additionally, what effects do overnight water storage conditions have on factors know to contribute to denture stomatitis, specifically colonization of intaglio denture surfaces by *Candida albicans*? To address these questions, Verhaeghe et al[202] systematically reviewed the professional literature to primarily evaluate the effect of overnight storage conditions on denture base colonization by *C. albicans*. A secondary question, the effect of the overnight storage conditions on denture dimensional stability, was also examined.

A systematic search of the literature from 1960 to 2018 initially identified 162 relevant articles. Upon application of inclusion/exclusion criteria and further manual searching, 4 studies were identified to address the primary research question. An additional 3 studies were included for the secondary research question.

Unfortunately, a meta-analysis could not be performed because of significant variation in study design, limited randomized controlled trials, poor power, risk of bias, inadequate demographic information, and varying experimental settings. Study treatments for overnight storage included dry storage, water storage, storage in water with an alkaline peroxide-based cleansing tablet, and storage in water with 0.5% sodium hypochlorite. Overnight storage time was often ill defined. The use of a standardized prestorage cleaning regimen was not established, and follow-up assessments were variable.

The authors indicated a few general suggestions that surfaced for the articles included in this systematic review: (1) Prestorage manual cleaning is significantly important to reduce *C. albicans* colonization of denture surfaces; (2) if prestorage manual cleaning is not possible, the use of an alkaline peroxide–based cleaning tablet should be recommended; (3) if an alkaline peroxide–based cleaning tablet is not available, overnight dry storage should be recommended for reducing *C. albicans* while imparting insignificant dimensional change in the denture; and (4) if the prestorage manual cleaning is not possible, storing the denture in water alone may promote *C. albicans* colonization and therefore is not recommended. Proper denture hygiene is important before overnight storage of complete dentures, and appropriate patient education in this regard is important.

Conventional removable partial prosthodontics

Implant restoration of missing teeth in partial edentulism is a popular solution. However, for those who cannot afford extensive implant therapy, lack sufficient residual bone volume, are not interested in invasive dental surgery, or are satisfied with existing removable partial denture (RPD) solutions, the more expensive and less hygienically accessible fixed implant treatment options are simply not a consideration. While the RPD therapy may be used in the management of Kennedy class I or II partial edentulism, the biomechanical impact of tooth versus soft-tissue support against functional loading must be appreciated. Incorporation of a short dental implant near the distal extent of an RPD extension base can dramatically improve prosthesis support, retention, and stability. To investigate clinical outcomes, Bellia et al[203] prospectively evaluated, at 1 and 4 years, the survival of short implants incorporated into RPD treatment of Kennedy class I and II partial edentulism.

Patients treated with Kennedy class I and II RPDs between 2004 and 2011 in one clinic and fulfilling specific

criteria were offered placement of a single short (5-6 mm in length and 5-6 mm in diameter) implant in the distal edentulous ridge. Twenty patients fulfilled eligibility requirements and were enrolled for treatment. These individuals received a total of 35 maxillary (n=7) and mandibular (n=28) implants between 2012 and 2014. Upon osseointegration, LOCATOR abutments (range, 1-4 mm height) were used to engage the existing prostheses. Implant survival and mobility, peri-implant bone loss evaluated with periapical radiographs, bleeding on probing (BOP), and probing depth (PD) were assessed at the time of prosthesis engagement, at 1-year follow-up, and at 4-year follow-up.

The results indicated that at the 4-year follow-up, 12 implants showed BOP. For PD, 15 implants showed 2 mm, 16 implants showed 3 mm, and 2 implants showed 4 mm. One implant was mobile, and 2 were lost for a survival rate of 94.3% (95% CI: 80.84-99.30). The mean bone loss was 1.04 ±1.88 mm.

Within the limitations of this preliminary clinical study, implant survival rate and the mean bone loss values recorded are comparable to those reported in current literature. RPD extension bases supported, retained, and stabilized by short, wide-platform dental implants with LOCATOR attachments can be considered a suitable treatment option for partially edentulous patients presenting reduced vertical height of the edentulous ridge. This approach serves to improve rotational prosthesis mechanics during functional loading and avoids invasive surgical interventions required for the placement of longer implants. Additional clinical trials should be pursued to demonstrate favorable longer term survival and associated patient benefits with the use of short implants as described here. Periodic standardized clinical and radiographic examinations used to assess implant survival and the occurrence, severity, and progression of bone resorption must be included.

While Bellia et al[203] demonstrated favorable clinical results when placing dental implants to assist with the support, retention, and stability of existing dental implants, Park et al[204] systematically reviewed the literature to assess impact on treatment outcomes with this clinical approach. Specifically, this review considered outcomes assessments before and after conversion from a conventional Kennedy class I RPD to an implant-assisted RPD. Success in treatment was evaluated with patient-reported outcome measures (PROMs), objective parameters of functional performance, and the occurrence of biological and mechanical complication.

After structured database searching and subsequent electronic and hand searches, a total of 6544 articles were initially identified. Exclusion based on selection criteria yielded 19 publications based on 13 independent studies (3 randomized controlled trials) appearing between 2008 and 2018.

Meta-analysis of available data indicated that after conversion to Kennedy class I implant-assisted RPDs, treatment outcomes across a wide range of parameters were significantly improved. General patient satisfaction and mastication were significantly improved ($P<.05$). In oral health-related quality of life, the total Oral Health Impact Profile scores improved, including improvements in physical pain and psychological disability ($P<.05$). Masticatory performance was improved ($P<.05$) in terms of maximum occlusal force, active occlusal contact area, and mandibular jaw movement timing (opening, closing, and cyclic movements). The weighted mean survival rate of implants (2.0-4.7 mm in diameter; 6-14 mm in length; mean follow-up, 2.3 years; range, 0.5-10 years) was 96.60%. The authors concluded that after conversion from a conventional Kennedy class I RPD to and implant-assisted RPD, the treatment outcomes were significantly improved across a wide range of parameters associated with implant dentistry, including patient-reported outcome measures and masticatory performance.

The widespread application of CAD-CAM technology offers significant convenience with respect to RPD frameworks design and manufacturing. Today, time-consuming and technique-sensitive conventional laboratory steps give way to straightforward and intuitive computer-based processes. However, as is so often the case, the question of accuracy of the definitive restoration remains unanswered. To shed light on this important question, Tasaka et al[205] compared the accuracy of RPD frameworks produced by workflows involving casting 3D-printed additive manufacturing patterns (AM-Cast) and workflows incorporating selective laser sintering (SLS).

A mandibular partially edentulous experimental model simulating a Kennedy class II, modification 1, clinical situation was used. Appropriate rest seats and axial abutment contours were provided. The model was digitally acquired with a dental laboratory scanner, and a CAD software program was used to design an experimental RPD framework according to the RPI concept.

To facilitate flow of molten alloy in the AM-Cast group, accessory sprues were placed between the tips of the buccal and lingual clasp arms of each clasp assembly resin pattern. To limit pattern distortion during polymerization, 2 cross-arch bars were incorporated in the patterns. Printed resin framework patterns were additively manufactured in a 3D printer, invested, and cast in cobalt-chromium alloy.

For SLS frameworks, the same CAD data used to produce resin patterns in the AM-Cast group were sent to a direct metal laser sintering machine. Framework orientation ensured parallelism between the occlusal surfaces of the rests and the machine base. A 1100- to 1200-mm/second sintering speed, 0.08- to 0.1-mm laser spot diameter, and 0.02-mm layer thickness were used.

After sintering, frameworks were annealed (1000 °C; 30 minutes) and homogenized (1150 °C; 30 minutes). Five AM-Cast and 5 SLS frameworks were fabricated. Three-dimensional scans of all frameworks were individually superimposed on original design (CAD) data and statistically assessed for fit.

The results indicated a range of differences in the AM-Cast frameworks (–0.185 ±0.138 to 0.352 ±0.143 mm) and in the SLS group (–0.166 ±0.009 to 0.123 ±0.009 mm). Significant differences were observed at the rests, proximal plates, connectors, and clasp arms. Regarding the rests, both lateral and medial displacements were observed for both manufacturing types relative to design data. The AM-Cast frameworks demonstrated large lateral discrepancies of the connectors joining clasp assemblies to lingual bar major connectors on the tooth-supported side. The SLS frameworks demonstrated significant discrepancies at the center of the lingual bar. Between the manufacturing techniques, fabrication accuracies appeared to differ depending on the specific RPD structural component.

The authors concluded that overall discrepancies were smaller for SLS framework, suggesting that it may be superior to AM-Cast in terms of fabrication accuracy and reproducibility. The authors were quick to indicate that the present study had limitations. Conventional casting could not be included as an experimental condition because standardization of hand-waxed patterns is difficult. Furthermore, while only one RPD design was used in this investigation, various designs are possible and should be studied. In particular, the configuration of major connectors, for which accuracy was found to be an issue in the SLS workflow, varies dramatically depending on design concept used and dental arch involved, thus requiring further investigation.

Conventional fixed prosthodontics

In vitro experiments, while informative, may not provide the information needed by clinicians for the day-to-day practice of fixed prosthodontics. Long-term in vivo data are often considered more desirable. Long-term clinical data on the survival of pressed lithium disilicate glass-ceramic restorations and the effect that different technical and clinical variables have on survival are lacking. With this in mind, a series of reports emerging from one private practice[206-208] involving a prospective database with controls for clinical and laboratory variables reported on recall findings of a substantial patient population. The purpose of the initial clinical report in this series[206] was to examine the 10-year survival of pressed lithium disilicate glass-ceramic monolithic and bilayer restorations and the relationship between clinical parameters and outcomes.

All participants required single complete coverage restorations in any area of the mouth, 3-unit fixed partial dentures, cantilevered anterior restorations, or foundation restorations on teeth, implant abutments, or a combination of the 2. Participants were offered gold, metal-ceramic, or lithium disilicate restorative options and informed of anticipated risks and benefits. Participants choosing lithium disilicate restorations were included in the study. Overall restoration survival was determined based on clinical criteria assessed at recall.

Five hundred and fifty-six patients (mean age, 62 years; range, 17-97 years; 40% men) electing lithium disilicate restorations were enrolled. Many patients received more than one restoration. Of the 1960 complete coverage lithium disilicate restorations provided (1410 monolithic; 550 bilayer), 7 failures (bulk fracture or large chip, affecting only monolithic restorations) were recorded indicating a 0.14% per year risk of failure. The average time to failure was 4.2 years. The 10-year estimated cumulative survival was 99.6% (95% CI: 99.4-99.8). The estimated cumulative survival was 96.5% for monolithic and 100% for bilayer restorations, at 10.4 and 7.9 years, respectively ($P<.05$). The risk for monolithic restoration failure was 0.2% per year. These failures occurred primarily in molars (5 of 7 failures) and in both arches (3 maxilla, 2 mandible). No failures were recorded for the bilayer restorations.

The authors concluded that pressed lithium disilicate restorations followed up in this single private practice were very successful over the 10.4-year observation period with an overall failure rate below 0.2% per year mainly associated with molar restorations. The risk of failure was minimal at any age for both men and women.

In similar fashion, a carefully developed prospective database emerging from the same private practice [207] was used to assess the effect of risk factors on adhesively bonded lithium disilicate glass-ceramic partial coverage restorations. Database parameters and recall methods were adopted from the previously reviewed publication.[206] The purpose of this clinical study was to report the 10.9-year survival of acid-etched, adhesively bonded, monolithic, pressed, lithium disilicate, partial coverage restorations and associated clinical parameters on outcomes.

Patients requiring partial coverage restorations in any area of the mouth were recruited. Participants were offered direct dental amalgam, direct composite resin, partial coverage cast gold, or lithium disilicate restorative options and informed of anticipated risks and benefits. They were also offered complete coverage restorations when appropriate. Only patients choosing lithium disilicate partial coverage restorations were enrolled. The overall survival of these lithium disilicate restorations was assessed relative to specific clinical factors (age, sex, dental arch, tooth position, type of partial coverage restoration, and ceramic thickness) at 6-month recall intervals. Fractured ceramics necessitating restoration remake were considered failures.

After 15 years of data collection, 304 participants (mean age, 62 years; range, 20-99 years; 40% men) possessing 556 pressed lithium disilicate partial coverage restorations (246 were inlays, 305 were onlays) were assessed. Six failures were recorded during the observation period (3 inlays, 3 onlays, molar regions only), with the average time to failure of 2.4 years (range, 0.8-9.2 years). The crude estimated failure risk was 0.3% per year, with the survivor function time at 10.9 years. The 10-year estimated cumulative survival was 95.6%. The estimated cumulative survival was 93.9% for inlays and 98.3% for onlays, at 9.9 and 9.8 years, respectively ($P<.05$). No significant difference in the survival was recorded between men and women, different age groups, or position in the dental arch, and thickness of the restoration had no significant influence on the survival ($P<.05$).

The authors concluded that their data indicated that properly managed monolithic pressed lithium disilicate partial coverage restorations exhibited excellent survival, yielding only 6 failures and a 10-year cumulative survival of 95.6% (overall failure rate of 0.3% per year, failures limited to molars). The potential confounding variables of tooth position, sex, age, or type of partial coverage restoration exhibited minimal to no effect on survival. Considering the substantial patient population and observation period, the current report can be used to guide clinicians in choosing minimally invasive, partial coverage, esthetic restorations.

A third publication originating from the same private prosthodontic practice[208] sought to investigate the 16.9-year survival of exclusively posterior pressed lithium disilicate complete and partial coverage restorations and the effects of associated parameters on clinical outcomes. Patients requiring either single-unit posterior partial coverage restorations, complete coverage restorations, or a combination were recruited. Participants were offered direct dental amalgam, direct composite resin, cast gold, metal-ceramic, or lithium disilicate restorations. Those requiring complete coverage restorations were given the options of complete cast gold, metal-ceramic, or glass-ceramic restorative options and informed of anticipated risks and benefits. Only participants who chose lithium disilicate partial and complete coverage restorations were enrolled. The effect of various clinical parameters on success of the restorations (age, sex, dental arch, tooth position, type of restoration, and ceramic thickness) was assessed at 6-month recall intervals. Fractured ceramics necessitating restoration remake were considered failures.

A total of 738 participants (mean age, 62 years; range, 20-99 years; 302 men) requiring 2392 lithium disilicate restorations (1782 complete coverage; 610 partial coverage) in posterior teeth were evaluated. A total of 22 failures (16 complete coverage; 6 partial coverage) were recorded with the average time to failure 3.5 years (range, 0.02-7.9 years). The overall estimated failure risk was 0.17% per year (0.16% complete coverage; 0.19% partial coverage). The overall 16.9-year estimated cumulative survival was 96.5%. The estimated cumulative survival was 96.8% for posterior complete and 95.3% for posterior partial restorations, at 10.5 and 16.9 years, respectively ($P<.05$). No significant difference in the survival was recorded between men and women, different age groups, or position in the dental arch, and thickness of the restoration had no significant influence on the survival. No statistically significant difference was found in the survival of posterior complete and partial coverage restorations among men and women, different age groups, or posterior tooth position ($P>.05$). The thickness of the restoration also had no influence on the survival ($P>.05$), and restorations with surfaces <1 mm and ≥1 mm performed similarly over 16.9 years.

The authors concluded that acid-etched, adhesively bonded, monolithic, pressed, lithium disilicate, complete and partial coverage restorations exhibited excellent survival in the posterior teeth up to 16 years of clinical function, demonstrating no significant differences in performance between complete and partial coverage restorations. The covariates of tooth position, sex, age, and restoration thickness do not impact survival. The authors indicated that their study provided ample evidence to guide clinicians in treatment selection and material options.

As reflected in these clinical reports, our appreciation for the durability of esthetic materials in the modern prosthodontics is critically important. To the end, contemporary dental laboratories generally track the clinical performance of restorations they manufacture and provide. In order to test the quality of material and restoration durability, Sulaiman et al[209] surveyed dental laboratories to determine the fracture rate of layered and monolithic lithium disilicate and zirconia single crowns and fixed partial dentures (FPDs) up to 7.5 years in clinical service.

Two major dental laboratories were engaged, both of which offer warranty services and use database systems capable of tracking restoration remakes secondary to material fracture. Data were gathered on 188 695 restorations (51 751 lithium disilicate, 36 198 monolithic, 15 553 layered; 136 944 zirconia, 93 848 monolithic, 43 096 layered) over a period of 7.5 years from 2010 to 2017. Lithium disilicate restorations were categorized into single crowns, FPDs, veneers, or onlays. Zirconia restorations were categorized into single crowns or FPDs, and then into anterior or posterior restorations. Restoration remakes due to poor fit, inappropriate shade, or poor marginal integrity were excluded from consideration.

The overall restoration fracture rate was 1.35%. For lithium disilicate, the fracture rate for monolithic single

crowns (0.96%) was significantly lower than that for layered single crowns (1.26%; $P<.05$), and the single crown fracture rate was significantly less than the FPD (monolithic and layered) fracture rate ($P<.001$). There was no significant difference in fracture rates between monolithic (3.66%) and layered FPDs (2.82%; $P=.151$), or between monolithic (1.15%) and layered veneers (1.21%; $P=.866$).

For zirconia, monolithic single crowns fractured at a lower rate (0.54%) than layered single crowns (2.83%) and monolithic fixed partial dentures (1.83%; $P<.001$), while layered single crowns (2.83%) fractured at a higher rate than layered FPDs (1.93%; $P<.001$). Monolithic zirconia anterior and posterior restorations fractured at a lower rate than layered anterior and posterior restorations ($P<.05$). Monolithic zirconia posterior restorations fractured at a lower rate than anterior restorations, while layered zirconia posterior restorations fractured at a higher rate than anterior restorations ($P<.05$).

Based on these findings, the authors concluded that the routine use of monolithic and layered lithium disilicate and zirconia ceramics demonstrates low and clinically acceptable fracture rates over a period of 7.5 years of function, with layered restorations demonstrating a higher fracture rate than monolithic restorations. Zirconia FPDs displayed a lower fracture rate than lithium disilicate FPDs, confirming the preferred use of zirconia for FPDs from a structural perspective. The authors indicated that the data presented can be valuable to clinicians, researchers, and manufacturers.

General implant prosthodontic considerations

Significant mechanical improvements have been introduced for dental implant screw joints over the past 30 years. However, retention screw loosening and screw joint failure may still adversely impact clinical success, particularly when it comes to single-tooth implant restorations. Colpak and Gumus[210] used an in vitro thermomechanical cycling experimental protocol to determine reverse torque values for abutment screws manufactured with various surface modifications.

Sixty abutment screws (grade 5 titanium alloy) were divided evenly into 2 groups (with and without thermomechanical cyclic loading). Each group was then divided into 3 subgroups according to screw surface treatment, including no treatment (NT; n=10), anodic oxidation (AO; n=10), and diamond-like carbon coating (DLC; n=10). The DLC coating is generally considered to provide excellent protection against abrasion, tribo-oxidation, and adhesive wear while permitting high thread surface pressures that may cause cold welding. All abutment screws were fastened (30 Ncm) to implants through stock abutments and tightened with a digital torque meter. Half of the resulting specimens were subjected to vertical thermomechanical cyclic loading (120 N; 240 000 cycles; 5 °C-55 °C) that represented approximately 1 year of clinical loading. Abutment screw reverse torque values were then measured. Percentage deviations (PDs, before-after thermomechanical cycling) were calculated and statistically analyzed.

The results indicated a decrease in reverse torque values for all groups after thermomechanical cycling indicating a generalized loss of screw joint preload. The loss of preload was greatest for the NT group, followed by the DLC group. The AO group demonstrated the least screw torque loss with and without thermomechanical cycling ($P<.001$ for each). A significant interaction was found between surface treatment and thermomechanical cycling ($P<.001$).

Within the limitations of this in vitro investigation, the authors concluded that abutment screw reverse torque values were greater for screw with AO and DLC surface treatments. AO treatment screws exhibited the lowest torque loss (maintained greater preload) with and without thermomechanical cycling. The authors suggested that further study of the possible influence of AO to maintain screw joint stability should be pursued.

For most of the modern dental implant era, titanium has been used because of its favorable biocompatibility, significant strength, resistance to corrosion, and potential for osseointegration. More recently zirconia was introduced as a possibility alternative implant material citing good biocompatibility and tissue integration with better esthetic characteristics. Improvements in reliability and strength of zirconia applications in implant dentistry are expected. The long-term success of dental implants may be influenced by microbial adhesion to implant, abutment, and restoration surfaces. To avoid adverse peri-implant soft-tissue responses, it would be helpful to know whether there are material-specific influences on microbiome development at early and late stages of biofilm formation. To better understand potential influences, Desch et al[211] reported on an in vivo model for biofilm formation used to evaluated biofilm volume, vitality, and diversity on zirconia and titanium (grade 4) abutment surfaces as a function of time.

Titanium and zirconia disks (Ø3×2 mm) cut from stock bars were processed to achieve a mean surface roughness comparable to that of an implant abutment (R_a of 0.3-0.4 μm). Disks (specimens) were then incorporated into recesses within maxillary complete-arch devices at buccal gingival posterior interproximal embrasures. With the devices in place, 8 specimens per device (4 titanium; 4 zirconia) were exposed to oral conditions in 12 volunteers for wearing times of 6, 24, 72, and 120 hours. At each time point, 2 randomly located specimens of each material were carefully removed for parallel analyses by confocal laser scanning microscopy (CLSM) and PacBio single-molecule real-time

sequencing (SMRT). A statistical analysis was performed, and the level of significance was set at 0.05.

CLSM revealed significant increases in biofilm volume over time on zirconia and titanium. The material did not significantly influence the volume or live/dead ratio at the individual time points investigated, although variations between volunteers were high. The composition of the microbiome was influenced by the age of the biofilm, but not by the material. The most frequently found bacteria were *Streptococcus spp*., followed by *Neisseria spp*., *Rothia spp*., *Haemophilus spp*., *Gemella spp*., and *Abiotrophia spp*.

Within the limitations of the study, the authors suggested that, while the quantity and diversity of the microbiome increased over time, there were no differences between zirconia and titanium in quantity and negligible differences in the abundances of adhered species. Further studies are necessary to obtain more microbiological information from hosts and evaluate other potential influencing factors. Differences between the microbiota samples may be dominated by the variability among study participants and developments correlated with biofilm age.

Recently, cone bean computed tomography (CBCT) has been recognized as an important tool in dentistry, particularly with respect to dental implant treatment planning. Apart from oral, dental, and jaw regions within the scan of specific interest to the treatment in question, CBCT scans inevitably include other head and neck anatomical areas. Significant incidental findings (IFs) related to regional structures are frequently indicated within the scan volume. Unfortunately, many dental clinicians lack the training necessary for the interpretation of IFs. To investigate this concern, Nguyen et al[212] conducted a retrospective analysis of IFs in CBCT scans made for older patients during dental implant treatment assessment, and to determine whether these IFs influenced the intended dental implant therapy. The authors defined an IF as one outside of the clinical focus of the CBCT examination and otherwise not known clinically or not detected with plain film imaging (bitewing, periapical, and/or panoramic imaging).

A retrospective review by a board-certified specialist was accomplished on 300 consecutive CBCT scans referred by a private dental practice for the purpose of implant planning on patients older than 40 years. CBCT machine, scan volume, and scan protocol remained consistent. The IFs were categorized into region (dentoalveolar, nondentoalveolar maxilla and mandible, paranasal sinuses, TMJ, nasopharyngeal/oropharyngeal airway, cervical spine, neurovascular canals) and influence on the course of treatment (no follow-up needed, significant IFs requiring follow-up but no treatment alteration, significant IFs requiring follow-up and treatment alteration).

The results indicated that IFs were observed in all CBCT scans (555 total; mean, 1.85 IFs/scan). The highest number of IFs was seen in the sinuses (34%), followed by dentoalveolar structures (31%), nasopharyngeal/oropharyngeal airway (12%), maxilla and mandible (10%), TMJ (6%), cervical spine (4%), and neurovascular canals (3%). A total of 37% of IFs required follow-up. For 12% of the patients, the detection of the IFs resulted in amendment or cancellation of the intended implant treatment plan.

The authors concluded that IFs in CBCT scan volumes within and beyond the region of interest are common and important to identify. The number of incidental findings per scan in an older population is likely greater than that in younger populations. The authors also emphasized the importance of interpreting CBCT volume in its entirety, regardless of the focused area of the scan based on the intended treatment plan.

Implant removable prosthodontics

Although ill defined, posterior mandibular alveolar bone loss in edentulous patients is thought to reflect the combined impact of multiple anatomic, physiologic, and prosthodontics factors. One unfavorable outcome of this bone loss is compromised oral functional for patients wearing conventional complete dentures (CDs). The addition of dental implants is believed to improve compromised function by enhancing prosthesis support, stability, and retention. In order to consider an optimal therapeutic approach, Oh et al[213] systematically reviewed current evidence related to posterior alveolar bone loss in the posterior mandibles of edentulous patients restored with mandibular complete dentures (CDs), 2-implant overdentures (2-IODs), and 4-implant overdentures (4-IODs).

A search of the professional dental literature was conducted in major databases to address the population, intervention, comparison, outcome (PICO) question, "Are mandibular IODs associated with greater posterior mandibular alveolar bone loss in edentulous patients than conventional mandibular CDs?" The search strategy initially identified 2806 articles. General article review identified 22 reports, of which 8 did not meet inclusion criteria and 7 were excluded for methodological reasons. Date from the remaining 7 studies were pooled, and a meta-analysis was performed to estimate mean differences in bone loss (95% CI; α=.05).

The results indicated no significant differences in posterior mandibular bone loss between 2-IODs and CDs (mean difference, –0.25 mm; 95% CI: –0.85-0.36; *P*=.43). Posterior mandibular bone loss was identified to be significantly less with 4-IODs than with 2-IODs (mean difference, –0.96 mm; 95% CI: –1.86-0.06; *P*=.04). In general, the data were highly heterogeneous with a wide range of variables (τ2>0.44; I^2>74%). The

included studies were found to have either moderate or high methodologic quality (STROBE checklist).

Within the limitation of this systematic review and meta-analysis and relative to mandibular posterior alveolar bone loss over time, the authors suggested that 4-IODs are associated with less bone loss than 2-IODs and that 2-IODs do not appear to be superior to conventional CDs. As is generally the case, the authors suggested that validation of these results is needed and should be accomplished with well-designed randomized controlled clinical investigations.

In like manner, the same lead author with a different group of colleagues (Oh et al[214]) investigated anterior maxillary alveolar bone loss in edentulous patients restored with maxillary complete dentures opposing either mandibular 2-implant overdentures (2-IODs) or mandibular complete dentures (CDs). The combination of a maxillary CD opposing a mandibular 2-IOD is thought to be reminiscent of prosthodontic conditions associated with what has become to be known as combination syndrome (Kelly[215]).

A systematic search of the dental literature was conducted in major databases to address the PICO question, "Are mandibular IODs associated with greater anterior alveolar bone loss in edentulous patients than conventional mandibular CDs?" The search strategy initially identified 2510 articles. General article review identified 14 reports. Risk of bias was assessed. After hand searching, the application of exclusion criteria, and assessment of methodology, 6 articles remained accounting for a total of 163 patients. Data from the remaining articles were pooled, and a meta-analysis was performed to estimate mean differences in bone loss (95% CI; α=.05).

The results indicated no statistically significant difference in bone loss in the anterior edentulous maxilla when opposed by mandibular 2-IODs as compared with mandibular CDs. The total estimate of weighted mean difference between 2-IODs and CDs was −1.40 mm (95% CI: −3.12-0.31; *P*=.11). The data were heterogeneous across the studies (τ2=5.53; I^2=95.21%). In addition, a subgroup analysis was conducted to assess that impact of implant splinting (bar-retained IODs). No significant impact could be identified (*P*>.29), and data were heterogeneous across studies (τ2=6.12; I^2=92.74%). None of the included studies were considered at high risk of bias.

Within the limitations of the systematic review and meta-analysis, the authors concluded that no significant difference in estimated anterior maxillary alveolar bone loss was found for edentulous patients wearing maxillary CDs opposing either mandibular 2-IODs or mandibular CDs. Again, the authors suggested that the results of this systematic review should be validated through well-designed randomized controlled clinical trials.

While clinical reports are not typically included in this annual publication, a recent publication involving novel, recently available, angle-correcting overdenture abutments (Novaloc; Institut Straumann AG) deserves a look. In this clinical report, Yue et al[216] presented the rehabilitation of a patient's edentulous maxillary arch.

Years after dental rehabilitation for generalized amelogenesis imperfecta, a 34-year-old man presented for additional dental therapy. The patient was in good general health, retained only mandibular anterior teeth, and desired improved social interactivity and more effective mastication. Based on diagnostic findings and patient desires, a treatment plan was developed to include surgical placement of 3 additional implants for a 5-implant maxillary overdenture supported by non-splinted attachments. The planned mandibular restoration involved a combination of implant- and tooth-supported fixed prosthodontic restorations. Minimal bone augmentation was an objective.

After implant placement and healing, overdenture abutments selection was considered. Upon assessing maxillary implant relative trajectories, 3 of the 5 maxillary implants demonstrated marked occlusal divergence. A means of angulation correction to achieve abutment parallelism was sought. Within the implant system (Straumann) used, an angle-correcting overdenture abutment system, recently brought to market, was selected. The Novaloc 15-degree angle-correcting abutments were fastened to the divergent implants, and straight abutments were placed on those that remained. The resulting near parallelism of abutments yielded a satisfactory path of prosthesis placement.

Using standard clinical and laboratory procedures, a maxillary palateless overdenture was fabricated incorporating a cobalt-chromium alloy reinforcing framework. Laboratory processing of attachments followed by a routine indirect method was used to incorporate 5 titanium housings within the denture base. The system uses polyetheretherketone (PEEK) attachment inserts. When compared with nylon inserts used by other attachment systems, PEEK is thought to demonstrate reduced wear during clinical use. Light retention force (white) PEEK inserts were chosen for the patient to permit adequate prosthesis retention given expected clinical conditions.

After prosthesis placement, the patient expressed satisfaction with the outcome, indicating favorable mastication and a natural appearance that fulfilled his objectives for pursuing treatment. Unfortunately, no clinical follow-up data were made available.

The authors concluded that having an angulated prefabricated overdenture stud-type abutment option can help establish attachment parallelism with divergent implants in a time- and cost-efficient manner. While this report involved Straumann implants, Novaloc abutments are also available for other major implant systems.

Combined implant divergence of up to 60 degrees can be accommodated with this system. A new abutment surface coating and the PEEK matrices may result in less wear under routine clinical conditions than other currently available systems. The authors suggested that in vitro and in vivo investigations should be conducted to discern long-term outcomes with the Novaloc system.

Implant fixed prosthodontics

A relatively recently reported and all too frequent adverse outcome associated with implant-supported fixed restorations is the propensity for interproximal contact loss (PCL). The tendency for the natural dentition to display mesial drift seems an oversimplified explanation because both mesial and distal PCL have been associated with implant restorations clinically. As the proximal gap is observed to increase over time, food impaction tends to occur placing the periodontal and peri-implant tissues at risk. Several articles appeared in the 2020 dental literature addressing this clinical phenomenon. Liang et al[217] evaluated the prevalence of PCL up to 18 years after implant prosthesis placement and evaluated potential associated factors.

A total of 317 patients who had received posterior fixed implant-supported dental restorations between 1999 and 2017 were enrolled in this study (120 men, mean age, 54 years). Restoration characteristics included 349 single-implant-supported crowns, 200 splinted implant-supported FPDs, 549 mesial contacts, 301 distal contacts, 26 screw-retained, 291 cemented, and average functional time 5.2 years (range, 0.3-18.2). Surgical implant placement and definitive implant restoration were accomplished with standard procedures. The definitive restoration proximal contacts were assessed with dental floss. If the floss passed through the proximal contact area with sufficient resistance, the proximal contacts were considered closed. Dental occlusion on implant restorations was adjusted to provide 25 μm of clearance light occlusal contact and definitive contact during heavy closure.

At follow-up, 1 examiner assessed 19 clinical factors, including proximal contact tightness, oral hygiene condition and habits, periodontal conditions, presence of plunger cusps, proximal food impaction, adjacent tooth vitality and mobility, opposing dentition, and occlusal scheme. Proximal contacts located both mesial and distal (if present) to implant restorations in question were evaluated with dental floss and qualified as tight, loose, or open. Chi-square test, univariate generalized estimating equation (GEE), and multivariate GEE were used to identify factors influencing PCL.

The rate of mesial PCL (27%) was significantly greater than that of distal PCL (5%), and both were observed to increase over time in function. Analyses identified 6 factors to be significantly associated with mesial PCL ($P<.05$), including patient age, years in implant function (>5 years; $P=.003$), frequency of interdental brush use, splinted or single-implant design, presence of plunger cusp, and food impaction. Although limited in occurrence, 3 factors, including restoration type, adjacent tooth vitality, and food impaction, were significantly associated with distal PCL ($P<.05$).

The authors concluded that mesial PCL for fixed implant restorations in partially edentulous patients was frequent and increased over time of restoration use. Patients should be made aware of the potential complication and instructed in the use of an occlusal retainer to prevent PCL. Although oral hygiene conditions were seen to contribute little to PCL, food impaction and the use of interdental brushes were significant. The authors suggest that prospective investigations addressing other possible factors, such as previous orthodontic treatment, growth factors, and parafunctional habits, should be conducted to better identify the etiologic basis for PCL. The authors cited the need for better pretreatment records (radiographs and orthodontic treatment records) and possible bias arising from a single follow-up examiner as limitations of the study design.

To investigate durability of restored proximal contacts from a subtly different perspective, Oh et al[218] systematically reviewed published reports addressing the odds of developing open proximal contacts (OPCs) between natural teeth and adjacent implant- and tooth-supported fixed prostheses. Additionally, the authors sought to estimate the odds of developing OPCs with the prosthesis as a predictor variable.

A comprehensive search of existing professional literature was conducted for clinical studies on the development of OPCs related to implant- or tooth-supported prostheses. The PICO question asked was, "Are the odds of developing OPCs greater with implant- or with tooth-supported prostheses?" Thirty-three reports emerged from the initial search. When subjected to inclusion criteria and judged on sufficiency of data, 14 studies remained for data extraction, including 9 related to tooth-supported restorations (5594 proximal contacts) and 5 reporting on implant-supported restorations (1719 proximal contacts). All studies had moderate to high methodologic quality. A meta-analysis was performed to estimate the odds of developing OPCs with implant- compared with tooth-supported prostheses (95% CI; $P<.05$).

The results (reported as odds ratios, ORs) indicated that an OPC was significantly more prevalent with implant-supported prostheses than with tooth-supported prostheses (OR, 2.46; 95% CI: 1.21-5.01; $P=.013$), although data were highly heterogeneous ($\tau 2=0.40$; $I^2=95.67\%$). Total estimates for developing OPCs were 41% (95% CI: 30% to 54%) for implant-supported prostheses and 22% (95% CI: 18% to 26%)

for tooth-supported prostheses. OPCs were more prevalent on mesial proximal surfaces of implant-supported prostheses (OR, 2.38; 95% CI: 0.94-6; *P*=.066) and distal proximal surfaces of tooth-supported prostheses (OR, 1.94; 95% CI: 1.09-3.45; *P*=.024). No significant associations for developing OPCs were found with sex, age, arch, splinting of implants/teeth, region, adjacent tooth vitality, retention type, opposing dentition, occlusal force, parafunctional activities, or follow-up time as a continuous variable. Based on 3 studies, OPCs were estimated to increase 9% per year with implant-supported prostheses (OR, 1.09; 95% CI: 0.71-1.67), increasing continuously throughout the follow-up period. The total estimate of OPC gap dimension between implant-supported prostheses and adjacent natural teeth was 245.8 μm (95% CI: 86.4-405.3 μm) based on 2 studies.

Within the limitations of this systematic review and meta-analysis, the authors concluded that OPCs were over twice as prevalent adjacent to implant-supported prostheses compared with tooth-supported prostheses. OPCs were twice as prevalent at the mesial compared with the distal proximal surfaces of implant-supported prostheses, and the opposite was found for tooth-supported prostheses. OPC dimensions progress over time from implant-supported restorations. Unfortunately, available data qualified as highly heterogeneous, thus necessitating future well-designed randomized clinical studies to validate the finding presented here. The authors cautioned that the limitations of the study included variations of effect size with different methods of clinical assessment and patient sampling across the studies. Although the initial publication search was designed to select articles conforming to established inclusion criteria, publication bias could not be ruled out because of inaccessibility of unpublished data.

A third publication approached the PCL issue from yet a different perspective. Saber et al[219] investigated the prevalence of PCL between implant-supported fixed prostheses and adjacent teeth and its impact on marginal bone loss. Their objective was to identify potential risk factors to this clinical problem, citing that sound and stable interproximal contacts generally provide a protective influence on associated periodontal and peri-implant supporting tissues.

This retrospective cohort study enrolled 83 recall-compliant patients (36 men; mean age, 57 years; range, 26-80 years) who received implant-supported fixed partial prostheses (119 cemented; 64 screw-retained; 121 mesial contacts; 62 distal contacts) at one facility from 2011 to 2017 and who met established inclusion and exclusion criteria. Interproximal contacts were clinically evaluated with 70-μm-thick waxed dental floss. Visual and periapical radiographic confirmation of PCL was accomplished. PCL was considered present if the floss passed without resistance. Plaque index, bleeding on probing, and radiographic bone loss around implants (radiographic baseline at prosthesis placement) were recorded at recall.

The results revealed the prevalence of PCL between implant-supported fixed prostheses and adjacent teeth was 32.8% (95% CI: 26.0% to 39.6%), showing high concordance with visual and radiographic confirmations (kappa=.876; *P*<.001). Food impaction was identified in 14.2% of the open proximal contacts. The prevalence of mesial PCL (42.1%) was significantly greater than that of distal PCL (14.5%), and anterior PCLs were greater than those identified in posterior regions. When PCLs were observed, the associated marginal bone loss (0.73 ±0.78 mm) was significantly greater (*P*=.017) than that in the presence of sound interproximal contacts.

PCLs occurred more frequently during loading phase (*P*=.05) and were significantly associated with patient complaints of open contact (*P*<.001) and food impaction (*P*=.001), as well as bleeding on probing on adjacent teeth (*P*=.024). Age, sex, smoking status, periodontal status, implant sites, and restoration type were not significantly associated with PCL or marginal bone loss (*P*>.05). In the presence of PCL, plaque index was significantly elevated on adjacent teeth (*P*=.048). Logistic regression showed that sites with PCL were 2.24 times more likely to present bleeding on probing (*P*=.028).

The authors concluded that PCL occurred with one-third of implant-supported fixed partial prostheses studied, and contact was lost nearly 4 times more often at mesial prosthetic surfaces than at distal surfaces. Additionally, a positive relationship exists between PCL and marginal bone loss. Therefore, periodic patient follow-up is essential in managing this complication, and retrievable implant restorations may prove beneficial from a prosthesis repair perspective once contact is lost. Future research to identify etiologic factors related to PCL is needed.

When 3 or more dental implants are placed in an edentulous arch to support a screw-retained fixed complete denture, the prosthesis may be designed to incorporate posteriorly directed cantilevers so that a complete compliment of posterior occlusal surfaces can be included. A lever system so designed may encounter high occlusal loading forces capable of transferring adverse biological and mechanical consequences to the system. Knowing the appropriate dimensional limits of cantilever length is critical for a stable and durable prosthesis design.

One guideline for defining cantilever length was offered by Dr Charles English in 1990.[220] In general, Dr English indicated that cantilevers extending from a fixed complete-arch implant restoration should be no longer than 1.5 times the linear distance between a line connecting the distal implants and the most anterior

implant. This linear measurement came to be known as the anterior-posterior (AP) spread. The use of AP spread in treatment planning and design has enjoyed a great deal of popularity, in part, because of its simplicity. Interested in justifying design criteria more soundly, Walter and Greenstein[221] critically analyzed available literature to assess the relationship between AP spread and other factors that may influence cantilever length for implant-supported fixed complete-arch restorations.

A comprehensive search of the professional literature produced 11 human clinical trials. The limited number of relevant publications permitted each report to be addressed and critiqued directly. In general, the available data seemed to indicate that the relationship between AP spread and cantilever length is not linear and that many influences (beam theory, maxillary versus mandibular cantilever location, number, and distribution of supporting implants, prosthetic materials, and framework design) should be considered when determining cantilever length.

The authors conclude that AP spread appears to be an empirical criterion, not one based on rigorous evidence or prospective clinical evaluations. Scientifically derived data that permit calculating cantilever length based solely on AP spread are lacking. Therefore, when designing cantilevers, the following should be considered:

- anticipate occlusal loads and load distributions when selecting the size, number, and design of implants to be placed;
- maximize implant distribution (AP spread) to reduce load per implant;
- incorporate a cross-arch splinting design and rigid materials when working with complete-arch restorations;
- develop the framework to have a cross-sectional design (I-beam effect) that resists loading; and
- minimize cantilever length whenever possible, particularly in the maxilla.

The authors also indicate that prostheses should be regularly monitored to assess structural integrity and occlusal accuracy. Implants and peri-implant tissues should be evaluated to ensure maintenance of biomechanical support.

Prosthodontic materials

High-performance polymers (HPPs) are semi-crystalline thermoplastic materials consisting of aromatic benzene molecules connected by ether or ketone functional groups. Polyetheretherketone (PEEK) and polyetherketoneketone (PEKK) are HPPs used in dentistry that may help meet the demand for a metal-free restoration alternative because of good biocompatibility, heat resistance, solvent resistance, excellent electrical insulation, and favorable wear and fatigue characteristics. Their natural radiolucency makes them apparent in CT, magnetic resonance imaging (MRI), and radiographic imaging with minimal artifact interference. These materials have been applied in the fabrication of dental implants, implant healing abutments, removable partial denture frameworks and clasps, and fixed prosthodontic restorations. HPPs can be thermoplastically formed and CAD-CAM milled or printed.

A concern prohibiting widespread application of HPPs in dentistry is their low translucency and unfavorable esthetic quality often requiring bonded resin or ceramic veneer additions. With this in mind, Gama et al[222] systematically reviewed the impact of surface pretreatments on the bond strength of common HPPs (PEEK and PEKK) and assessed postconditioning bond durability.

The professional literature was searched through March 2019 to address the focused question, "Does surface pretreatments and/or bonding agent application impact the bond strength between composite veneering resin and HPP?" A total of 11 articles were included in the qualitative synthesis. A quantitative analysis was performed with data extracted from 8 of the 11 selected articles, which included a total of 5066 in vitro specimens. Risk of bias was assessed, and random effects meta-analyses were applied to estimate mean differences in shear bond strength (SBS) and tensile bond strength (TBS) relative to surface pretreatments and bonding agents after 24 hours and thermocycling.

The results revealed that a low risk of bias was observed in most studies. Compared with nontreated controls, PEEK pretreatments associated with Visio.link (bredent GmbH) increased TBS by 26.72 MPa (95% CI: 19.69-33.76; $P<.001$) and increased SBS by 4.86 MPa (95% CI: 2.61-7.10; $P<.001$). Airborne-particle abrasion with 50-μm alumina improved SBS by 4.90 MPa (95% CI: 3.90-5.90; $P<.001$), and airborne-particle abrasion with silica-coated CoJet (3M ESPE) improved SBS by 4.51 MPa (95% CI: 1.85-7.18; $P<.001$). Compared with nontreated controls, Visio.link and Signum PEEK Bond (Kulzer GmbH) increased SBS by 33.76 MPa (95% CI: 18.72-48.81; $P<.001$) and 33.28 MPa (95% CI: 17.48-49.07; $P<.001$), respectively. No differences ($P>.05$) were found between Visio.link and Signum PEEK Bond or Monobond Plus/Heliobond (Ivoclar Vivadent AG). Similar results were observed for PEKK specimens.

The authors concluded that the bond strength between HPP and veneering composite resin increased significantly with surface treatment. This was particularly true when PEEK was used. For PEKK, tribochemical silica coating applied in association with 98% sulfuric acid etching seemed to be the best way to strengthen the bond with the resin veneer. Limitations of this systematic review included methodological differences in the selected reports, differing specimen aging protocols, and

a general lack of clinical data. The authors suggested that well-controlled clinical investigations in HPP bonding are necessary to establish a reliable HPP adhesive protocol for long-term bond stability.

To continue the focus on HPPs, Paratelli et al[223] present a scoping review to systematically map research reported in this area, as well as to identify any existing gaps in knowledge regarding PEEK material behavior when applied to implant restorations. Specifically, the authors formulated the following research question, "What is known from the literature about the application of PEEK in implant prosthodontics?" Relevant literature on PEEK in implant prosthodontics published through August 2018 was identified. Qualitative and quantitative syntheses were carried out for 13 original research studies.

The results indicated that PEEK has been applied in the fabrication of implant-supported fixed restorations (43%), definitive and interim implant abutments (35%), implant abutment screws (15%), and implant overdenture retentive inserts (7%). Only 38% of the identified studies were clinical in nature, 15% were observational, and 47% were in vitro. In total, in vivo data on 162 restorations and in vitro data on 106 specimens were identified. The studies included did not permit the reliable estimation of long-term restoration survival or prosthetic component success rates.

With respect to PEEK frameworks for implant-supported FPDs and single crowns, 2 case series, 2 uncontrolled clinical trials, and 2 in vitro studies lacking controls were identified. Failure of these restorations typically occurred adhesively between framework and veneering materials. From 4 in vivo reports on implant-supported fixed complete dentures, the mean survival over 12 months was 98.87%, and the mean success was 85.05%. Of the complications encountered, 64.28% were mechanical in nature (77.8% adhesive failures; 11.1% framework fractures; 11.1% discolorations), and 35.72% were biologic (soft-tissue lesions and unpleasant taste). Five reports identified on the use of PEEK for definitive or interim restorative abutments showed excellent success and survival rates up to 2 years in function. There were only 2 in vitro studies on PEEK implant abutment screws. Only 1 randomized clinical trial addressed PEEK round bar retention clips, and results indicated 100% success and survival over a short 6-month observation period.

The authors concluded that given the paucity of evidence on the viability of PEEK as an implant-prosthodontic material, its use cannot yet be endorsed. Additionally, the lack of high-quality evidence suggests that undertaking a rigorous systematic review is not currently appropriate or necessary. Further laboratory and clinical research is needed to better appreciate this material's suitability in implant dentistry specifically and prosthodontics in general. If used, suggested protocols for managing PEEK should be carefully followed to reduce the incidence of prosthodontic complications, bearing in mind that long-term outcomes remain uncertain.

The growing attractiveness of zirconia for conventional fixed prosthodontic restorations relates to favorable mechanical properties, capacity for monolithic fabrication, and relative tooth color appearance. When tooth preparation provides adequate resistance and retention form, zirconia crowns may be luted with conventional cements. However, in instances of nonretentive tooth preparation, adhesive luting must be considered. Considering currently available processes, Steiner et al[224] evaluated how cement type and priming protocol affect the shear bond strength on zirconia ceramics.

A total of 170 CAD-CAM–fabricated yttria-stabilized tetragonal zirconia polycrystal (Y-TZP) Ø3.3×3.0-mm cylinders (Vita YZ T; VITA Zahnfabrik) were bonded to flat 31.0×7.0×5.0-mm zirconia ceramic plates. The zirconia surfaces were airborne-particle abraded (Al_2O_3; particle size 50 μm; 0.1-MPa pressure; 10-mm distance), ultrasonically cleaned, and assigned to 17 groups of 10 specimens each. Seven commercially available resin cements and 3 surface pretreatment protocols were used to bond cylinders to plates. Ten specimens in each cement group were pretreated with a universal primer (Signum Zirconia Bond I+II; Kulzer GmbH), 10 specimens per group were bonded without pretreatment, and 10 specimens per group were pretreated with system-specific zirconia primers recommended for 3 of the cements. In total, 170 bonded specimens were stored in water, thermocycled, and submitted to shear bond load-to-failure tests.

The results indicated that mean shear bond strengths in the unprimed group showed large variations between 2.52 ±3.01 MPa and 33.15 ±7.35 MPa. Pretreatment with a universal primer significantly ($P<.05$) improved shear bond strengths in all groups ranging from 21.80 ±12.51 to 57.20 ±11.40 MPa. Compared with the unprimed group, system-specific primers also improved shear bond strengths significantly ($P<.01$). However, only one system-specific primer achieved a shear bond strength superior to the universal primer ($P<.01$). A statistical correlation of medium strength between fracture type and shear bond strength was demonstrated ($P<.001$), with cohesively fractured specimens demonstrating higher shear bond strengths (37.24 ±19.87 MPa) than adhesively fractured specimens (23.10 ±17.65 MPa). This correlation was significant ($P<.001$).

Based on these findings, the authors offered several conclusions. Airborne-particle abrasion alone, as a surface pretreatment, was insufficient to optimize the shear bond strength with zirconia. Surface pretreatments with each of the tested zirconia primers enhanced the bond strength. Cement type has a relevant influence on shear bond strength with zirconia. Finally, the authors

suggested that to predictably achieve high shear bond strengths to zirconia, the use of a strong bonding resin cement together with the MDP-containing universal primer is both supported by this in vitro experimentation and recommended.

PERIODONTICS, ALVEOLAR BONE, AND PERI-IMPLANT TISSUES

This year's review covered topics relating to the etiology, assessment, and prevalence of periodontal disease; the systemic health conditions affecting the periodontium; periodontal treatment therapies; the soft tissues adjacent to teeth and implants; bone biology and medication-related osteonecrosis of the jaw; alveolar ridge preservation and alveolar bone augmentation techniques; and peri-implant diseases.

An ongoing problem in the periodontal literature is the distorted interpretation or "spin" found in many periodontal literature abstracts which makes the research findings seem more favorable. Wu et al[225] performed an analysis of spin in abstracts of randomized controlled trials (RCTs) in periodontology and implant dentistry and explored its associated factors and influence on the subsequent literature. PubMed was searched to identify recent RCTs in periodontology and implant dentistry, whose primary outcome was found to be not significant statistically. Spin in abstracts was assessed and categorized according to predetermined spin strategies. The associations between study characteristics and the presence or severity of spin were analyzed with multivariable logistic regressions.

They determined that of the 196 abstracts included, 69.9% had demonstrated some type of spin. Of these, 29.1% demonstrated spin in the results section, and 64.3% had spin in the conclusion section. The main spin strategies in the results and conclusion sections were focusing on secondary outcomes and within-group comparisons. Understanding that RCTs are designed to test the null hypothesis for primary outcomes, reporting of secondary outcomes in the results and conclusion sections is not statistically supported.

Unfortunately, abstracts with spin also had adverse scientific influence on subsequent publications. Of the 34 subsequent inappropriate citations, 18 citations (52.9%) interpreted nonsignificant results as significant, 12 citations (35.3%) described irrelevant topics, and 4 citations (11.8%) claimed efficacy or recommended treatments based on nonsignificant results.

The presence of spin was also associated with the number of centers. Single-center studies were more likely to present spin in abstracts than multicenter reports. Studies in implant dentistry were associated with decreased severity of spin in comparison to periodontal tissue treatment.

The authors concluded that the frequency of spin is relatively high among published RCT abstracts in periodontology and implant dentistry. Findings reported in these abstracts need to be interpreted with caution. The danger for the field of periodontics and implant dentistry is that the presence of spin weakens the importance of primary outcomes, distorts the initial aims of trials, and most importantly misleads readers in clinical decision-making. Responsibility also lies within the editorial review process. Abstract reporting should be direct, clear, and transparent. For readers, clinical decision-making should base on access and reading of full texts and not only the abstracts.

Periodontal disease prevalence, etiology, and treatment

Periodontitis is an inflammatory disease triggered by a microbial dysbiosis that affects the supporting tissues, eventually leading to tooth loss when untreated. Viruses are also present within the oral cavity. But there is limited knowledge about their relationship to periodontal disease. Gao et al[226] introduced a new mouse model of periodontal disease to examine the effects of a polymicrobial infection on periodontal ligament (PDL), changes in bone loss, the host immune response, and the microbiome or virome by using shotgun sequencing. Periodontal pathogens were used as the polymicrobial oral inoculum in BALB/cByJ mice. As expected, the polymicrobial infection triggered significant alveolar bone loss, a heightened antibody response, and an elevated cytokine immune response. Most importantly, they found a significant shift in viral diversity and virome composition along with widening of the PDL space. Changes in the PDL space were present at sites far away from the site of insult, indicating that the polymicrobial radius of effect extends beyond the bone loss areas. Associations were found between bone loss, specific viral and bacterial species, immune genes, and PDL space changes. These findings may have significant implications for the treatment of periodontal disease which has limited research into antiviral therapies.

For effective treatment of periodontal disease, an accurate diagnosis of active disease before destruction of the periodontium occurs is required. In a systematic review, Arias-Bujanda et al[227] conducted a systematic review examining the accuracy of single molecular biomarkers for the diagnosis of periodontitis in the saliva. Articles on molecular biomarkers in saliva providing a binary contingency table (or sensitivity and specificity values and group sample sizes) in individuals with clinically diagnosed periodontitis were considered eligible for inclusion. The methodological quality for each article was assessed. Meta-analyses were performed with the Hierarchical Summary Receiver Operating Characteristic model. They found that meta-analysis was possible for

only 5 of the 32 biomarkers studied. The highest values of sensitivity for the diagnosis of periodontitis were obtained for IL1β (78.7%), followed by MMP8 (72.5%), IL6, and hemoglobin (72.0% for both molecules); the lowest sensitivity value was for MMP9 (70.3%). In terms of specificity estimates, MMP9 had the best result (81.5%), followed by IL1β (78.0%) and hemoglobin (75.2%); MMP8 had the lowest specificity (70.5%). This review demonstrated that MMP8, MMP9, IL1βb, IL6, and hemoglobin are salivary biomarkers with good capability to detect periodontitis in systemically healthy patients. Currently, MMP8 and IL1β are the most researched biomarkers in the field, both showing clinically fair effectiveness for the diagnosis of periodontitis.

Azurocidin is a neutrophil-derived protein in gingival crevicular fluid (GCF) which may correlate with the presence of active periodontal disease. Nalmpantis et al[228] conducted a study to evaluate azurocidin as a potential biomarker for chronic periodontitis. One hundred and one patients participated in the study, divided into 2 groups. Forty-eight were included in the periodontally healthy group (HP), and 53 in the chronic periodontitis group (CP). Clinical indices included probing depth (PD), recession (REC), clinical attachment level (CAL), bleeding on probing (BOP), and plaque (PL). Pooled GCF samples were collected with paper strips, and the levels of azurocidin were analyzed with ELISA. Statistical comparisons were performed with nonparametric tests (Mann-Whitney) at the 0.05 level. They demonstrated that while demographic data were comparable between the 2 groups, clinical parameters and the levels of azurocidin were statistically significantly higher in the CP group than those in the HP group. Quantitative data from ELISA demonstrated a high diagnostic accuracy of azurocidin. Azurocidin in GCF should be considered a promising biomarker for periodontal disease.

Being able to make an immediate chairside determination of a patient's periodontal diagnosis would be greatly beneficial. Arweiler et al[229] conducted a controlled clinical trial to determine clinical applicability of a newly developed chairside bacterial test (CST) for the most relevant periodontal pathogens. Examining 125 participants (100 with periodontitis, 25 healthy), 2 sulcus fluid samples each were collected and pooled for further analysis. Samples were analyzed with CST, and results (positive signals for every pathogen and control) were visually detected by eye. As a reference, quantitative polymerase chain reaction (qPCR) was performed. This CST was able to detect *Treponema denticola* (*T. denticola*), *Tannerella forsythia* (*T. forsythia*), *Porphyromonas gingivalis* (*P. gingivalis*), *Prevotella intermedia* (*P. intermedia*), and *Aggregatibacter actinomycetemcomitans* (*A. a.*). The sensitivities of CST to qPCR were as follows: *T. denticola* (91.3%); *T. forsythia* (86.3%); *P. gingivalis* (83.8%); *P. intermedia* (85.7%), and *A. a.* (100%). Regarding the clinical diagnosis, the CST assay and the qPCR method reached a sensitivity of 87.82% and 94%, respectively. The specificity for both methods was 100%. The authors concluded that this newly developed CST can detect 5 typical periodontal pathogens with a somewhat lower sensitivity toward qPCR.

Advancements in ultrasound technologies have allowed for the measurement of periodontal structures without the use of ionizing radiation. Tattan et al[230] evaluated the correlation and accuracy of ultrasound in measuring periodontal dimensions, compared with direct clinical and CBCT methods. Using a 24-MHz ultrasound probe prototype, specifically designed for intraoral use, periodontal soft-tissue dimensions and crestal bone levels were measured at 40 teeth and 20 single missing tooth spaces from 20 patients scheduled to receive a dental implant surgery. The ultrasound images were interpreted by 2 calibrated examiners. Ultrasound readings were compared with direct clinical and CBCT readings by using ICC and Bland-Altman analysis. Four parameters were measured for teeth (interdental papilla height, mid-facial soft-tissue height, mucosal thickness, and crestal bone level), and 2 parameters for edentulous ridges (soft-tissue height and mucosal thickness). The mean difference in mucosal thickness (tooth) between the ultrasound and direct readings was −0.015 mm without statistical significance. Examiner agreement between ultrasound and CBCT ranged from 0.654 to 0.849 among the measured parameters. The mean differences between ultrasound and CBCT range from −0.213 to 0.455 mm, without statistical significance. Ultrasonic imaging can be valuable for accurate and real-time periodontal diagnosis without concerns about ionizing radiation.

Notch signaling pathway plays an important role in osteoblast differentiation and bone remodeling. "Notch signaling" controls osteoclastogenesis indirectly, by managing the expression level of osteoclastogenic factors on osteoblasts' surface, or directly by regulating osteoclasts' differentiation. Recent studies have shown Notch signaling in bone remodeling that is complex and cell dependent. Mijailovic et al[231] analyzed the expression of Notch signaling molecules, bone remodeling mediators, and proinflammatory cytokines in patients with periodontitis and determined their potential correlations. This study included 130 individuals: 40 with aggressive periodontitis (AP group), 40 with CP group, and 50 periodontally healthy controls. Total RNA was extracted from gingival crevicular fluid samples, and relative gene expression of investigated molecules (Notch 1, Notch 2, Jagged 1, Hes 1, Hey 1, TNF-α, IL-17, RANKL, and OPG) was determined by reverse transcriptase real-time polymerase chain reaction (RT-qPCR). In the AP group, a significant increase of Notch 2, TNF-α, IL-17, and

RANKL and a significant decrease of Notch 1 and Jagged 1 expression were observed compared with the control group. Notch 2 and RANKL were also overexpressed in the CP group compared with controls. Significant correlations were observed in the AP group between expression levels of the analyzed genes. These findings implicate Notch 2 overexpression in the pathogenesis of bone resorption in aggressive and chronic periodontitis. The downregulation of Notch 1 and Jagged 1 and loss of their osteoprotective function might cause a more excessive osteoclast formation and contribute to greater osteolysis in aggressive periodontitis.

Periodontal diseases and systemic health relationships

Periodontitis has been identified as a moderate but independent risk factor for cardiovascular (CV) disease and progression. Schulz et al[232] studied the effect of subgingival colonization with selected periodontal pathogens on the occurrence of further adverse CV events in a cohort of patients with CV disease. The prevalence of severe periodontitis, including the detection of numerous periodontal pathogens, was analyzed in 1002 patients with CV disease. Periodontal pathogens detected included *A. a.*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *T. denticola*, *Peptostreptococcus micros*, *Fusobacterium nucleatum* (*F. nucleatum*), *Campylobacter rectus*, *Eubacterium nodatum*, *Eikenella corrodens* (*E. corrodens*), *Capnocytophaga sputigena*, *Capnocytophaga gingivalis*, and *Capnocytophaga ochracea*. The prognostic impact of periodontal pathogens for combined CV endpoint (stroke/TIA, myocardial infarction, CV death, death from stroke) was evaluated after a 3-year follow-up period. Hazard ratios (HRs) were adjusted for established CV risk factors applying Cox regression. They found that the decreased occurrence of *E. corrodens* was shown to be an independent predictor for adverse CV events after 3 years of follow-up. This unique finding implies that control of a recurrence of *E. corrodens* was associated with a reduced risk of adverse CV events in patients with CV disease. The pathophysiological background underlying this association should be investigated in further studies.

Periodontitis significantly increases the risk of diabetic complications. Impaired cardiac function has likewise been demonstrated to be a comorbidity. Wang et al[233] conducted a clinical trial investigating the effects of periodontal therapy on cardiac function in patients with type 2 diabetes mellitus (T2DM) and periodontitis. Fifty-eight participants with T2DM and periodontitis were randomly allocated to a treatment group (n=29) receiving nonsurgical periodontal therapy or a control group (n=29) having only oral hygiene instructions with delayed periodontal treatment until completion of this 6-month study. The left ventricle (LV) diastolic function was assessed by echocardiography with the tissue Doppler imaging index (E/e' ratio); and LV hypertrophy was evaluated by LV mass index (LVMI). Blood samples were collected for biochemical analyses. The intention-to-treat analysis showed that periodontal treatment significantly reduced the E/e' ratio by 1.66, along with marked improvement of periodontal conditions. LVMI was not altered at the 6-month follow-up. The serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a cardiac stress biomarker, C-reactive protein, and interleukin-6 decreased numerically, but this difference did not reach statistical significance. This present study provided evidence that nonsurgical periodontal therapy may improve cardiac diastolic function in patients diagnosed with type 2 diabetes with periodontitis.

The effect of periodontitis severity levels on acute myocardial infarction (AMI) remains unexplored. Gomes-Filho et al[234] investigated the association between levels of periodontitis severity (exposure) and AMI (outcome). In this case-control study, of 621 participants, 207 individuals treated in the emergency department of a hospital diagnosed with a first AMI event were compared with 414 individuals without a diagnosis of AMI. Levels of periodontitis severity were determined with the American Academy of Periodontology criteria. A conditional logistic regression analysis was performed, and ORs and CIs were obtained. The adjusted association measurements showed a positive association between both severe and moderate periodontitis. It demonstrated that among those with moderate and severe periodontitis, the chance of having AMI was approximately 2 to 4 times greater than among those without periodontitis. The findings demonstrated that there is an association between the severity of the periodontal condition and AMI, suggesting a possible relationship among the levels of periodontitis severity and the cardiovascular condition.

It is well established that diabetes can influence the incidence and severity of periodontal disease. Continuing research is also examining the effect of treatment of periodontitis upon systemic inflammation. A study conducted by Preshaw et al[235] examined the impact of periodontal treatment on systemic inflammation in type 2 diabetes. Adults with type 2 diabetes (n=83) and without diabetes (controls, n=75) were recruited, and participants with periodontitis received periodontal treatment and 12 months' follow-up. Biomarkers for periodontal inflammation (gingival crevicular fluid interleukin-6, TNF-α, ILβ, interferon-γ, MMP8, MMP9, adiponectin) and serum markers of inflammation and diabetes control (glycated hemoglobin, high-sensitivity C-reactive protein, interleukin-6, TNF-α, ILβ, interferon-γ, leptin, adiponectin) were measured. Structural equation modeling was used to evaluate periodontal treatment effects on oral and systemic inflammation. Periodontal treatment resulted in significant improvements in clinical status and reductions in gingival

crevicular fluid biomarkers from baseline to month 12. Structural equation modeling identified that, at baseline, individuals with diabetes and periodontitis had significantly higher systemic inflammation than nondiabetic controls with periodontitis, with no significant differences between groups for oral inflammation. There was a greater reduction in systemic inflammation after periodontal treatment in individuals with diabetes and periodontitis than in those with periodontitis but not diabetes. Diabetes and periodontitis together appear to increase systemic inflammation, with evidence of reductions after periodontal treatment.

There is also increasing recognition that multimorbidity in chronic inflammatory diseases may reflect shared pathologic mechanisms. Chronic obstructive pulmonary disease (COPD) and periodontitis frequently co-occur and share features of aberrant neutrophil responses. However, this may reflect common disease risk factors (smoking, age, and socio-economic status), not shared pathophysiology. COPD and alpha-1 antitrypsin deficiency (a disease associated with heightened neutrophilic inflammation and COPD) may be such a common pathophysiology. Sapey et al[236] investigated associations between periodontitis and chronic obstructive pulmonary disease (COPD) with and without alpha-1 antitrypsin deficiency (AATD), including neutrophil functions implicated in tissue damage. The presence and severity of periodontitis and lung disease were assessed in 156 patients with COPD with and without AATD accounting for common confounding factors. Saliva and systemic inflammatory markers were measured by ELISA together with neutrophil migration. They found that COPD and AATD patients exhibited higher prevalence of periodontitis than unselected community-dwelling populations even when risk factors were considered. Periodontitis severity was associated with lung disease severity. Neutrophil migratory accuracy declined in stage II-IV periodontitis patients with COPD or AATD compared with COPD or AATD with no or stage I periodontitis. Of clinical importance was the improvement in dental habits appeared to be associated with a reduction in exacerbation frequency in COPD. These results support shared pathophysiology between periodontitis and COPD, especially when associated with AATD. This may reflect an amplification of neutrophilic inflammation and altered neutrophil functions, already described in periodontitis, COPD, and AATD.

Smoking is a known risk factor for periodontal disease. With the increasing incidence of the electronic cigarette (vaping) habit, the effect of this habit upon periodontal disease activity is being more closely examined. Jeong et al[237] examined the association of conventional cigarette smoking and electronic cigarette vaping with periodontal disease in South Korean adults. Data from 13 551 participants, a subset derived from the Korean National Health and Nutrition Examination Survey conducted between 2013 and 2015, were examined. Participants were divided into 4 categories: electronic cigarette vapers, conventional cigarette smokers, ex-users, and nonusers. Periodontal status was measured by the Community Periodontal Index. Multiple logistic regression analysis was performed to examine the association of periodontal disease with smoking and vaping individually. Out of 187 men and 35 women who vaped electronic cigarette, 67 (35.8%) men and 10 (28.6%) women had periodontal diseases. Out of 1957 men and 363 women who smoked conventional cigarettes, 861 (44.0%) men and 121 (35.3%) women had periodontal diseases. Periodontal disease was more prevalent in vaper and smoker groups than among nonusers in men. Furthermore, both vaping and smoking had significant relation to dental caries, toothache, and dental damage. Electronic and conventional cigarette use was each significantly associated with increased periodontal disease rates. This study suggests that vaping is not a safe alternative to smoking.

Poor sleep behavior appears to have adverse effects on health by metabolic disruption and immunity suppression. Sleep disturbance is strongly associated with diabetes, cardiovascular diseases, and some cancers. Alqaderi et al[238] examined the association between sleep duration and periodontal disease in a national US population study in the National Health and Nutrition Examination Survey (NHANES). The data were collected from individuals aged $\geq$30 years and included 3624 participants in the United States NHANES 2013 to 2014. A weighted multivariable logistic regression modeling quantified the association between sleep and severe periodontal disease. They tested for diabetes as an effect modifier, adjusting for potential confounders such as smoking status, sex, age, education level, and frequency of dental visit. Individuals who slept >7 h/night with no trouble sleeping were 40% less likely to have severe periodontal disease adjusting for known cofactors. Additionally, diabetes was a significant positive effect modifier of the relationship between sleep and severe periodontal disease. This cross-sectional representative study of an adult US population revealed a statistically significant association between sleep duration and severe periodontitis, and this relationship was stronger among individuals with diabetes than among individuals without diabetes.

Periodontal treatment therapies

An initial course of treatment of an acute periodontal infection is the use of systemic antibiotics. Teughels et al[239] conducted a systematic review to answer the question "In patients with periodontitis, what is the efficacy of adjunctive systemic antimicrobials, in comparison with subgingival debridement plus a placebo, in

terms of probing pocket depth (PPD) reduction, in randomized clinical trials with at least 6 months of follow-up?" Thirty-four articles (28 studies) were included. Data on clinical outcome variables changes were pooled and analyzed with weighted mean differences. For PPD, statistically significant benefits were observed in both short-term and long-term studies. Additionally, statistically significant benefits were also found for clinical attachment level, bleeding on probing, pocket closure, and frequency of residual pockets. The best outcomes were observed for the combination of amoxicillin plus metronidazole, followed by metronidazole alone and azithromycin. However, adverse events were more frequently reported in groups with systemic antimicrobials.

Over the last decade, there has been an increased interest in the use of probiotics for enhancing periodontal health. The positive effect of a combination probiotic of 2 *Lactobacilli reuteri* (*L. reuteri*) strains as an additive to scaling and root planing has been demonstrated. Laleman et al[240] conducted a study examining the adjunctive effect of an *L. reuteri* probiotic on the reinstrumentation of residual pockets. This randomized, double-blind, placebo-controlled study included 39 previously non-surgically treated patients with periodontitis. A reinstrumentation was carried out, and probiotic and/or placebo drops were applied according to the study protocol. Patients afterward received probiotic lozenges to use 2×/d for 12 weeks. PPD, recession, bleeding on probing, and plaque levels were analyzed. No effects of the probiotic drops could be found. However, after 24 weeks, the overall PPD in the probiotic lozenges group was significantly lower than that in the control lozenges. This difference was even more pronounced in moderately deep (4-6 mm) and deep (≥7 mm) pockets. In the probiotic lozenges group, there were also significantly more pockets converting from ≥4 mm at baseline to ≤3 mm at 24 weeks and fewer sites in need for surgery. However, the probiotic products did not influence the microbiological counts of the periodontopathogens.

A common dilemma in the surgical treatment of periodontal disease is the decision to use flap procedures versus regenerative procedures for the treatment of intrabony defects. Nibali et al[241] conducted a systematic review and meta-analysis examining the appropriateness and expected outcomes of regenerative surgery or access flap treatment of intrabony defects. Electronic and hand searches were performed to identify randomized clinical trials on regenerative treatment of deep intrabony defects (≥3 mm) with a follow-up of at least 12 months. Primary outcome variables were PPD reduction, CAL gain, and tooth loss. Secondary outcome variables were recession (REC), radiographic bone gain, pocket closure, patient reported outcomes, and adverse events. A meta-analysis was carried out when possible. To evaluate treatment effect, odds ratios were combined for dichotomous data and mean differences for continuous data with a random-effect model. A total of 79 RCTs (88 articles) published from 1990 to 2019 and accounting for 3042 participants and 3612 intrabony defects were included in this systematic review. Only 10 of included studies were rated at low risk of bias. A total of 13 meta-analyses were performed. All regenerative procedures provided adjunctive benefit in terms of CAL gain compared with open flap debridement alone. Both enamel matrix derivative (EMD) and guided tissue regeneration (GTR) were superior to OFD alone in improving CAL, although with moderate-high heterogeneity. Among biomaterials, the addition of deproteinized bovine bone mineral (DBBM) improved the clinical outcomes of both GTR with resorbable barriers and EMD. Papillary preservation flaps enhanced the clinical outcomes. The strength of evidence was low to moderate.

From this systematic review, the advantage of papillary preservation flaps (PPFs) is suggested. Aslan et al[242] examined the question as whether or not a PPF technique requires the addition of a bone substitute to be effective. Their study compared the clinical efficacy of the Entire Papilla Preservation Technique (EPP) alone and in combination with enamel matrix proteins plus bovine-derived bone substitutes (EPP EMD+BS) in the treatment of isolated interdental intrabony defects. Thirty participants, each with one isolated intrabony defect, were randomly assigned to EPP EMD+BS or EPP alone. Clinical outcomes were assessed 1 year after the surgery. Early healing phase was uneventful for all participants, and 100% primary wound closure was maintained throughout the study period. Intragroup differences between baseline and 1 year were statistically significant in both groups in terms of CAL gain and PD reduction. No statistically significant differences were detected in REC. No statistically significant differences were detected in terms of CAL gain, PD reduction, or increase in gingival recession between the groups treated with EPP EMD+BS or EPP alone.

The successful surgical treatment of furcation defect is less predictable than non–furcation-associated intrabony defects. When a furcation defect is combined with an intrabony defect, achieving positive outcomes can be even more challenging. Cortellini et al[243] examined the use of PPF in the treatment of furcation defects associated with an intrabony defect. The aim of the study was to describe specific designs for PPFs and minimally invasive surgery to be used in compromised molars and report proof-of-principle data with 3- to 16-year follow-up in severely compromised molars because of the presence of combined furcation and intrabony defects. Forty-nine participants with furcated molars and deep intrabony defects were treated with PPFs, application of periodontal regenerative devices. Improvement as a

consequence of therapy was defined as tooth retention, reduction in horizontal and vertical furcation involvement, decrease in probing depths, and increases in clinical attachment level. Participants were maintained with regular supportive periodontal care. At 1 year, 100% of maxillary and 92% of mandibular molars showed improvements. An important outcome was the lack of improvements observed in molars with baseline hypermobility. Improvement in vertical subclassification was observed in 87.5% of maxillary and 84.6% of mandibular molars. One-year improvements were maintained over the 3- to 16-year follow-up.

During a guided tissue regeneration (GTR) procedure, the periosteum is elevated with the flap, and occlusive guided tissue membranes are placed over the defect, thereby excluding any contribution of gingival cells and osteoblasts from the periosteum. GTR procedures with an occlusive membrane can deprive the wound from a huge regenerative influence of the gingiva and the periosteum. To enhance the regenerative capacity of the gingival periodontal structures while maintaining cell exclusiveness, a perforated barrier membrane (PBM) was developed. It showed improved clinical outcomes when compared with occlusive membranes (OMs). Simvastatin (SMV), similar to other statins, acts as an inhibitor of the mevalonate pathway and consequently cholesterol synthesis. SMV is also reported to stimulate VEGF release in a dose-dependent manner which promotes osteoblast differentiation and bone nodule formation. Issa et al[244] presented a study designed to evaluate clinically and biochemically the use of PBM combined with simvastatin (SMV) gel with and without an associated EDTA root surface etching. Forty patients having moderate-to-severe chronic periodontitis with 40 intrabony defects were randomly divided into 4 treatment groups (10 sites each). Patients in group 1 received 1.2% SMV gel and occlusive membrane for covering the defect. Patients in group 2 received 1.2% SMV gel and PBM for covering the defect. Group 3 received 24% EDTA root surface etching, 1.2% SMV gel, and defect coverage with OM (eOM). Patients in group 4 were treated as in group 3, but the defect was covered with PBM (ePBM). Clinical parameters were recorded at baseline before surgical procedures and were reassessed at 6 and 9 months after therapy. The mean concentration of SMV in gingival crevicular fluid (GCF) was estimated by reverse-phase high-performance liquid chromatography at days 1, 7, 14, 21, and 30. At 6- and 9-month observation periods, groups 3 and 4 showed a statistically significant improvement in PD reduction and CAL gain compared with groups 1 and 2. Group 4 showed statistically significant higher defect fill than groups 1, 2, and 3. Group 2 showed statistically significant higher defect fill than group 1 and group 3. Bone density was significantly increased with no significant difference between the 4 groups at 6- and 9-month observation periods. SMV-GCF concentration in group 4 showed the highest mean concentration with no significant difference compared with that of group 3. The use of perforated barrier membranes in association with SMV enhances the clinical hard-tissue parameters compared with occlusive ones in treating intrabony periodontal defects.

Long-term tooth retention is the goal of periodontal therapy. Petsos et al[245] conducted a study to evaluate tooth loss (TL) during 10 years of supportive periodontal therapy (SPT) in periodontally compromised patients and to identify factors influencing TL on the patient level. Patients were re-examined 120 ±12 months after active periodontal therapy. TL and risk factors influencing TL on the patient level (smoking, initial diagnosis, SPT adherence, interleukin-1 polymorphism, cardiovascular diseases, age at baseline, bleeding on probing/BOP, change of practitioner, insurance status, number of SPT, and marital and educational status) were assessed. One hundred patients (52 women, mean age 65.6 ±11 years) lost 121 of 2428 teeth (1.21 teeth/patient; 0.12 teeth/patient/year) during 10 years of SPT. Forty-two of these teeth were lost for periodontal reasons (0.42 teeth/patient; 0.04 teeth/patient/year). Significantly more teeth were lost because of reasons other than periodontal disease. Smoking, baseline severity of periodontitis, nonadherent SPT, positive interleukin-1 polymorphism, marital and educational status, private insurance, older age at baseline and BOP, and small number of SPT were identified as patient-related risk factors for TL. Only a small number of teeth were lost in periodontally compromised patients showing the positive effect of a well-established periodontal treatment concept.

An additional study demonstrated the importance of supportive therapy in long-term maintenance for periodontal and implant therapy patients. Amerio et al[246] conducted a systematic review examining the effect of patient compliance on the outcomes of supportive therapy. Electronic and manual literature searches were carried out to assess patient compliance during maintenance. The main outcomes were compliance definition, degree of compliance, and patient-related factors. Owing to the heterogeneity of the data reported across studies, descriptive statistics were performed to shed light on compliance rate and the patient-related factors. A total of 39 articles were included. Unfortunately, no consensus regarding the definition of "compliance" was found in the analyzed literature. It is striking that the percentage of full compliers and non-compliers ranged from 3.3% to 86.8% and 1.69% to 64.4%, respectively. Smoking habit and history of periodontal disease were found to be associated with patients' compliance. Inadequate information or motivation was found to be the main patient-reported reason for noncompliance. Despite the high variability across

studies, compliance with the supportive periodontal or peri-implant maintenance therapy was found to be unsatisfactory. The authors suggest that "attitudes, psychological traits, and construct associated with compliance remain largely unknown, and still, lack of information and motivation are paramount to be addressed during the periodontal/implant therapy to increase patient compliance."

Soft-tissue adjacent teeth and implants

When evaluating the outcomes of periodontal plastic surgery procedures, the literature has primarily focused on easily quantifiable clinical outcomes such as recession and attachment levels. Recently, studies are also examining patient-centered outcomes. Cairo et al[247] conducted a systematic review of RCTs to examine the effect of different flap designs and graft materials for root coverage, in terms of esthetics, patient satisfaction, and self-reported morbidity (postoperative pain or discomfort). After a comprehensive literature search was performed, a mixed-modelling approach to network meta-analysis was used to formulate direct and indirect comparisons among treatments for root coverage esthetic score (RES), with its individual components, and for subjective patient-reported satisfaction and postoperative pain/discomfort (visual analog scale or VAS of 100). Twenty-six RCTs involving 867 treated patients (1708 recessions) were included. Coronally advanced flap (CAF)+CTG, tunnel (TUN)+CTG, and CAF+graft substitutes (GS) were significantly associated with higher RES than CAF alone. No significant difference between CAF+CTG and TUN+CTG was detected. As would be expected, the addition of CTG resulted in a less natural tissue texture and gingival color than CAF. CTG techniques were associated with increased morbidity.

Precise volumetric investigations with 3D digital methodologies, concerning soft-tissue alterations after root coverage procedures, are not usual but are becoming more common. Zuhr et al[248] conducted a randomized clinical trial to compare the clinical and volumetric outcomes of the TUN technique with CTG versus CAF with EMD 2 years after gingival recession (GR) treatment. Using 3D intraoral scanning, this methodology facilities accurate measurement of changes in tissue thickness. Twenty-three patients contributed 45 Miller class I or II GR defects. At baseline and follow-up examinations, study casts were collected. Their three-dimensional scans allowed precise computer-assisted measurement of REC, complete root coverage (CRC), percentage of root coverage (RC), and pointwise (pTHK) and mean areal (aTHK) marginal soft-tissue thickness. Clinical examination delivered periodontal probing depths (PPD) and height of keratinized tissue. Twenty-four months after surgery, digitally evaluated CRC was present in 60.0% of the TUN+CTG-treated sites and 0.0% of the CAF+EMD-treated sites, meaning a certain relapse of the gingival margin was associated with both approaches. RC amounted to 94.0% of TUN+CTG and 57.3% of CAF+EMD. REC reduction (RECred) was significantly greater for TUN+CTG than that for CAF+EMD. pTHK and aTHK values were significantly greater in the TUN+CTG group than those in the CAF+EMD group. Statistical analysis detected positive correlations between THK and both RC and RECred. Two years after surgery, CTG showed better clinical and volumetric outcomes than EMD.

Successful treatment of class III and class IV recessions in the mandibular anterior region is difficult to obtain. Mercado et al[249] compared clinical and patient-centered outcomes of CTG with those of EMD in the treatment of multiple class III-IV Miller periodontal recession defects on mandibular anterior teeth. This randomized clinical study evaluated 41 patients at 3 years of follow-up. A total of 156 teeth were divided into 2 groups: test (CTG+EMD, 79 teeth) and control (CTG only, 77 teeth). Clinical REC, keratinized tissue (KT) width, percentage of root coverage, and patient-centered outcomes were compared between the 2 groups. At 36 months of the follow-up, a patient-level analysis showed that REC in the test group was reduced significantly (5.71 ±0.58 mm to 1.57 ±0.85 mm) compared with that in controls (5.94 ±0.46 mm to 2.51 ±0.62 mm), while KT width increased in the test group (1.51 ±0.26 mm to 4.18 ±0.34 mm) and was significantly greater than that in controls (1.65 ±0.21 mm to 2.90 ±0.20 mm). At 36 months, tooth-level analysis (class III and class IV groups) found less residual REC and increased KT in the test group than in controls. Additionally, significantly less pain was reported at 2, 7, and 14 days after surgery in the test group.

This same group of authors examined the treatment of class I and class II defects with CTG for both maxillary and mandibular anterior teeth with and without EMD.[250] This prospective clinical study evaluated 80 patients over a 3-year follow-up in a private periodontal practice. A total of 144 maxillary and mandibular anterior teeth were divided into 2 groups: group 1 (CTG+EMD, 80 teeth) and group 2 (CTG only, 64 teeth). REC, KT width, percent root overage, patient-centered outcomes, and pain on a visual analog scale (P-VAS) were compared. At 3-year follow-up on a patient level, statistically significant changes in REC were achieved in both group 1 (4.65 ±1.84 to 0.39 ±0.19 mm) and group 2 (4.43 ±1.11 to 0.92 ±0.43 mm). Complete root coverage was achieved in 66.4% of group 1 and 50.1% of group 2. At both the patient and tooth levels, 3-year outcomes were superior for group 1 than those for group 2 in terms of percent root coverage, REC, and KT width. CAL was reduced in group 1 compared with group 2 at the tooth-level

analysis only. Significantly less pain/P-VAS was reported at the 2 weeks after surgery in group 1.

Bone biology and medication-related osteonecrosis of the jaw

Studies examining the onset mechanism for osteonecrosis of the jaw (ONJ) secondary to bisphosphonate use have primarily focused on bone remodeling, biofilm formation, and epithelial cell proliferation and migration. However, the involvement of stromal cells, especially fibroblasts, in the oral cavity is unclear. Taniguchi et al[251] examined the effect of bisphosphonates (BPs) on orthotopic periodontal ligament fibroblasts with respect to oxidative stress compared with ectopically obtained fibroblasts. Normal human periodontal ligament fibroblasts (HPdLFs) and normal human dermal fibroblasts (NHDFs) were used to gain insight into the functional differences in sensitivity and reactions to BPs. Cell growth assay, measurement of reactive oxygen species (ROS) and nitric oxide (NO) production, and wound-healing assay in vitro were performed. Maxillary first molars were extracted in C57BL/6 mice and either BP, N-acetyl-cysteine (NAC) and BP, or saline were administered. The BP-induced IC50 values were significantly lower in HPdLFs than those in NHDFs. BP resulted in an increase in ROS, but not NO generation in HPdLFs. BPs also inhibited proliferation and migration of HPdLFs but not NHDFs, while the addition of an ROS inhibitor (NAC) reversed those inhibitions. Impaired wound healing of the socket was observed in a BRONJ mouse model where BP was administered and then the tooth was extracted. When NAC was administered before tooth extraction, wound healing was significantly improved. This animal model suggests that the preoperative administration of the reactive oxygen species inhibitor, N-acetyl-cysteine, may decrease healing complications associated with BP-induced ONJ. This well-established antioxidant has been used in the treatment of cystic fibrosis.

A temporary discontinuation (drug holiday) of high-dose antiresorptive (AR) agents has been proposed to reduce the risk of medication-related osteonecrosis of the jaw (MRONJ). Ottesen et al[252] conducted a systematic review to answer the question: Is a high-dose AR drug holiday, at the time of tooth extraction or dentoalveolar surgery, necessary to prevent the development of MRONJ? RCTs, cohort and cross-sectional studies, surveys, and case reports with more than 5 patients were included. Valuable information on AR drug holiday could be extracted from 14 of 371 reviewed articles. Among these, 3 were prospective and 11 were retrospective studies involving high-dose AR drug holidays. In 2 studies, patients were being treated with denosumab, but neither showed that a drug holiday was effective. The remaining 12 studies evaluated bisphosphonate treatment, and 2 of these studies found no reason to use AR drug holiday before surgery. Three studies recommended drug holidays, whereas most studies recommended assessing each patient separately. The only article incorporating the PICO approach was a non-randomized, prospective study with a control group. This study concluded that drug holiday was not necessary. Thus, there is no evidence for drug holiday. However, this conclusion is clearly affected by a limited number of eligible patients and great interpatient variations. It appears that high-level evidence for AR drug holiday is almost impossible to obtain.

Proton pump inhibitors (PPIs) are widely prescribed for the treatment of gastric reflux disease. Recent evidence suggests that PPIs might influence bone metabolism. Ursomanno et al[253] conducted a study to determine if peri-implant bone loss severity could be associated with PPI use. Dental, medical, and radiographic histories of patients receiving dental implants in a university setting were retrospectively reviewed. Bone loss around each implant was evaluated radiographically by direct measurement of crestal bone loss and by counting the number of radiographically evident exposed threads. PPI use and the presence of systemic factors were confirmed by medical record examination. Confidence intervals (CI) and *P* values of mean differences between PPI and non-PPI groups were computed. A total of 1480 implants from 635 patients were included. Greater crestal implant bone loss was associated with patients having a history of PPI use. Mean crestal bone loss of 1.60 mm was noted at implants from PPI patients compared with 1.01 mm in the non-PPI group. After adjustment for systemic factors, those effects persisted, demonstrating crestal implant bone loss of 1.87 mm for PPI patients and 1.04 mm for non-PPI patients. Acknowledging limitations associated with retrospective studies, the data suggest that PPI medications are related to elevated crestal bone at implant sites.

Glyburide, a medication used in the management of diabetes, is an inhibitor of NLRP3 inflammasome. Excessive mechanical stress, such as traumatic occlusion, induces expression of IL1β and may be involved in bone resorption. NLRP3 inflammasomes have been linked to IL1β expression. Arita et al[254] examined whether glyburide could suppress occlusal trauma in rats (age 7 weeks). In the trauma group, wire was attached to maxillary right first molar occlusal surfaces resulting in occlusal trauma with mandibular right first molars. In the trauma+glyburide group, the NLRP3 inhibitor glyburide was administered orally every 24 hours from 1 day before the induction of occlusal trauma. Rats were euthanized after 5 or 10 days, and maxillary first molars were harvested with the adjacent tissues for histopathologic investigation. Immunohistochemical expression of IL1β, NLRP3, and RANKL was also assessed. On day 5, bone

resorption was significantly greater in the trauma group than that in the control group or the trauma+glyburide group, and there were significantly greater numbers of osteoclasts and cells positive for IL1β, NLRP3, and RANKL in the trauma group. This study suggests that the NLRP3/IL1β pathway might be associated with bone resorption induced by traumatic occlusion.

Alveolar ridge preservation, alveolar ridge, and sinus augmentation

A proposed benefit of ridge preservation procedures is to reduce the need for subsequent grafting at the time of implant placement. When considering implant placement in the maxilla, secondary bone augmentation may necessitate sinus augmentation. Park et al[255] examined the benefits of ridge preservation in terms of surgical invasiveness of implant placement compared with natural healing in the maxilla. This retrospective study included 178 patients with 206 implants placed at ridge-preserved sites and 493 patients with 656 implants placed at naturally healed sites in maxillary anterior and posterior regions. Patient- and implant-related data were collected from electronic dental records and included additional augmentation procedures performed before or during implant placement with related surgical complications. Cumulative survival rates and annual peri-implant marginal bone loss between the 2 groups were compared. The follow-up period was 24.4 ±18.1 months for ridge-preserved sites and 45.7 ±29.6 months for naturally healed sites. Sinus augmentation was performed at similar frequencies in the 2 groups, but a lateral approach was applied significantly more at naturally healed sites (37.2%) than at ridge-preserved sites (8.3%). Ridge preservation can be clinically beneficial for minimizing the invasiveness of implant surgery by simplifying the procedure when sinus augmentation is expected in the maxilla.

There are relatively few RCTs examining the benefit of ridge preservation (RP) at molar sites. Duong et al[256] designed a 3-arm cohort study to histologically compare the healing outcome between natural healing after molar tooth extraction and 2 different techniques of RP with freeze-dried bone allograft (FDBA) and a non-resorbable dense polytetrafluoroethylene (dPTFE) membrane, or an absorbable collagen sponge as a barrier. Seventy-nine patients requiring extraction and delayed implant placement were placed into 3 groups: extraction alone (control); ridge preserved with FDBA; and either dPTFE (Test1) or collagen sponge (Test2). Bone cores were harvested from implant osteotomies at approximately 3 months after extraction for histomorphometric analysis to determine the percentage of vital bone, residual graft, and connective or other tissue. Ridge dimension changes were also evaluated radiographically using CBCT. Results indicated that the percentage of vital bone was significantly greater in the control group than that in the Test1 group but was not statistically different among other groups. The Test2 group showed significantly less connective or other tissue than the control and Test1. The percentage of residual graft was significantly lower in Test1 than that in Test2. RP at molar sites with FDBA and an absorbable collagen sponge may be a sufficient and economic way to preserve the ridge dimension without interfering with the amount of new bone formation. The collagen also does not require a secondary intervention to remove the barrier as is the case with dPTFE procedures.

The ideal timing of implant placement is another important treatment variable after a ridge preservation procedure. Nelson and Mealey[257] examined the histologic difference in healing between ridge preservation sites treated with a combination allograft of 70% mineralized and 30% demineralized freeze-dried bone allograft (FDBA) evaluated at 8 to 10 weeks (short term) versus 18 to 20 weeks (long term) after extractions. Changes in morphological ridge dimensions were also evaluated. Forty-four patients with a single-rooted tooth to be extracted and replaced by a dental implant were recruited for this study. At the time of extraction, measurements were made with a custom acrylic resin stent, and the extraction socket was grafted with the combination allograft and covered with a nonresorbable membrane. Patients were randomly assigned to the short-term or long-term healing group. Sites were re-entered for study measurements, a bone core sample, and implant placement. Bone cores obtained during implant placement were analyzed histologically to determine percentages of vital bone, residual graft, and connective or other tissues. Thirty-eight of the 44 patients completed the study, 19 in each group. There was a significant difference between the 2 groups for mean percent vital bone formation (short term=18.17%, long term=40.32%) and percentage of residual graft (short term=41.54%, long term=23.59%). Delaying the placement of the implant after a ridge preservation procedure resulted in approximately twice as much vital bone and half as much residual graft material after 18 to 20 weeks of healing compared with only 8 to 10 weeks of healing.

A connective tissue graft (CTG) is often used in immediate implant placement and provisionalization (IIPP) in the esthetic zone. However, the benefit of a CTG with respect to the tissue stability remains unclear. In an RCT of 42 patients, Jiang et al[258] examined hard- and soft-tissue alterations associated with IIPP implants with or without CTGs. Single unsalvageable maxillary incisors were replaced with IIPP. Patients were randomly assigned to receive a simultaneous CTG (test group) or not (control group). Digital scans and CBCT images were obtained before extraction and after 6 months. Mid-facial gingival margin migrations, soft-tissue contour changes,

and hard-tissue remodeling were analyzed and compared between the 2 groups using a 3-dimensional superimposition method. Forty participants completed the study. The test group showed significantly less buccal tissue collapse in the area 2 to 5 mm apical to the gingival margin. In both groups, the mid-facial gingival margin migrated in an apical-palatal direction, and the void socket, except for a triangular space in the buccal-coronal region, demonstrated radiographic new bone formation without statistically significant differences.

Autogenous bone is still considered the standard for bone grafting materials. Morbidity associated with harvesting the autogenous graft is a disadvantage. Additionally, the effect of the harvesting procedure on the graft's osteogenic response is operator and patient specific. Tabassum et al[259] examined the osteogenic response of autogenous bone collected during implant osteotomy preparation using 2 different drilling protocols and evaluated/compared the capacity for proliferation and differentiation of the collected bone particles. Autogenous bone particles were harvested from 20 patients during implant osteotomy preparation with 2 different drilling protocols: (1) the standard drilling protocol with saline irrigation according to the manufacturer's recommendation, and (2) a low-speed drilling protocol at <200 rpm without saline irrigation. Bone samples collected were cultured in growth medium, and after 2 to 3 weeks, cells that grew out from bone grafts were cultured in the normal medium, as well as in osteogenic medium, for days 0, 4, 7, and 20. Scanning electron microscopy, alizarin red/toluidine blue staining, DNA, ALP, and calcium content measurements were performed. The total DNA content was significantly higher for low-speed drilling samples than that for standard drilling samples on day 4, 7, and 20 in the normal medium and on day 7 and 20 in the osteogenic medium. Calcium measurements and mineralized matrix formation observed with alizarin red/toluidine blue staining were significantly higher in the low-speed drilling group than those in the standard drilling group. These finding may influence the operator's selection of osteotomy drill speeds during implant placement if autogenous bone particles are to be collected.

In guided bone regeneration procedures (GBR), physical slumping of the bone graft beneath the barrier decreases the available volume for regeneration. Because of this reduced volume effect, tenting screws (TS) are often recommended. Cesar Neto et al[260] conducted a study radiographically examining the influence of TSs for primarily horizontal guided bone augmentation. Twenty-eight patients in need of staged bone augmentation were consecutively treated in a private practice. DBBM particulate bone substitute material and a resorbable collagen membrane were used in all patients who were divided into 2 groups: control (conventional GBR; n=22) and test (TS+GBR; n=22). CBCT images were obtained before augmentation and after 6-8 months for comparison using superimposition. Alveolar ridge width (RW) and ridge width change (RWchange) were assessed at 1, 3, 5, and 7 mm below the bone crest. Forty-four sites in 28 patients were evaluated. Results indicated that there were no differences between groups for RW at baseline (TS: 5.87 ±2.41; control: 5.36 ±1.65). Regarding RWchange, ridges that received TS displayed an additional effect at 1 and 3 mm below the crest compared with controls. The final RW was greater in the TS group than that the control group at 1-, 3-, and 5-mm levels.

When a dental surgeon evaluates the feasibility of a sinus augmentation procedure based on a radiographic evaluation of the maxillary sinus, peripheral consequential findings may be identified. If pathology is suspected, the surgeon may elect to refer the patient to an ENT specialist. A common challenge for this dental surgeon is deciding what radiographic criteria should be used to support this referral. Janner et al[261] conducted a study designed to compare maxillary sinus evaluations rendered by ENT specialist's and dentist's using CBCT imaging of asymptomatic patients before implant placement in the posterior maxilla. Secondary objectives were to determine factors influencing the agreement of the raters and to propose subsequent ENT referral guidelines based on intradisciplinary and interdisciplinary consensus. Two ENT specialists and 2 oral surgeons assessed 100 CBCT data sets of healthy patients referred for dental implant placement in the posterior maxilla. Operators were tasked to assess the possibility of sinus floor elevation or the necessity for further diagnostic examinations based solely on radiographic findings. Inter-rater agreements within the same specialty were calculated. The correlation between all 4 raters was generally fair to moderate. The intraspecialty comparison showed lower correlation between dentists than between ENT specialists. Absence of membrane thickening and total or subtotal sinus opacification showed the highest predictive value leading to consensus in favor of sinus floor elevation and ENT referral, respectively. Flat membrane thickening with irregular surface morphology was associated with disagreement between examiners. Dome-shaped membrane thickenings were often considered for referral by dentists, but not by ENTs. The assessment of maxillary sinuses using CBCT imaging resulted in an unsatisfactory agreement between ENT specialists and oral surgeons.

The sinus bone walls are considered the most important source for osteoprogenitor cells. Therefore, increased distance between the grafted area and the maxillary sinus walls may decrease bone formation. Pignaton et al[262] evaluated anorganic bovine bone (ABB) graft remodeling in sinus lift graft procedures with respect to distance to native bone in the maxillary

sinuses. Bilateral sinus grafting was performed in 20 patients with residual bone height <5 mm before implant placement. After 8 months, biopsy samples were harvested, and a histomorphometric analysis was performed to determine bone formation relative to the distance from the native sinus bone. In grafted areas, the percentages of new bone (NB), residual graft material (rABB), and soft tissue (ST) were evaluated. A total of 103 biopsy samples were evaluated, and percentages of NB, rABB, and ST were calculated for each millimeter of distance away from native bone. The first millimeter within the grafted area (closer to the native bone) contained more NB than other portions of the graft and less rABB than the second millimeter of the graft. More ST occupied the third millimeter and fourth millimeter of the grafted area than the first 2 mm. The distance of the graft from the native bone influenced bone formation after maxillary sinus augmentation.

The necessity for simultaneous placement of grafting materials in osteotome sinus floor elevation (OSFE) is increasingly being questioned. However, there is a paucity of comparative data on long-term outcomes of implants placed with OSFE with or without bone grafting. Therefore, Qian et al[263] assessed the long-term clinical and radiographic results of implants placed using OSFE with or without bone grafting. Forty-five patients were randomly assigned into 2 groups. Group 1 received OSFE with DBBM grafting, and group 2 received OSFE without grafting. Patients were recalled at 1, 3, 5, and 10 years after surgery. Implant survival, endo-sinus bone gain (ESBG), marginal bone loss (MBL), peri-implant bone height (PBH, distance from the most coronal to most apical level of bone-to-implant contact), prosthesis survival and hardware complications, and peri-implant soft-tissue conditions were assessed. Forty patients attended the 10-year examination. Mean residual bone height was 4.58 ±1.28 mm. The 10-year cumulative survival rate was 90.7% for group 1 and 95.0% for group 2. The PBH was 5.89 ±1.24 mm for group 1 and 5.74 ±1.43 mm for group 2 at 10 years. The ESBG of both groups remained stable after 3 years. No significant differences in MBL and peri-implant tissue parameters were identified suggesting that OSFE with or without grafting yielded predictable clinical outcomes.

The results of several preliminary studies support the use of augmented corticotomy as a therapeutic approach to improve the limited periodontal soft and hard tissues in patients requiring orthodontic treatment. However, evidence for the impact of augmented corticotomy on periodontal tissues, especially the soft tissue, remains limited. Jing et al[264] examined soft- and hard-tissue changes after augmented corticotomy in Chinese adult patients with Angle skeletal class III malocclusion. This nonrandomized controlled trial included 357 anterior teeth in 30 Chinese adult patients for whom the proposed treatment was augmented corticotomy. Jaws receiving surgery were allocated to a test group (S or surgical group, n=47), and jaws not receiving surgery were allocated to a control group (NS or nonsurgical group, n=13). Changes in the periodontal biotype, width of the keratinized gingiva (WKG), and labial and lingual horizontal bone thicknesses (BTs) were compared 6 months after surgery by univariate and multivariate analyses. After adjustment for confounding variables, average gains of 0.473 mm in the WKG and 0.649 mm in the labial BT were found in the S group relative to the NS group. The odds of transition from a thin periodontal biotype to a thick biotype in the S group were approximately 230 times those in the NS group. The odds of the reverse biotype transition in the NS group were about 83 times those in the S group.

Peri-implant disease and treatment

The efficacy and safety of antibiotic use at the time of implant placement remain controversial. Canullo et al[265] conducted a systematic review to determine if antibiotic prophylaxis reduces implant failure and postoperative infection in healthy patients who receive dental implants. Patient- and implant-level data were extracted for the desired outcomes. The risk ratio and the 95% confidence interval (CI) were calculated as meta-analytic effects. Nine studies that included 1984 patients and 3588 implants were selected. A total of 885 patients (1617 implants) received no antibiotics or a placebo therapy before the implant surgery; 1099 patients (1971 implants) were treated with antibiotic therapy. The patient-level meta-analysis showed a statistically significant reduction in the rate of early implant failure associated with the use of antibiotics. Similar results were obtained after pooling implant-level data with a fixed-effect model. The results of this systematic review with meta-analysis indicate that antibiotic prophylaxis appears to prevent early implant failures in healthy patients.

For years dentists have appreciated that natural tooth restoration contour may interfere with periodontal health and that restoration overcontouring is a greater periodontal hazard than undercontouring. These basic concepts originally directed at natural teeth also hold true for implants. When the axial contour of implant restorations prohibits hygiene access, peri-implantitis may result. Additionally, implant restorations with shallower emergence angles (EAs) and straight or concave interproximal profiles may also help to minimize the risk of peri-implantitis with bone-level implants. When considering splinted implant prosthesis, the impact of the prosthetic connection on the incidence of peri-implant disease should be considered. Yi et al[266] analyzed the prevalence of peri-implantitis when the restoration is splinted to implants mesial, distal, or both. Additionally, other prosthetic features were considered, including emergence

angle (EA), emergence profile, and crown/implant ratio. A total of 169 patients (349 implants) were retrospectively included in this study. Peri-implantitis was diagnosed based on peri-implant bone loss and probing depth. Radiographs made 1 and 5 years after prosthesis insertion facilitated assessment of peri-implant marginal bone loss (MBL), emergence angle (EA), emergence profile (EP), and crown/implant ratio (CIR). The splinted position of the prosthesis was also recorded. A multivariable generalized estimating equation was used to analyze the influence of each feature in question on the prevalence of peri-implantitis. Similar to the results of other studies, the EA showed significant correlation with MBL. A statistically greater prevalence of peri-implantitis was observed with EA $\geq$30 degrees, with convex EP, and when a bone-level implant was splinted to adjacent implants both mesial and distal. A similar correlation was not observed for tissue-level implants. CIR had no effect on the prevalence of peri-implantitis. The authors concluded that overcontouring of the implant prosthesis is a critical local confounder for peri-implantitis and that the splinting of restorations appears to impose a higher risk for peri-implantitis.

Disagreement exists between recent systematic reviews regarding the efficacy of the "one abutment–one time" protocol. Despite studies indicating favorable results for protocols that avoid disconnection of abutments, there exists wide methodologic variations related to the stage of alveolar socket healing, loading protocol, number of disconnections, prosthesis retention, abutment design, follow-up time, and even the design of implants. A study that isolates abutment disconnections as the only variable between the groups within a biologically stable clinical situation is needed. Praça et al[267] conducted such a study and evaluated the influence of abutment disconnections and reconnections on peri-implant marginal bone loss. Twenty-four participants receiving single-unit implants were randomly assigned to 2 groups: the definitive abutment group (DEF) where definitive abutments were connected at the time of implant placement; and the healing abutment group (HEA, control) where healing abutments were disconnected and reconnected 3 times, at 8, 10, and 12 weeks after surgery. Peri-implant marginal bone level was measured immediately after surgery (baseline), 8 weeks, 6 months, 12 months, and 24 months. Implant stability (resonance frequency analysis) and peri-implant health (peri-implant probing) were assessed. Results indicated no significant differences at the end of 2 years, with mean bone levels of −0.18 ±0.12 mm (DEF) and −0.13 ±0.13 mm (HEA) and cumulative bone losses of −0.61 ±0.10 mm (DEF) and −0.81 ±0.15 mm (HEA). Bone-level changes showed statistically significant differences only between 0 and 2 months (DEF: −0.70 ±0.12 mm; HEA: −0.36 ±0.10 mm) and between 2 and 6 months (DEF: −0.11 ±0.11 mm; HEA: −0.65 ±0.14 mm). No differences were observed between the groups for implant stability, probing depth, or bleeding on probing. Using a well-controlled experimental protocol, authors conclude that immediate and definitive connection of prosthetic abutments did not reduce bone loss when compared with several disconnections/reconnections of healing abutments over time.

Implant surface modifications may facilitate enhanced soft-tissue adhesion resulting in clinical and radiographic benefits once implants are exposed to the contaminated environment of the oral cavity. To study this proposed transmucosal benefit, Salvi et al[268] evaluated and compared peri-implant soft tissues in contact with implants possessing a modified hydrophilic sandblasted and acid-etched neck (mSLA; test group) to soft tissues in contact with a machined implant neck (M; control group). Implants (4.1 mm diameter, 1.8 mm transmucosal neck height) were randomly placed in healed posterior maxillary and mandibular sites having pristine bone. The modified Sulcus Bleeding Index (mSBI, primary outcome) was assessed at baseline, 6 months, 12 months, and 36 months. Secondary outcomes included the assessment of PPD, REC, and CAL. Standardized radiographs were taken at time of implant placement, baseline, 12 months, and 36 months. Of the 43 randomized participants, 38 (19 test and 19 control) completed the 36-month follow-up. Implant survival rates were 95.5% (test) and 100% (control). At 36 months, 77.6% of test implants and 78.9% of control implants had no bleeding sites (mSBI=0). The 36-month success rate was 86.4% (test) and 85.7% (control). At 36 months, the mean radiographic bone-level change from baseline was 0.33 ±0.69 mm (test) and 0.12 ±0.3 mm (control). Results of mSLA and machined titanium necks were not statistically different.

Multiple implant surface modifications have been proposed for the treatment of peri-implantitis, yet none has been identified as most effective. Lasserre et al[269] studied the efficacy of implantoplasty and glycine air polishing for the surgical management of peri-implantitis. This prospective, randomized, parallel-group trial included 31 patients with 42 implants affected by peri-implantitis. Patients underwent surgical treatment using implantoplasty (n=22, test group) or glycine air polishing (n=20, control group). The clinical parameters Plaque Index (PI), bleeding on probing (BOP), suppuration on probing (SOP), PPD, relative attachment level (RAL), and mucosal recession were assessed at baseline before surgery and after surgery at 3 months and 6 months. Bone loss was recorded at baseline and 6 months. The authors determined that PI remained low in both groups for the duration of the study. Mean BOP, SOP, PPD, and RAL were greatly reduced at 3 months in both groups and remained low between 3 months and 6 months. There were no

statistically significant differences between groups for any parameter. Composite treatment outcomes for both groups were similar, irrespective of the definition. Within the limitations of this 6-month follow-up study, implantoplasty is as effective as glycine air polishing for the surgical management of peri-implantitis.

IMPLANT DENTISTRY

This review of the scientific literature in implant dentistry targets the practicing restorative dentist. It qualitatively screens published and indexed articles in the PubMed database for the year 2020. The foci of the review are clinical relevance, quality of study design, and long-term reporting. Included in the review are a detailed description of the performed search, exclusion criteria, and inclusion criteria.

The following search was performed in PubMed: "dental implant" OR "dental implants" OR "dental implantation" OR "dental implantations" OR "oral implant" OR "oral implants" OR "oral implantology" OR "osseointegration" OR "osseointegrated". Several PubMed filters were applied to these results: date from 1 January 2020 to 31 December 2020 (5866 articles), English language (5706 articles), human studies (2147 articles), clinical trial (220 articles), and meta-analysis (111 articles). A total of 221 articles were initially screened by title for pertinence, then by abstracts, and full texts were reviewed for final inclusion based on clinical significance and study design. To be included, articles had to be published in journals referenced in Journal Citation Report, be related to the field of dental implants, be relevant to treatment planning decisions, and be available in full text to the reviewer.

This year's review includes 24 articles comprised of 14 randomized controlled clinical trials, 1 prospective clinical trial, and 9 meta-analyses of clinical trials. The topics studied are the history of periodontal disease as a risk indicator for peri-implant health (1 article); effect of smoking levels on implant failure (1 article); the use of a single midline implant for mandibular overdentures (2 articles); the use of implants with removable partial dentures (2 articles); soft- and hard-tissue anatomy and augmentation (5 articles); implant position, abutment, and prosthetic variables on outcomes (3 articles); short implants (4 articles); implant placement with freehand versus guided protocols (5 articles); digital versus conventional workflow outcomes and efficiency for single-unit restorations (1 article).

A history of periodontal disease is a well-known risk factor for peri-implantitis. Lin et al[270] performed a meta-analysis of 13 articles to evaluate whether a history of periodontal disease remains a risk indicator for patients undergoing supportive therapy. Past periodontal disease was associated with significantly worse implant survival rates, marginal bone loss, bleeding on probing, and pocket depth at rough surface implants. However, for machined surface implants, a history of periodontal disease does not negatively impact outcomes in a statistically significant manner. This meta-analysis of clinical data associate peri-implantitis to a history of periodontitis and indicate the relationship is more significant with rough surface implants. This finding demonstrates the link between a biofilm-mediated immune response that is more profound at rough, plaque-retaining, implant surfaces.

Another systemic link extensively studied in association with implant failure is smoking. Using a meta-analytical approach, Naseri et al[271] assessed what number of cigarettes smoked per day would have a significant effect on the relative risk (RR) of implant failure. Twenty-three articles were reviewed. Results indicated that >20 cigarettes/d have a statistically significant impact on the RR of implant failure when compared with nonsmokers. This finding is true at both the implant level (RR: 2.45; CI: 1.42-4.22; P=.001) and the patient level (RR: 4; CI: 2.72-5.89; P<.001) for >20 cigarettes/d when compared with nonsmokers.

Next several studies pertaining to mandibular implant-supported overdentures are reviewed, focusing on implant survival, patient satisfaction, or Oral Health Quality of Life (OHQoL). Hartmann et al[272] performed a short but well-designed randomized trial comparing OHQoL to mastication function in patients who had adapted to new maxillary and mandibular complete dentures (baseline) and then received mandibular implants for overdentures. After dropouts, 37 patients answered questionnaires at baseline and at 1, 6, and 12 months after receiving mandibular implant overdentures. Baseline satisfaction was similar in all patients. The 3 treatment groups were randomly allocated with mandibular implant prostheses: Group I (11 patients, single-implant overdentures), group II (13 patients, 2-implant overdentures), and group III (13 patients, 4-implant fixed dentures). Although all groups showed significant improvements at baseline, group III showed a higher effect size value (ES=0.57, a large effect), followed by group II (ES=0.43, a medium effect) and group I (ES=0.36, a medium effect). All treatments resulted in an improved masticatory function after the insertion of implant prostheses. Although the overall effect of the prosthesis type was not significant, slightly better performance seems to occur with a greater number of implants (group I versus II) and from removable to fixed prostheses.

The findings suggest that implant overdentures involving 1 or 2 implants are quite similar, while a 4-implant fixed prosthesis results in slight better patient-related outcomes. Well-controlled baseline treatment (recently inserted new complete dentures) permitted

authors to statistically demonstrate that implant support for mandibular overdentures improved OHQoL despite a low number of patients observed, which makes these findings relevant.

Abou-Ayash et al[273] performed a 2-year randomized controlled trial to compare immediate and delayed loading protocols for single-implant overdentures. Data were collected from 158 patients at 4 months and 131 patients at 2 years. Physical and mental components of the OHQoL indexes did not improve at either time point. Only in the immediate loading group did physical OHQoL components improve significantly from baseline to 2 years, but the authors did not infer clinical conclusions from these data. Overall, the treatment protocol of a single-implant overdenture did not improve OHQoL when compared with baseline, and the authors did not recommend this treatment approach with that aim in mind. This is another reminder that in simply reviewing results, we should not disregard the outcomes studied and their clinical relevance.

Ease of use and reduced cost of mini-implants might lead one to consider their use to facilitate support and retention of existing removable partial dentures (RPDs) to improve patient satisfaction. Al Jaghsi et al[274] and Mundt et al[275] reported on a randomized controlled multicenter clinical trial evaluating the use of mini-implants under 2 loading protocols: immediate loading (38 patients, 22 women; mean age, 66.4 years; 40 RPDs) and 4-month delayed loading (38 patients, 25 women; mean age, 65.4 years; 39 RPDs). Patients presented wearing RPDs with unfavorable abutment distributions (no canine and at most 2 posterior teeth in one or both quadrants). Patients received strategically placed mini-implants with ball abutments. In the immediate loading group, implants that achieved 35 Ncm insertion torque were connected to the RPD with O-rings attachments (6 patients) and those that did not achieve the requisite insertion torque were loaded using a soft liner placed in the attachment areas (in 32 patients). For the delayed loading group, all RPD bases were relieved over the implants to prevent functional/retentive loading. After 4 months, the soft relined RPDs and all RPDs in the delayed loading group received O-ring attachment.

Mundt et al[275] evaluated mastication efficiency (mixing of 2-colored chewing gum as measured by the circular variance of hue) at baseline (before implant placement), 2 weeks, 4 months, 4.5 months, and 12 months after surgery. As expected, mastication efficiency was better after immediate loading than after delayed loading ($P<.001$). For patients receiving immediate soft reline material and patients subjected to the delayed loading protocol, mastication efficiency was reduced postsurgically. However, mastication efficiency immediately increased with incorporation of O-ring attachments in the RPDs, and the variance of hue values after 1 year was very similar in the groups.

Authors concluded that mastication performance can be improved by the strategical surgical placement of mini-implants under existing RPDs with existing unfavorable tooth support. This improvement occurred more quickly by using an immediate loading versus a delayed loading protocol.

For the same experimental population, Al Jaghsi et al[274] measured patient satisfaction at baseline (before implant placement), 2 weeks, 4 months, 4.5 months, 12 months, 2 years, and 3 years after surgery. Satisfaction at 4 months was superior for the immediate loading group, but delayed loading at the 4.5 months yielded satisfaction improvements to a similar level. Overall, satisfaction ratings were mostly "very good" or "good" throughout the length of the study for all satisfaction domains (general satisfaction; RPD retention, stability, and support; eating; speaking; and esthetics) and across both groups. The authors indicated that mini-implants may be used with existing RPDs to improve abutment distribution to optimize functional loading conditions and significantly improve patient satisfaction. The studies by Jaghsi et al[274] and Mundt et al[275] provided ample support for continued clinical analysis and implementation of implant-assisted RPDs.

The multifactorial nature of treatment decisions in the esthetic zone sparked the review 2 studies on the predictive value of preoperatory anatomy and additional studies assessing outcomes for implant placement in native bone, guided bone regeneration, and connective tissue grafts.[276-280]

In the first study, Lee et al[276] focused on data from a randomized controlled trial involving 39 patients who received immediately loaded implants placed with or without flaps and without bone grafts in the esthetic zone between second maxillary premolars. Initial hard- and soft-tissue dimensions were recorded and correlated to the 12-month outcome. Gingival recession at the midfacial gingival margin was statistically correlated to preoperatory gingival thickness 3 mm apical to the gingival margin (GT3). Results demonstrated that postoperative recession was less at 0.23 mm with GT3<1 mm compared with 0.63 mm with GT3>1 mm ($P=.01$). Additionally, flap elevation was associated with greater facial recession (0.25 mm with GT3<1 mm) compared with reduced facial recession (0.08 mm with GT3>1 mm) without flap elevation ($P=.04$).

In a controlled clinical trial, Avila-Ortiz et al[277] compared extraction alone (control) with extraction with socket preservation by using an allograft and barrier membrane (test) up to 14 weeks and before implant placement. The results showed that volumetric bone variation was less in the socket preservation group, but soft-tissue variation is not significantly different between

groups. However, in 48.1% of controls, an additional augmentation procedure was needed before implant placement, while only 11.5% of socket preservation sites required preimplantation augmentation. Linear regression analysis demonstrated that, when compared with soft-tissue thickness and keratinized mucosa width, baseline facial bone thickness is the strongest predictor of alveolar resorption.

Another valuable comparison is the effect on clinical outcomes of guided bone regeneration and connective tissue grafting. De Bruyckere et al[278] performed a randomized controlled trial to evaluate facial alveolar concavity reconstruction at the time of implant placement. The control group (n=19) received guided bone regeneration (GBR: Bio Oss+collagen membrane) and submerged healing, while the test group (n-21) received connective tissue grafting (from palate) with open healing. Results indicated that pink and white esthetic scores were similar for both groups and ranged from 8.43 to 10.48. Patient-related outcomes risk (PROMs) suggested more edema, hematoma, use of pain medication, and bleeding in the GBR controls. At 1 year, esthetic evaluation by the patients demonstrated no differences between the groups. However, the mucosal scaring index was 2.53 in the control group and 1.10 in the test group and achieved statistical difference (P=.017). Color mismatch was also more frequent in the controls (58%) than in test participants (24%). These soft-tissue outcomes were attributed to the need for releasing incisions in GBR controls. The authors suggested that, given similar esthetic outcomes at the patient level for the procedures investigated, the least invasive intervention could be selected to reestablish facial alveolar convexity at the time of implant placement.

Jonker et al[279] conducted an interesting prospective controlled trial to evaluate esthetic and patient-reported outcomes for implants placed with a 2-stage GBR procedure and implants placed in native bone. Twenty-three patients with facial bone defects of <4 mm were allocated to the 2-stage GBR group, while 22 patients were assigned to have implants placed in native bone. Outcomes at 12 months demonstrated similar pink and white esthetic scores regardless of surgical approach. Patient-reported outcomes for mucosa and crown appearance were similar. No other differences between groups were identified. It appears that operators may select the treatment approach at the time of implant placement and engage in GBR without further complications.

Finally, Waller et al[280] published an important study looking at 20 patients receiving 26 posterior implants followed up for 7.5 years. The clinical protocol compared spontaneous healing (11 patients) to guided bone regeneration (9 patients) for implants demonstrating a small noncontained facial bone dehiscence of ≤5 mm. Probing depth, bleeding index, plaque index, and implant survival were similar at all time points up to 7.5 years. Facial vertical changes were not significantly different between the groups at all analyzed timepoints (P=.61). The vertical facial defect depth measured on CBCT was significantly greater (P=.019) in the spontaneous healing group (2.51 mm) than that in the GBR group (1.66 mm). Bone thickness was significantly greater for the GBR group (P=.008).

The authors concluded that GBR may be justified in the management for small facial vertical bone dehiscences. However, the necessity of GBR for clinical implant success must be questioned based on the current data. Despite the limited sample size and favorable bone-level outcomes, one can consider clinical outcomes to be similar whether GBR is used or not in posterior areas with bone defects ≤5 mm. It is important to appreciate that these results should not be applied to similar osseous defects in more esthetic areas.

Implant position and prosthetic variables are important to clinical outcomes. de Siqueira et al[281] conducted a 5-year randomized, split-mouth, clinical trial involving 27 subcrestal implants and 28 equicrestal implants. Clinical and radiographic outcomes were assessed at insertion, 4 months, 8 months, and 60 months. No statistically significant differences were identified between the groups with regard to marginal bone loss, soft-tissue recession, or soft-tissue thickness.

The outcomes of different workflows for zirconia abutments with tapered implant connections were evaluated in a randomized controlled trial by Wittneben et al.[282] Forty patients were randomly allocated to 2 experimental groups: Group A received a pressed lithium disilicate crown (facial cut-back and porcelain veneer) bonded to a prefabricated stock zirconia abutment; and group B received a 1-piece CAD-CAM zirconia abutment-crown with the hand-layered porcelain veneer.

At 3 years, 39 patients were evaluated (clinical, esthetic, and radiographic parameters). Crown survival was 89% for group A and 90% for group B (porcelain fracture on 2 crowns and patient dissatisfaction with 1 crown). Clinical and radiographic outcomes were similar in both groups. Pink and white esthetic scores were similar in both groups ranging from 7.32 to 8.88. Crown length increased from 6 to 36 months.

In a meta-analysis of 5 randomized controlled trials and 2 prospective cohorts, Yu et al[283] compared internal tapered and internal nontapered implant connections. Similar survival rates were identified for both connection designs. However, internal tapered connections demonstrated decreased probing depths and marginal bone-level changes, suggesting an association with lower inflammation levels. This result is consistent with previous reports demonstrating similar clinical and radiographic outcomes in well-controlled protocols that

included healthy patients without a history of peri-implantitis.

The use of short dental implants may eliminate the need for bone grafting, permitting implant-assisted restorations in areas of reduced osseous volume. By using this advantageous approach, the review of a unique study design in edentulous mandibles,[284] medium-term[285] outcomes of short implants, and a meta-analysis of short implants used in posterior locations[286,287] is in order.

Guida et al[284] enrolled 30 patients with edentulous mandible treatment planned to receive 5 interforaminal were randomly allocated to a control group (n=15, 11-mm-long implants) and a test group (n=15, 6-mm-long implants). All patients were provided mandibular fixed complete dentures. Patients recalled at 3 years demonstrated no implants or restoration loss and similar clinical and radiographic outcomes for test and control groups. This study design permits optimal comparison between short (6 mm) and long (11 mm) implants for the rehabilitation of edentulous mandibles. While 3-year results may be considered medium term, the results presented here should not be ignored because of the rarity of this robust study design.

Vazouras et al[285] studied medium-term outcomes of short implants in a meta-analysis that included 20 trials (11 were randomized controlled trials and 9 prospective studies) assessing various outcome variables. The most relevant outcomes pertain to mean failure rates of 1% over 1 to 3 years and 8% at 5 years. Additionally, single-unit implant restorations register a mean failure rate of 4%, while implant-supported fixed partial dentures showed a 2% failure rate. After 3 years, the pooled failure risk for short implants supporting single crowns was 9%, compared with a 6% failure risk for short implants supporting fixed partial dentures. Given that only limited long-term reports are available, these outcomes for short implants are different from those typically expected for conventional longer implants. Long-term studies are needed to validate the use of short implants in these treatment approaches. For now, short implants are supported for use based on these clinically acceptable outcomes in short to medium terms.

By using meta-analysis, Xu et al[286] evaluated the most challenging application of short implants, that being supported with single restorations in the posterior maxilla. Five trials were included. Results indicated that short-term survival rates are similar for short implants and longer implants. However, in the long term, short implants demonstrate statistically poorer survival rates than longer implants for single-unit restoration of the posterior maxilla, displaying a relative risk of 0.99 (P=.01). These results warrant further investigation to better understand clinical outcomes and limitations of short implants supporting single restorations in the posterior maxilla.

Iezzi et al[287] reported on a meta-analysis used to evaluate outcomes of short versus long implants in augmented sites supporting fixed partial dentures in posterior atrophic jaws. A total of 20 randomized controlled trials were included to evaluate 1-, 3-, and 5-year outcomes. No differences could be demonstrated except a statistically lower incidence of complications with short implants at 1 and 3 years, but not at 5 years. This result supports the application of short implants to avoid complex surgical procedures in difficult anatomical situations.

Considering freehand and guided surgical implant placement protocols, Aydemir and Arısan[288] evaluated micron tracking technology, a navigation instrument derived from the complex frameless stereotactic surgery units used in neurosurgery. Video-optical trackers generate precise congruency between CBCT-based virtual planning, spatial position of markers on the handpiece, and known anatomic structures. The aim of the study was to compare this dynamic surgical navigation to a freehand surgical method by using a split-mouth randomized trial design involving 86 implants. All deviations recorded between surgical methods were significantly different and in favor of the dynamic navigation, including linear coronal implant deviations (mean: 0.72 mm, SD: 0.26, 95% CI: 0.39-1.02, P<.001), linear apex implant deviations (mean: 0.69 mm, SD: 0.36, 95% CI: 0.19-1.19, P<.001), and angular implant deviations (mean: 5.33 degrees, SD: 1.63, 95% CI: 7.17-3.48, P<.001). The authors concluded that the surgical navigation approach can be used to transfer virtual implant planning to the patient with improved accuracy.

Gargallo-albiol et al[289] reported on a meta-analysis (10 randomized trials) comparing the accuracy of fully guided versus half-guided and fully guided versus freehand implant placement. Accuracy of implant placement was defined as linear and angular errors measured at coronal or apical aspects of the implant. At the coronal level, the mean difference between fully guided versus half-guided protocols was 0.51 mm (P<.001) and 1.18 mm (P=.01) between fully guided versus freehand. Chair time was not significantly different for any of the techniques. It is notable for most of these studies that measurement accuracy can influence significant differences. As such, one must keep in mind absolute measurement values and consider results within the perspective of clinical practice and true clinical relevance.

In a randomized controlled clinic trail that enrolled 24 patients, Kraft et al[290] compared the accuracy of partially guided implant surgery to that of fully guided surgery for implants placed immediately at the time of tooth extraction. Surgical approaches differed, in that fully guided surgeries included the final wide-diameter osteotomy drill and placement of the implant through the guide. In the partially guided surgeries, a narrower

final drill was used, and implants were placed freehand. Torque at insertion was recorded for all implants. Observation of final implant positions revealed that angular implant deviations and linear coronal deviations did not differ significantly between groups. With respect to linear apical implant deviations, partially guided surgeries were significantly more accurate. Finally, no significant differences in insertion torque values were recorded. This article is of interest because it demonstrates that the 2 different guided approaches can be used with similar success for placement of implants at the time of extraction, which is typically a challenging clinical procedure.

Tattan et al[291] acquired 7 published articles for meta-analysis to compare static computer-aided implant placement (sCAIP), partially guided implant placement (PGIP), and free-hand implant placement (FHIP). sCAIP involves the use of a restrictive surgical guide generated by using preoperative digital planning. PGIP involves the use of a prosthetically generated surgical guide that is used during some but not all osteotomy preparations and implant placement. Outcome variables of interest in this meta-analysis include deviations in implant placement depth, implant angulation, and implant 3D position. Overall implant success rates and patient perceptions associated with the 3 surgical approaches were similar. sCAIP was associated with superior accuracy in implant placements (lower implant deviations for planned positions) when compared with PGIP and FHIP for all variables of interest.

In a randomized controlled clinical trial, Yimarj et al[292] looked at the accuracy of both sCAIP (restrictive guide) and dCAIP (virtual navigation permitting intraoperative accommodation) surgical approaches. The results demonstrated that both sCAIP and dCAIP resulted in similar accuracy. Outcomes of the previous 5 articles[288-292] clearly demonstrated that guided surgical approaches should be considered in clinical situations where implant placement accuracy is paramount.

Finally, in a meta-analysis that included data extracted from 10 published studies (214 patients, 278 single-implant crowns), de Oliveira et al[293] analyzed the efficiency and patient preference for digital versus conventional prosthodontic workflows for single-implant-supported crowns. Digital scans allowed for a reduction in mean clinical time (range, 6.39 to 20 minutes) compared with conventional impressions (range, 11.7-28.46 minutes), which may or may not be clinically significant. Patients generally expressed a preference for digital scans. Crown adjustment and delivery time on the digital side ranged from 1.96 to 14 minutes, whereas on the conventional side, it was 3.02 to 12 minutes. The total process time (impression+fabrication+adjustment/delivery times) ranged from 36.8 to 185.4 minutes for the digital workflow compared with 55.6 to 332 minutes for conventional processes. The main difference in total process time was in the fabrication time, not scanning, impression, or delivery times.

DENTAL MATERIALS AND THERAPEUTICS

Silver diamine fluoride

In 2019, there were far fewer articles related to silver diamine fluoride (SDF) than in recent years. Three articles described parental and patient acceptance of SDF as it related to management of early childhood caries. The first was a qualitative interview of 19 parents of children with caries in primary teeth that had been treated with 2 applications of SDF followed by fluoride varnish.[294] Of greatest concern for these parents was evidence of product safety and effectiveness, and some minimal concern with black staining. Most were accepting of SDF as a nonrestorative option for caries management but desired more information regarding benefits, effectiveness, and any potential safety risks. A similar study was reported for a population of 59 parents from an indigenous community in Canada.[295] Interviews were done through focus groups and sharing circles with a focus on members' views on SDF as an alternative to pediatric dental surgery to treat early childhood caries under general anesthesia. Major themes emerging from these interviews include fear of surgery under general anesthesia, fear of pain after such surgery, the need for more information on SDF treatment, and concern regarding black staining of treated lesions. Overall, there was acceptance of SDF as an alternative, provided that more information is made available and that general anesthesia can be avoided. One systematic review and meta-analysis assessed parental acceptance and esthetic outcomes after SDF treatment of primary dentitions.[296] Eight studies were included, and the significant findings were higher acceptance of staining on posterior teeth versus anterior teeth ($P<.001$; OR, 0.23; 95% CI: 0.15-0.34) and greater acceptance for SDF use on anterior teeth of uncooperative children as compared with cooperative children ($P<.001$; OR, 0.27; 95% CI: 0.17-0.4). Another common theme was the increased acceptance with better pretreatment information regarding SDF. All 3 of these publications emphasize the need to better inform parents of the efficacy, safety, and esthetic outcomes of SDF treatment to gain greater parental and patient acceptance.

Articles related to the clinical effectiveness of SDF can be found in the cariology section of this publication, with one exception of a related article that assessed the impact of SDF management of early childhood caries on the frequency of emergency visits.[297] The article notes that children with advanced disease often require treatment under general anesthesia and are subjected to long waitlists before treatment. These delays can result in a

greater need for emergency visits during this wait period. This study attempted to determine whether SDF treatment could reduce the need for emergency visits in waitlisted patients. Ninety-seven patients treated with SDF during the waitlist period were compared with 216 that did not receive SDF treatment. The incidence of emergency visits was approximately 80% lower in the SDF-treated group (4.1% versus 17.6%; OR, 0.18; 95% CI: 0.06-0.54). This demonstrates a significant potential to reduce both cost and suffering in children waitlisted for later treatment under sedation or general anesthesia.

One systematic review reported on the performance of potassium iodide in reducing the dark staining caused by SDF.[298] The technique comprised topically applying potassium iodide immediately after SDF when treating carious tooth structure. Six articles were included of which 5 reported varying levels of reduction in stain when compared with SDF alone. One article reported no significant effect, and 1 case report indicated return of some staining after 6 months. The overall conclusion was that because of the methodologic variations in the studies, there was still insufficient evidence to support a tangible benefit of SDF+potassium iodide on tooth staining. Considering the general acceptance of lesion staining by patients and parents, the added value of this additional step in the SDF treatment protocol is questionable.

Early reported uses of silver ion compounds for arresting caries included the application of silver nitrate followed immediately by fluoride varnish. The physical appearance of the arrested lesions resulting from this method was identical to that observed with SDF, but few trials reported head-to-head comparisons between the 2 methods. One article in 2020 reported a randomized comparison of semi-annual applications of 25% silver nitrate followed by 5% fluoride varnish to semi-annual applications of 38% SDF followed by a placebo varnish.[299] The mean number of arrested decayed surfaces was the primary outcome of interest. There were 535 children assigned to each of the 2 treatment groups and followed up for 30 months. Results showed no significant difference in mean arrested decayed surfaces of 0.88 (P=.694; 95% CI: −0.351-0.526). This well-powered study showed that 25% silver nitrate followed by 5% fluoride varnish is at least as effective as 38% SDF in arresting early childhood caries. These results broaden the choice of silver and fluoride products that could possibly address issues of cost or availability.

One aticle addressed potential toxicity of SDF based on a pharmacokinetic model to predict silver disposition in children.[300] The mathematical model was assessed by comparing the predicted values of physiologic silver concentrations with data from published animal and human studies after the oral ingestion of silver. The mathematically predicted silver concentrations were within the 95% confidence interval of observed plasma and tissue concentrations in the animal and human data. When applied to a pediatric population, the model predicted that for a given SDF dose simulating treatment, the peak physiologic silver concentrations increased by a factor of 1.3 to 5.2 folds in children as compared with adults, dependent upon the age of the child. Peak predicted concentrations, however, were well below what are considered toxic concentrations, and when considering the half-life of silver in children, concentrations were predicted to return to baseline levels within 2 weeks after SDF application.

Finally, 1 article reported on the teaching and utilization of silver diamine fluoride and Hall-style crowns in pediatric residency programs within the United States.[301] A 29-question electronic survey was completed by 82 programs, and results were compared with a similar survey conducted in 2015. The use of SDF increased from 26% of respondents in 2015 to 100% in 2020. Hall-style crown technique was taught in 90% of programs and used clinically in 69% of programs in 2020. One reported driver of higher utilization for both techniques included long wait times for access to the operating room.

Silver diamine fluoride continues to be expanding in use with a growing body of evidence demonstrating safety and effectiveness. SDF has become a mainstay for the management of early childhood and adult root-surface caries, but in 2020, it filled an additional important role as an interim and non−aerosol-generating treatment option during the COVID-19 pandemic. The dental community can look forward to future studies that will assess the impact and effectiveness of this additional role.

Sealants

Three notable articles were published in 2020 related to the clinical effectiveness of pit and fissure sealants. The first looked at a public health program in Beijing, China, where nearly 3000 students, approximately half receiving sealants and half not receiving sealants, were followed up for 3 years [302] The primary outcome was caries incidence on first permanent molars where after 28 months, the yes/no risk ratio for sealant versus no sealant caries was 0.73 (95% CI: 0.60-0.90, P=.001). A second artcle described a review of the relative effectiveness of sealants and fluoride varnishes in preventing caries on the occlusal surfaces of permanent teeth in children and adolescents.[303] The intent was to update a review originally published in 2006 with 2 subsequent updates in 2010 and 2016. Eleven trials were included with 3374 participants aged 5 to 10 years, 3 of the trials being new since the most recent 2016 review. Seven trials compared sealants to fluoride varnish for preventing caries in permanent first molars resulting in uncertain superiority of either method (OR, 0.67; 95% CI: 0.67-1.19). One of the

7 trials measuring missing, decayed, and filled permanent surfaces at 2 years suggested a small benefit for sealants over fluoride varnish. Another small study with a high risk of bias reported a benefit for sealants after 4 and 9 years. Three trials compared glass ionomer sealants to fluoride varnish and found no benefit of one over the other. Sealants plus fluoride varnish was compared with fluoride varnish alone in one split-mouth trial that reported more favorable results with the combination of sealants with fluoride varnish. Most notably, 5 trials tracked adverse events in 1801 individuals for up to 9 years and reported that none were observed or reported. The overall conclusion was that it is still not possible to suggest superiority of one intervention over the other, but the available evidence with very low certainty suggests that sealant plus fluoride varnish could be more efficacious than fluoride varnish alone. The authors noted that there are 14 ongoing trials that will hopefully provide a more definitive conclusion in the future. The third article was a similar systematic review of the effectiveness of sealants in preventing and arresting caries in primary molars.[304] Similar to the previous review of permanent molars, this review could not identify any superiority between resin-based and glass ionomer sealants, conventional and newly developed resin-based sealants, chemical- and light-activated resin-based sealants, resin-based sealants plus fluoride varnish versus fluoride varnish alone, and resin-based sealant with topical fluoride versus resin infiltration with topical fluoride. The authors noted that the primary limitations of these studies were low to very low certainty because of a high risk of bias. This is a shortcoming heard far too often in dental research.

One very interesting study included sealants as a component of the preventive services delivered in all 3 intervention arms of a multicenter, parallel-group, patient randomized controlled trial.[305] The intervention arms were (1) conventional caries removal/restoration plus preventive (diet, plaque removal, fluorides, and fissure sealants), (2) biological management (sealing in carious tooth structure) plus prevention, and (3) prevention alone. Participants were children aged 3 to 7 years with one or more primary molars with caries, and the outcomes measured over 3 years were (1) children with one or more episodes of dental pain and/or infection and (2) the number of episodes of dental pain and/or infection. The 1144 participants were nearly equally distributed among the 3 arms, and the median follow-up duration was 34 months. Surprisingly, there was no evidence of superiority in either measure among any of the 3 arms. The proportion of individuals with at least one episode of pain/infection was 42% for conventional restoration plus prevention, 40% for biological management plus prevention, and 45% for prevention alone. The mean number of episodes of pain/infection was 0.62 for conventional restoration plus prevention, 0.58 for biological management plus prevention, and 0.72 for prevention alone. The overall conclusion was no evidence of a difference between the 3 treatment approaches for the incidence or number of episodes of pain and infection in these participants considered to be at high caries risk. While these are very interesting results, there are many more outcomes beyond pain and infection that will need to be considered when translating results such as these into guidelines and policy.

Sealants have been an early component of quality measures, and 4 publications this past year addressed the use and structure of sealant-based dental quality measures. Two articles addressed improvements in the method of measurement, and the third publication was a completely revised methodology for measuring sealant quality. The first article describes a Medicaid-based feasibility study of a revised methodology where the measure numerator eliminated teeth previously restored, sealed, or missing, and the denominator was a sealant applied by the same dentists within 9 months of an initial preventive visit.[306] The previously used method did not eliminate unsealable teeth from the numerator. Single-county results showed that overall, 11% of all eligible teeth were sealed, and only 9% of dentists applied sealants within the 9-month period to 40% of the eligible teeth. These results demonstrated the feasibility of investigating Medicaid claims data to assess provider adherence to sealant guidelines. A second artcle described a similar methodology with dental electronic health record data instead of claims data.[307] Three measures were assessed: (1) the proportion of patients with sealable teeth who receive sealants, (2) the proportion of patients who had at least one of their sealable teeth sealed, and 3) the proportion of patients who received sealant on all their sealable teeth. The results showed that for measure 1, 48.1% of 6- to 9-year-old children received one or more sealants compared with 32.4% of 10- to 14-year-old children. When evaluating children receiving sealants on at least one of their sealable teeth (measure 2), 43.2% of 6- to 9-year-olds and 28.4% of 10- to 14-year-olds received sealants. For children receiving sealants on all eligible teeth, the prevalence dropped to 35.5% for 6- to 9-year-olds and 21% for 10- to 14-year-olds. These results confirmed that a methodology determining prevalence of sealants on sealable teeth was feasible with 3 different outcomes. In concert with these studies, the Dental Quality Alliance introduced a new set of sealant quality measures in 2020 that moved away from a measure of sealant incidence to one more aligned with the prevalence. The new method also eliminated teeth that could be determined as being unsealable through claims data.[308,309] The new DQA measures determine the percentage of children at a specified age (10 for first molars and 15 for second

molars) who have ever received sealants on a permanent first molar and second molar teeth. The measures further delineate whether a child received at least 1 molar sealant or all 4 molars sealed. The denominator eliminated children who had received restorations, extractions, endodontic, prosthodontic, and other dental treatments on all 4 eligible molars in the 48 months before eligibility. This method is a huge departure from the prior DQA sealant measure methodology and is similar to other child health measures of preventive treatment prevalence, such as childhood vaccinations.

Resin-based composites

The vast majority of articles related to resin-based composites addressed various techniques for placement. An assessment of the influence of preparation technique compared Er,Cr:YSSG laser to diamond rotary instrument preparation and assessed restoration performance over a 60-month period with World Dental Federation (FDI) criteria.[310] The study was complicated a bit by incorporating 2 different resin composites, Filtek Silorane (3M-ESPE) silorane-based and Kalore (GC) methacrylate-based materials. A total of 72 restorations were placed in 18 patients, each in 1 of 4 similar-sized occlusal molar lesions. After 60 months, restoration retention was 100% for all restorations, and there was no significant difference among preparation method or material for marginal adaptation, marginal staining, surface staining, color match, and translucency. There was also no incidence of recurrent caries or reported postoperative sensitivity. A 36-month randomized controlled trial compared selective caries removal to total caries removal before placement of resin composite restorations in primary teeth.[311] One hundred twenty teeth with deep occlusal or proximal lesions were randomly assigned to total caries removal or selective removal and evaluated with the U.S. Public Health Service (USPHS) criteria. Measures of Delta or Charlie for marginal integrity were considered a failure. At 36 months, restoration survival was 81% for total caries removal and 57% for selective caries removal (P=.004). Restorations with selective caries removal had a 3.44-times greater probability of failure, and the 2 strongest predictors of failure were teeth with class II cavities and children with gingival bleeding over 20% (a surrogate measure for oral hygiene). A 10-year randomized split-mouth trial compared the marginal quality of class I and class II microhybrid restorations light-polymerized by using 2 different protocols.[312] Fifty patients each received 2 molar or premolar restorations polymerized with either a conventional powered 600-650 mW/cm^2 polymerization light for 20 seconds per increment or a high-power 1200-1300 mW/cm^2 polymerization light for 10 seconds per increment. Evaluation was carried out with a modified USPHS and SemiQUAntative Clinical Evaluation (SQUACE) criteria. Alfa scores were not significantly different between the 2 polymerization methods for both marginal discoloration and marginal adaptation at the 10-year follow-up; however, both measures declined significantly compared with baseline. The effect of using a resin-modified glass ionomer liner under resin composite restorations of root surface lesions was investigated in a split-mouth randomized controlled trial.[313] Thirty-nine patients presenting with at least 2 root surface carious lesions were assigned to either lined or unlined restorations veneered with a nanohybrid resin composite (Clearfil Majesty Esthetic; Kuraray Noritake). A total of 100 restorations were evaluated for several clinical parameters at 5 years with the modified Havemann criteria. Twelve restorations were considered failed; however, there was no difference between the materials in marginal adaptation or marginal staining. Four additional carious lesions were detected in adjacent tooth structure at the cavosurface margin, but no significant differences could be confirmed between the lined and unlined restorations. Another technique study compared the performance of direct placement of resin-based composite restorations with a semidirect method, where restorations were fabricated chairside on a flexible silicone die of the prepared tooth and cemented with a resin-based cement.[314] After 24 months, the 48 restorations were evaluated with the FDI criteria, and no differences could be found between the 2 techniques.

Three articles compared the relative clinical performance of 2 different restorative materials, one of which was a resin-based composite. One longer trial compared glass ionomer to resin composite restorations in class I and class II restorations.[315] After 10 years of service, 84 glass ionomer and 88 resin composite restorations were evaluated with the modified USPHS criteria. The overall clinical recall rate for all restorations after 10 years was a surprising 88.6%. A difference between materials was noted for marginal discoloration (P=.022), with glass ionomer showing greater discoloration. A significant change in color match (P<.05) was observed in the glass ionomer over the 10 years, but no significant degradation was measured in anatomical form, secondary caries, postoperative sensitivity, surface texture, and retention for either material. Both materials demonstrated a relatively good level of performance over the 10 years. A shorter 2-year trial compared the clinical performance of a glass-hybrid system with a nanohybrid resin composite (Tetric EvoCeram; Ivoclar Vivadent AG) in 2-surface class II cavities.[316] The study was conducted in 4 dental schools with a total of 360 restorations by using a split mouth design with random assignment of materials to molar lesions. Evaluation was done with the FDI criteria. At 2 years, success rates were similar at 93.6% for the glass-hybrid and 94.5% for the nanohybrid resin composite. Both materials appear to be performing well over

this relatively short period. A second nearly identical trial was reported comparing the glass-hybrid (EQUIA Forte; GC Corp) with a nano-ceramic composite (CeramX One Universal; Dentsply Sirona) in 148 noncarious cervical lesions.[317] Restorations were evaluated at 24 months (126 recalled), and again, no significant differences were found between materials for retention, recurrent caries, or tooth sensitivity, but unlike the previous study, differences were noted between them for marginal adaptation, with the resin composite showing better results. Again, this was a very short trial where differences in performance may not yet be apparent.

Amalgam

This past year has seen an unprecedented misuse of science in the public arena as a political tool to drive agendas. Where science was lacking, it seemed to magically appear out of thin air. Where science should have provided objectivity and guidance, it was distorted to either support or debunk a particular viewpoint. The most significant publication related to amalgam in 2020 appeared to fit that general pattern where a complete lack of new, supporting evidence did not get in the way of instituting a significant policy change. The U.S. Food and Drug Administration issued new recommendations for the use of dental amalgam in patients that may be at greater risk for potential health effects of mercury.[318] The agency updated recommendations to avoid the use of amalgam in a list of potentially high-risk groups including pregnant women and their developing fetuses; women who are planning to become pregnant; nursing women and their newborns and infants; children, especially those younger than 6 years of age; people with preexisting neurological diseases such as multiple sclerosis, Alzheimer's disease, or Parkinson's disease; people with impaired kidney function; and people with known heightened sensitivity (allergy) to mercury or other components of dental amalgam. The agency repeated the prior recommendation that it did not recommend removing or replacing existing amalgam restorations that were functioning appropriately unless it was considered a "medical necessity." Adding the list of potentially high-risk groups represented a dramatic change from more than 3 decades of science-based policy recommendations. This change was not a result of newly published evidence but based on "several speakers, including those representing underserved communities, who expressed concern about the cumulative effect of mercury vapor exposure from dental amalgam" that presented at the November 2019 meeting of the Immunology Devices Panel of the Medical Devices Advisory Committee. As in prior reviews, it appears the underlying science has not changed, but the outcome is a telling testament to value being placed on opinion, theories, and conjecture, not objective science.

Ironically, several articles were published in 2020 that dealt with potential effects of amalgam in some of the high-risk groups sited in the updated FDA recommendations. One article described an analysis of mercury and selenium levels in several tissues of women and newborns from 2 different regions of Croatia known to have different levels of seafood consumption.[319] The levels of both metals in hair, blood or serum, placenta, and cord blood or serum increased with increasing seafood consumption. Higher numbers of amalgam restorations correlated with increased mercury levels in maternal and cord serum, and the higher blood levels of mercury reflected the predominant organic methylmercury derived from seafood. Another study in pregnant women measured the association between amalgam restoration presence or amalgam restoration replacement and gestational hypertension.[320] This study assessed both the blood pressure and blood mercury concentrations in each trimester of 1817 women recruited from 10 Canadian cities. The number of amalgam restorations was again found to be weakly correlated with blood mercury concentrations, but there was no evidence of an association with gestational hypertension (OR, 1.32; 95% CI: 0.86-1.42).

A large case-control study investigated the association between amalgam fillings and the risk of multiple sclerosis in participants that were part of the Taiwanese National Health Insurance Research Database.[321] Two groups of propensity-matched individuals (612 in each group) were compared, and no significant association could be found for risk of MS between those with and those without amalgam restorations (OR, 0.82; 95% CI: 0.65-1.05). Stratification by sex also did not reveal any significant association. The same database was used to investigate the association between the neurological expression of essential tremor and the presence of amalgam fillings.[322] This case-control comparison included 3008 participants in each of 2 propensity-matched groups and again could not find a statistically significant association between essential tremor and amalgam fillings.

A case-control study of first grade, sixth grade, and ninth grade children compared salivary mercury levels of children with attention-deficit/hyperactivity disorder (ADHD) with those of age-matched children without the disorder (90 in each group).[323] The results showed a mild positive association between salivary mercury and ADHD, but the association was not statistically significant and thus the authors concluded there was insufficient evidence to establish an association between the ADHD and salivary mercury. This study did not address the specific source of salivary mercury as being amalgam or correlate any associations with the presence or number of amalgam fillings.

One study reported on the occupational exposure of dental personnel to mercury in urine and hair that was presumed to be from both occupational and personal exposure to dental amalgam.[324] Samples from 50 participants were assessed with atomic absorption spectroscopy, and results indicated that both hair and urine levels were well below acceptable risk levels for occupationally exposed persons. Levels were also shown to correlate with the number of amalgam restorations in these participants, a finding that has been well established in numerous prior studies.

The Norwegian Ministry of Health and Care Services conducted an experiment on participants with health complaints that patients self-attributed to amalgam restorations.[325] The target group consisted of patients with unexplained physical symptoms self-attributed to amalgam restorations, and the comparison group consisted of patients with unexplained physical symptoms that were not self-attributed to amalgam restorations. The primary outcome was self-reported general health complaints over the 12 months after complete removal of all amalgam restorations. Not surprisingly, those that thought amalgam was the source of their problems had 10 times fewer postremoval complaints than those that did not attribute their problems to amalgam.

There were only a couple of notable articles related to the clinical performance of amalgam. The first was a systematic review and meta-analysis of material alternatives for the restoration of posterior permanent teeth with a minimum follow-up of 5 years [326] Forty-three prospective and retrospective studies were included, with only 13 being randomized controlled trials. Results showed that gold crowns had the highest performance with an annual failure rate of 0.29%, followed by metal-ceramic crowns with an annual failure rate of 0.52%, and surprisingly there was no significant difference between amalgam and composite resin as direct restorations, with composite resin demonstrating an annual failure rate of 2.19%. Glass ionomer was noted as demonstrating a significantly higher failure rate than either amalgam or composite resin.

A second article was a cross-sectional survey that looked at the prevalence of secondary caries across different restorative materials and patient-related factors.[327] A total of 4036 restorations in 450 patients were surveyed during routine examination with a total of 146 exhibiting secondary caries, or an overall prevalence of 3.6%. Factors associated with secondary caries were caries risk status, smoking habits, restoration class, and restorative material, with caries prevalence being higher with composites, class II restorations, and high-caries-risk smokers. The most frequent lesion location was gingival margins, and 72% of restorations with a secondary caries diagnosed were scheduled for replacement.

Overall, the use of dental amalgam as a direct restorative material continues to decline as the material continues to come under ever greater scrutiny. The preponderance of evidence demonstrates that it remains a safe and efficacious alternative, but its eventual fate may not be determined by the evidence.

COVID-19

A review of dental research in the year 2020 would not be complete without addressing what is likely the most significant cause of global disruption of dental services in history. The COVID-19 pandemic virtually shut down delivery of care within just a few weeks, and the profession faced questions and issues that required evidence-supported responses where there was little or no evidence. The scientific community was quick to respond by pulling together numerous reviews of materials, devices, and protocols related to the control of aerosols and airborne pathogens. This response was largely responsible for dentistry to rapidly develop policy, recommendations, and protocols that enabled an unprecedented recovery of services and maintenance of oral health.

Perhaps the most comprehensive and applied guidance was the U.S. Centers for Disease Control and Prevention Guidance for Dental Settings: Interim Prevention and Control Guidance for Dental Settings During the Coronavirus Disease 2019 (COVID-19) Pandemic.[328] This living document provided consistency in addressing protocols for infection control, patient treatment, and workplace safety that were based in science, and where science was lacking, upon sound reason and logic. The first section of this document addressed the following recommended infection control practices for routine dental care during the pandemic: teledental and triage protocols, screening triage of everyone entering a dental health-care facility, monitoring and managing dental health-care personnel (DHCP), creating a response process for exposures among DHPC and others, the implementation of universal source controls, administering preadmission or preprocedure diagnostic SARS-CoV-2 testing of patients, administrative controls and work practices, universal use of personal protective equipment (PPE), implementation of universal source control measures, physical distancing, PPE supply optimization, hand hygiene, equipment considerations, use of engineering controls, environmental infection control, sterilization and disinfection of patient-care items, and education and training. Section 2 of this document provided more specific guidance on the recommended infection prevention and control practices when providing dental care to a patient with suspected or confirmed SARS-CoV-2 infection. This guidance document is a resource that is updated on a regular basis and has become an essential tool for guiding the operations

of dental practices as they navigate through this unprecedented challenge.

In 2020, researchers quickly scoured the literature in search of anything related to SARS-CoV-2 that could provide support and guidance for the dental community. The result was a series of systematic reviews addressing biosafety measures and dental office protocols for managing and protecting patients and DHCP.[329-335] A number of common themes emerged from these reviews that have provided the foundation for many of the recommendations outlined in the U.S. Centers for Disease Control and Prevention Guidance for Dental Settings guidance. These include telephone screening and interviewing of patients before and after arrival; taking patient temperature and mask wearing upon arrival; waiting room disinfection and patient distancing; limiting elective nonemergency and aerosol-producing procedures; proper use of personal protective equipment during delivery of care; minimizing aerosol production from rotary or ultrasonic instrumentation; use of interim treatments such as SDF, high-speed evacuation, and dental dam to reduce aerosols; and in-office management of PPE and infectious waste.

More focused systematic reviews addressed questions related to the effectiveness of specific infection-control practices. A review of the use of preprocedural mouthwashes containing 1% hydrogen peroxide resulted in a finding that out of nearly 1000 articles, none provided any evidence of a virucidal effect.[336] A review of the effectiveness and efficacy of respiratory PPE found that face masks and face shields used in combination were more effective than either one used alone, and that in general, respiratory PPEs are effective against aerosolized microbes.[337] One review investigated the oral signs and symptoms of COVID-19 as an aid for early diagnosis of infection.[338] Forty studies were included with over 10 000 patients from 19 countries. The findings were that gustatory impairment in the form of taste disorders was the most common oral manifestation with a prevalence of 45% (95% CI: 34% to 55%) and showed greater frequency in women patients (OR, 1.64; 95% CI: 1.23-2.17). Less common oral mucosal lesions were noted as developing approximately 7 to 14 days after symptom onset and were more likely coinfections and secondary manifestations of COVID-19. Finally, a systematic review that included 9 studies looked at the use of saliva as a diagnostic specimen to detect SARS-CoV-2 infection in suspected patients.[339] Most of the studies reported no statistical difference between nasopharyngeal or sputum specimens and saliva samples in the measured levels of viral load. This finding could lead to much more convenient noninvasive testing in both professional and at-home settings in the future.

The rapid response by dental research and policy-generating entities to the COVID-19 crisis resulted in the ability to quickly, safely, and effectively resume active dental treatment and prevention. The overall effect of the COVID-19 disruption on oral health will likely be studied for years to come, but the impact would certainly be much more severe had we not experienced this worldwide coordinated effort by scientists and oral health organizations.

OCCLUSION AND TEMPOROMANDIBULAR DISORDERS (TMDS)

Anatomy

Auvenshine and Pettit[340] published an overview of the hyoid bone, a small horseshoe-shaped bone located between the mandible and the shoulder girdle. Even though classified as a freely floating or sesamoid bone, it is anything but freely floating. It is firmly attached to the mandible, the tongue, the shoulder girdle, the skull, the vertebral column, and the scapula.

Phylogenetically, it began as an ossification within the tongue and has evolved to a position that is at the level of the fourth cervical vertebrae in man. The hyoid bone has existed in relative obscurity until recently because of increasing interest in its role in sleep medicine. The hyoid bone is believed to play an important role in maintaining the pharyngeal airway because of intimate relationships with the mandible and the tongue.

The hyoid functions in mastication and swallowing, as well as in phonation and breathing. The hyoid bone contributes to maintenance of head posture through intricate relationships with the mandible and the cervical spine. The dental occlusion plays an important role in hyoid stability, and tension within the jaw muscles can affect the hyoid musculature. The hyoid musculature facilitates airway protection by improving minimum oropharynx area and total volume. Focused investigation is needed to detail the relationship between the muscles of mastication, suprahyoid muscles, and infrahyoid muscles to include the effect on airway constriction and obstructive sleep apnea.

By using radiographic assessments, Koç[341] discussed the prevalence of temporomandibular joint (TMJ) bony changes in osteoarthritis (OA) across a wide patient age range. The study included CBCT images from 150 patients (43 men, 107 women; mean age, 37.26 years; range, 10 to 90 years) referred for TMJ evaluation. Each TMJ was evaluated separately for the presence of osseous changes at the condylar head or articular fossa/eminence and for joint space narrowing. A total of 101 (67.3%) patients presented 1 or more osseous changes. There were no significant differences in the prevalence of osseous changes between right and left TMJs. Significant mean age differences were identified for condylar erosion, osteophytes, loose bodies, erosion within the articular fossa, and joint space narrowing. The author

concluded that degenerative TMJ changes may reflect an age-related bone remodeling process. Older patients may demonstrate more findings associated with OA, such as condylar/articular erosion, osteophytes, loose joint bodies, and joint space narrowing.

Seo et al[342] reported on condylar dimensional changes in TMJs with disc displacement (DD). DD is one of the most common TMJ disorders. It occurs in all ages and both sexes, but mainly in women aged 20 to 40 years. DD is frequently accompanied by clicking, pain, and/or limited mandibular depression. It generally progresses from joint reduction to nonreduction.

MRI is a good imaging technique for the diagnosis of TMJ-DD because it illustrates the position and shape of the articular disc. Its accuracy in demonstrating the position and form of the disc may be as high as 95%. As DD progresses, it becomes associated with development of bony condylar changes. Computed tomography (CT) has been considered the imaging modality of choice for osseous TMJ changes. Multidetector CT (MDCT) and CBCT are widely used as well. These techniques allow 2D multiplanar reformation and secondary 3D reconstruction of the data, providing real-time display modes, including oblique linear and curved multiplanar reformation with transaxial cross-sectional slices.

Studies have investigated the relationships between DD and condylar dimensions, but most used MRI for evaluating condylar dimensions. Although MRI provides a high degree of diagnostic accuracy in determining the disc position, it has limitations for evaluating condylar dimensions because of its low spatial resolution and limited number of available axial views. In addition, MRI provides a less accurate representation of the condylar morphology than CT (either MDCT or CBCT) because MRI is not amenable to postprocessing image reorientation. To evaluate changes in condylar dimensions associated with TMJ-DD, both CT and MRI should be used for evaluating condylar morphology and disc position, respectively.

In the present study, TMJ disc position was classified based on the MRI findings as follows:

- Normal disc position (NR)—In the closed-mouth position, the intermediate zone of the disc was interposed between the condyle and the posterior slope of the articular eminence. When the jaw opened, the disc remained interposed between the osseous components.
- DD with reduction (DDR)—In the closed-mouth position, the disc was in an anterior position relative to the condylar head, and the disc was reduced upon opening of the mouth.
- DD without reduction (DDNR)—In the closed-mouth position, the disc was in an anterior position relative to the condylar head, and the disc did not reduce with opening of the mouth.

The following linear dimensions were obtained from CT images:

- Condylar depth (anteroposterior condylar dimension)—the average value of 3 distances between the anterior and posterior limits of the condyle in the sagittal plane, which were measured in the medial half, center, and lateral half along the horizontal long axis of the condyle.
- Condylar height (vertical condylar dimension)—the distance between the point at which the long axis intersected the superior surface of the condyle and an internally tangent circle drawn at the most curved area between the condylar head and neck.
- Condylar width (mediolateral condylar dimension)—distance between the medial and lateral poles of the condyle, measured in the central coronal plane of the condyle.

The following angles were obtained from CT images:

- Anterior condylar angle—the angle between the neck and head of the condyle, measured in the central sagittal plane of the condyle.
- Medial condylar angle—the internal angle between the neck and the horizontal long axis of the condyle, measured in the central coronal plane of the condyle.
- Horizontal condylar angle—the angle between the horizontal long axis of the condyle and the coronal plane, measured in an axial image.

Many studies have attempted to clarify changes in condylar morphology associated with TMJ-DD. In general, condyles with TMJ-DD show altered morphologies, such as decreased height, distal inclination, and reduced volume. These morphologic alterations are because of regressive changes in the condyles associated with TMJ-DD. These changes indicate that condyles with TMJ-DD are quantitatively different from those with NR. However, it has not been clearly established which dimension of the condyle is influenced by TMJ-DD because most previous investigations used MRI or 2-dimensional images for analyzing the condylar dimensions. Although a few studies used CT images for analyzing the condylar dimensions, they did not define TMJ-DD status by using MRI or assess sex differences in condylar morphology.

The present investigation suggests that all linear dimensions recorded were significantly associated with TMJ-DD, but each dimension was differently associated with TMJ-DD status. Condylar depth and height were significantly different only between NR or DDR and DDNR, but condylar width was significantly different between NR and DDR, as well as between DDR and

DDNR. Both condylar depth and height were reduced in condyles with DDNR compared with NR or DDR. However, there was no significant difference between NR and DDR (NR=DDR>DDNR).

Previous studies have demonstrated that condylar resorption is highly prevalent in TMJs with DD because TMJ-DD is commonly accompanied by OA. Because OA begins in the condylar cartilage and normal stress on aberrant cartilage is considered a risk factor for condylar resorption, bony changes in condylar depth and height may be associated with condylar resorption, and changes in depth and height may be more evident in condyles with DDNR than in those with DDR.

In contrast to condylar depth and height, condylar width gradually decreased from NR to DDNR (NR>DDR>DDNR). The decrease in condylar width may be associated with resorption of the lateral condylar pole in the early stages of TMJ-DD. The TMJ disc is firmly fixed at the medial and lateral poles in posterior aspects of the condyle. If the disc is significantly displaced to the anterior, the medial and lateral attachments will be stretched, and the relevant side of the condyles will be affected. Advanced resorption of the posterosuperior surface of the lateral condylar pole has been reported in the presence of TMJ-DD. In condyles with TMJ-DD, the coronal dimension of the condyle may initially be affected by the resorption of the lateral pole, whereas the sagittal dimension may not be significantly affected. As DD progresses to DDNR, bone resorption may be more evident over the entire condyle, which may lead to reduced condylar depth, height, and width. As a result, condylar width may be initially affected before condylar depth and height are significantly decreased in the late stages of TMJ-DD (DDNR).

For angular dimension, condyles with TMJ-DD exhibited a smaller anterior angle than those with NR (NR>DDR=DDNR). As described previously, the superior aspect of the lateral pole of the condyle is initially affected in the presence of TMJ-DD. As the posterosuperior surface of the lateral pole begins to be resorbed, the anterior angle of the condyle may become more acute in the sagittal plane. The presence of osteophytes indicates areas of new cartilage and bone formation, which appear radiographically as a marginal bony outgrowth. Osteophytes are mainly formed on the anterosuperior surface of the condyle reducing the anterior angle in the sagittal plane. The medial angle was not significantly influenced by TMJ-DD, possibly associated with individual variations, not pathologic condylar bony changes.

Condyles with DDNR had a significantly larger horizontal condylar angles than those with NR or DDR conditions (NR=DDR<DDNR). Condyles with larger horizontal condylar angles may be explained by arthritic changes associated with DD. In the presence of TMJ-DD, bone resorption and apposition occur at opposite sides of the condyle in the axial plane and may cause changes in the horizontal condylar angle.

Proliferation is an adaptive or reparative change thought to compensate for destroyed soft and hard tissues of the TMJ, whereas regression is believed to result from destruction or remodeling. Results indicated that condyles with TMJ-DD had decreased linear dimensions that became more severe when TMJ-DD progressed. These findings suggest that regressive changes dominate proliferative changes in condyles with DD, specifically when TMJ-DD progressed to a severe condition. Condylar depth, condylar height, and horizontal condylar angle did not demonstrate significant differences between NR and DDR, which may be associated with proliferative changes in the early stages of TMJ-DD (DDR).

In this study, condylar height and width were significantly greater in men than in women. Because men have larger skeletal frames than women, the difference in condylar height and width was expected. However, no linear or angular dimensional changes associated with TMJ-DD differed between sexes. Although DD occurs more commonly in women than in men, results suggest that there may be no sex effects on condylar dimensions with respect to TMJ-DD status.

It remains undetermined if disc displacement is a cause or a sign of temporomandibular joint osteoarthritis (TMJ-OA). Altered preexisting condylar dimensions might cause TMJ-DD, or TMJ-DD might cause altered condylar dimensions. Although a cause-and-effect relationship remains unclear, this study suggests that TMJ-DD may affect condylar morphology. The progress of DD appears to be associated with a change in condylar morphology, specifically with respect to linear dimensions. Compared with condyles having normal disc position and function, condyles with DDR showed decreased condylar widths. These changes gradually became worse with progress to DDNR. In addition, condylar depth and height also significantly decreased with progress from DDR to DDNR.

As changes in condylar morphology are important to the long-term stability of complex prosthodontic, orthodontic, and orthognathic therapy, results suggests that clinicians must be careful when diagnosing and treating patients with TMJ-DD.

Botox

Almutairi et al[343] offered a systematic review on the role of Botox (botulinum toxin or BTX) in the management of TMJ disorders. Many people who suffer from TMD-associated severe chronic pain pursue medical interventions. With a relatively new and emerging treatment modality, BTX has gained much popularity. This systematic review assessed the status of BTX treatment

for TMDs and its impact on managing pain and other associated symptoms.

A detailed electronic search of the literature was conducted to identify relevant randomized controlled trials (RCTs) in the topic area. Initial findings were subjected to inclusion and exclusion criteria and then assessed for bias by using the framework outlined in the Cochrane Handbook. The search yielded 5 RCTs that were included in the review. Primary focus was the clinical evaluation of pain by using different diagnostic tools to qualitatively assess the effectiveness of BTX treatment in the management of temporomandibular myofascial pain. Secondary outcomes included measurement of changes in mouth opening, psychological status, day-to-day functional and social activities, and muscle hyperactivity.

The results of this systematic review supported the benefits of BTX in reducing the symptoms associated with TMDs, but further research is required to show BTX effectiveness. To achieve this, RCTs with a large sample size, homogeneous study design, long follow-up periods, and standardized diagnostic method must be reported.

Diagnosis

Lee et al[344] were interested in developing a diagnostic tool for automated detection of TMJ-OA from CBCT images by using artificial intelligence. CBCT images of patients diagnosed with TMDs were used. Single-shot detection, an object detection model, was trained with 3514 sagittal CBCT images of TMJs that indicated signs of osseous changes in the mandibular condyle. The region of interest (condylar head) was defined and classified into 2 categories (indeterminate for TMJ-OA and TMJ-OA) according to image analysis criteria for the diagnosis of TMDs. The model was tested with 2 sets of 300 images in total. The average accuracy, precision, recall, and F1 score over the 2 test sets were 0.86, 0.85, 0.84, and 0.84, respectively. Automated detection of TMJ-OA from sagittal CBCT images is possible with a deep neural networks model. It may be used to support clinicians with diagnosis and treatment decision-making for TMJ-OA.

Constantinides et al[345] accomplished a systematic review of the literature addressing the reliability of kinesiography versus MRI for diagnosis of TMJ internal derangement (ID). A literature survey was carried out through PubMed, SCOPUS, LILIACS, and the Cochrane Library to locate randomized clinical trials, controlled trials, prospective cohort studies, or retrospective studies (with or without a control group), that examined the diagnostic reliability of recording devices of mandibular movements in comparison to MRI. Results of this review indicated that current scientific evidence does not support the clinical usefulness of the jaw-tracking devices for the diagnosis of TMDs because their diagnostic reliability is poor.

Growth and development

Glerup et al[346] determined the prevalence of TMJ/orofacial symptoms, dysfunctions, and deformities associated with juvenile idiopathic arthritis (JIA) 17 years after disease onset. Data were extracted from a prospective, population-based Nordic JIA cohort with disease diagnosis from 1997 to 2000. In total, 420 consecutive patients were eligible for orofacial evaluation of TMJ involvement. Follow-up visits included the collection of demographic data, a standardized clinical orofacial examination, and full-face CBCT. For comparison, 200 age-matched healthy controls were included.

Of 420 eligible participants with JIA, 265 (63%) were included (mean age, 23.5 ±4.2 years) and completed a standardized clinical orofacial examination. Of these, 245 received full-face CBCTs. At least 1 orofacial symptom was reported by 33% of patients. Compared with controls, the JIA group reported TMJ pain, TMJ morning stiffness, and limitation on mastication significantly more frequently. Among participants reporting complaints, the number of symptoms was higher in JIA. The mean maximum incisal opening was lower in the JIA group, and TMJ pain on palpation was more frequent ($P<.001$). Condylar deformities and erosions assessed by CBCT were observed in 61% of the JIA group, showing bilateral changes in about 70%. Risk factors for condylar deformities included orofacial dysfunction and biologic treatment. Enthesitis-related arthritis was protective.

This study of the long-term consequences of TMJ involvement in a population-based JIA cohort reported persistence of TMJ symptoms, dysfunctions, and damage into adulthood. The authors suggested that interdisciplinary follow-up of patients with JIA into adulthood is prudent.

Shu et al[347] sought information on the relationship between cephalometric features and internal derangements (IDs) of the TMJs. A systematic review was designed, and PubMed, Embase, and Scopus databases were searched for cephalometric studies comparing the craniofacial morphology between women with TMJ-ID and controls. The Newcastle-Ottawa Scale (NOS) was used for quality assessment. Weighted mean differences for cephalometric measurements were pooled for subsequent meta-analyses.

A total of 14 of the 1038 original articles collected were selected into the review and reported on 772 patients with TMJ-ID and 423 controls. These records were eventually pooled for analysis after the NOS quality assessment. Compared with the controls, patients with TMJ-ID possessed a smaller, retruded, and clockwise-rotated mandible. Certain craniofacial morphologic features were found strongly associated with the presence of TMJ-ID, especially the size and position of the mandible.

Imaging

By using a retrospective observational study design, Tonin et al[348] addressed the correlation between age, sex, and the number of MRI-based TMD diagnoses. MRI records representing 456 TMJ examinations on 228 patients (158 women; mean age, 44.45 years; 70 men; mean age, 39.09 years) evaluated between 2005 and 2014 were randomly assembled. Patients were referred for TMJ MRIs secondary to clinical signs and symptoms of TMJ dysfunction, including TMJ pain (acute or chronic, unilateral or bilateral); mandibular deviation or deflection; limited interincisal distance or limited mouth opening; and joint noise or clicking during mandibular depression and elevation. Patients were excluded if they presented a history of rheumatoid arthritis, agenesis, hyperplasia, hypoplasia, or malignant neoplasms of the mandibular condyle; bone ankylosis; or previous TMJ or facial surgery that might interfere with image analysis. The presence of the following conditions in MRI images was assessed: (1) morphological changes of the mandibular condyle or articular tubercle; (2) disc displacement with reduction or DDWR; (3) disc displacement without reduction or DDWOR; (4) bone edema; (5) effusion; and (6) avascular necrosis.

DDWR was the most frequently identified condition, both isolated from (90 patients) or associated with (194 patients) other findings, followed by morphological changes (83 patients) and effusion (74 patients). Both DDWR and DDWOR were observed alone or in association with one or more additional findings. Morphologic alterations, bone edema, effusion, and avascular necrosis were always observed in association with one or more findings, but never alone. Proportionally, DDWR, effusion, edema, and avascular necrosis were more common in men, while morphologic alterations and DDWOR were more common in women.

The results of this investigation suggest that patients with TMD should pursue treatment soon after the first signs and symptoms of the disease appear. Early intervention may prevent additional problems associated with disc displacement and morphologic TMJ changes. It also appears that women may be more susceptible than men for developing a greater number of concomitant conditions, possibly related to known hormonal influences.

Occlusion

TMDs are a heterogeneous group of conditions affecting the TMJs, masticatory muscles, and associated structures. They are the main cause of non-odontogenic orofacial pain and are known to have a multifactorial etiologic profile, involving anatomical, neurological, endocrine, psychosocial, and cognitive-behavioral factors. To investigate the impact of jaw morphology on TMDs, Colonna et al[349] conducted a comparative analysis by using 3D imaging.

Some severe malocclusion traits (for example, excessive horizontal overlap), that may mirror peculiar skeletal features, are occasionally present in association with TMDs. Thus, facial morphology, not necessarily dental occlusion, may be associated with TMDs. A hyperdivergent jaw growth pattern and class II skeletal profile are also associated with a higher frequency of TMJ disc displacement and degenerative disorders. The results of the present study suggest an association between TMJ pain and certain craniofacial morphologic features. Individuals suffering with TMJ pain were seen to have less condylar volumes and greater gonial angles than controls.

Chen et al[350] investigated dental malocclusion resulting from the changes in condylar position after a unilateral open disc repositioning surgery. Thirty-two patients had MRIs before and immediately after surgery. Occlusion was checked, and changes in the joint space and condylar position were measured in the MRIs. The paired *t* test was used for analysis.

The results indicated that the incidence of the posterior open occlusion on the affected side was 100% at baseline, 87.5% at 3 days, 71.9% at 7 days, 9.4% at 3 months, 3.1% at 6 months, and 3.1% at the last postsurgical follow-up. Mean condylar movements were 2.67 mm in the affected joints and 0.32 mm in normal joints. There were significant differences for the anterior (P=.03), superior (P<.001), and posterior (P<.001) joint spaces of the affected joints as demonstrated in MRIs.

Joint spaces significantly increased postsurgically, and condylar positions changed significantly anterior and inferiorly resulting in posterior open articulation. Condylar positions returned to presurgical norms 3 months after surgery. Authors concluded that unilateral disc repositioning results in stable occlusion over time.

Pain

Koca et al[351] studied whether clinical or MRI findings were more closely correlated in patients with TMJ pain. The specific aim of the study was to evaluate the relationship between pain and MRI parameters in the TMJ. A total of 350 patients (179 men, 171 women; mean age, 31 years), providing data on 700 TMJs, were included in this cross-sectional study.

IDs seen even in asymptomatic individuals are the most common TMJ pathology. The term derangement infers a change in normal anatomy and movement of the TMJ, including functional relationships involving the articular disc. The most common cause of ID, also known as disc displacement, is maladaptation between the condyle, the temporal bone, and the articular disc. Disc displacement may be anterior with or without reduction (DDWR/DDWOR) or posterior displacement. Subsequent condylar degeneration may involve osteophytes,

erosion, and sclerosis of the condyle, articular eminence, or glenoid fossa.

MRI is a useful technique to detect ID, as it allows direct visualization of the articular disc in both open- and close-mouth positions. Furthermore, MRI allows detection of morphologic and inflammatory TMJ changes. This technique is performed using nonionizing radiofrequency (RF) waves. Visualization of joint effusion, or inflammatory changes in the synovial membrane and retrodiscal tissue, is influenced by the morphology and position of the articular disc and can be detected by MRI. Disc morphology can be described as biconcave (normal), biplane (flat), thickened, biconvex, fragmented, or destroyed. These morphologic variants may develop relative to one another in the TMJ.

The results indicated that DDWR occurs significantly more in men, while DDWOR was more common in women. Moderate forms of condyle degeneration were found more frequently in men, while more sever forms were more common in women. Individuals with DDWR and DDWOR displayed higher pain levels than individuals with normal disc position ($P<.001$). Regarding condyle degeneration, the greatest pain levels were seen with the most severe forms of degeneration. For joint effusion, pain levels experienced by patients who demonstrated joint effusion were significantly greater than pain levels in those without joint effusion ($P<.05$). Regarding disc distortions, significantly greater pain was observed with folded-type, lengthened-type, and rounded-type disc distortion than in the normal disc group ($P<.001$). Normal-type condyle degeneration was commonly associated with normal-type disc position, moderate-type condyle degeneration was associated with DDWR, and severe-type condyle degeneration was seen commonly with DDWOR ($P<.05$). Normal-type disc form was commonly associated with normal-type disc position, lengthened-type disc form was associated with DDWR, and folded-type disc form was seen commonly with DDWOR ($P<.05$).

TMJ surgery

Rahman et al[352] reported on the use of dermal fat graft as an interpositional material in TMJ ankylosis surgery. Management of TMJ ankylosis is primarily through surgical intervention, and the placement of interpositional materials is necessary to prevention of TMJ reankylosis after arthroplasty. Early aggressive postoperative physiotherapy is essential for the prevention or treatment of TMJ hypomobility or reankyloses. Recently, it has been shown that abdominal dermis fat helps promote smooth, pain-free joint function, and the graft is stable after surgical placement and less prone to fragmentation.

This study included 15 patients and 18 joints affected by TMJ ankylosis. The average duration of ankyloses was 6.28 years. Patient age ranged from 6 to 30 years (mean age, 12.6 years), and there were twice as many women and men. External trauma was the most common predisposing cause (93%), followed by ear infection (7%).

Procedural results reported were favorable. The abdominal dermis fat graft appears to offer promise as the material of choice for interpositional grafting. Authors indicate that a major disadvantage of this procedure is a visible abdominal scar at the donor site. This esthetic concern is particularly prevalent in young patients and may impact the decision to use this approach.

Younis et al[353] reported on both viability and volumetric analysis of free autogenous dermis fat graft as the interpositional material to prevent heterogeneous calcification after TMJ gap arthroplasty in the management of ankylosis. Objectives included assessment of graft viability, tissue changes associated with the graft, and volume retention as indicated by MRI. Fifteen patients with TMJ ankylosis were treated by using gap arthroplasty with abdominal dermis interpositional fat grafting. Patients were randomized into 2 groups. Postoperative MRI graft assessment was completed at 3-6 months in group 1 and at 1–2 years in group 2. T1- and T2-weighed images were used with fat suppression (FS) sequences in all the 3 planes.

Both group 1 (7 patients, 11 joints) and group 2 (8 patients, 13 joints) showed the presence of viable fat on T1 and T2 images and confirmed by FS images. Minor tissue changes were observed at the center of the graft in 5 patients of group 1 and 3 patients of group 2. Average volume of the graft was 4.154 cm^3 at 3–6 months and 4.269 cm^3 at 1–2 years. When compared with the original graft volumes (4.583 cm^3 in group 1, 4.712 cm^3 in group 2), the difference was not statistically significant ($P<.005$). MRI shows long-term survival of autogenous dermis fat graft without significant volumetric reduction. This, along with positive clinical results, demonstrates dermis fat to be a viable choice as an interpositional material for the management of TMJ ankylosis.

In another article, Younis et al[354] compared abdominal dermis fat graft to conventional temporalis myofascial flap interposition in the treatment of TMJ ankylosis. The temporalis myofascial flap remains the most common interpositional material used in this surgical correction. However, patients may complain of pain during movement, unesthetic bulging in the temporal region, and trismus because of scar contracture when the temporalis technique. The main aim of this study was to evaluate the efficacy of the abdominal dermis fat graft versus the temporalis myofascial flap approach in the treatment of TMJ ankylosis and to see which offers greater advantage to the patients.

A total of 30 TMJ ankylosis patients were randomly assigned to 2 groups of 15 patients each. All the patients underwent TMJ ankylosis release under general anesthesia. Group A received an abdominal dermis fat

interposition graft, and group B received the temporalis myofascial flap approach. Patients were assessed for preoperative and postoperative mouth opening (immediate and 6 months postoperatively), pain during physiotherapy, donor and surgical site complications, and recurrence of ankylosis.

The mean maximum interincisal opening in dermis fat group was significantly greater than that in the temporalis group both at immediate (P=.041) and 6-month postoperative periods (P=.001). Physiotherapy was less painful in the dermis fat group than in the temporalis group. Hypertrophic scar developed at the donor site in 2 patients in the dermis-fat group. However, scarring was located below the beltline and was minimally noticeable. A total of 9 patients (4 in group A, 5 in group B) developed temporary facial nerve weakness. No incidence of reankylosis was noted in either group.

The authors suggested that dermis fat interpositional grafting in TMJ ankylosis surgery showed better results than the conventional temporalis myofascial flap approach in terms of postoperative mouth opening, physiotherapy, and jaw function, including esthetically acceptable results.

Castro et al[355] used MRI to investigate the spatial position of the articular disc, before and after orthognathic surgery, in patients treated with bimaxillary surgical advancement (maxillomandibular advancement or MMA) with counterclockwise rotation, with or without concomitant TMJ surgical disc repositioning. Specific aims of this study were to evaluate if disc position was preserved by the surgical intervention and compare symptoms before and after surgery.

Patients receiving surgery between May 2008 and July 2014 for correction of class II malocclusion and high occlusal plane angle were included. Inclusion criteria consist of (1) preoperative dentofacial deformity treated with maxillomandibular advancement surgery involving counterclockwise rotation, (2) preoperative MRIs, and (3) postoperative MRIs obtained at least 6 months after surgery. Patients were excluded if they demonstrated (1) phenotypic expression of craniofacial syndromes; (2) class III malocclusion; (3) previous TMJ or maxillomandibular surgery; or (4) incomplete records or unwillingness to participate in the study. Three experienced surgeons who had the same technical training for involved procedures evaluated all MRIs. Patients were divided into 2 groups: Group 1 received orthognathic surgery only (MMA), and group 2 was treated with orthognathic surgery and concomitant articular disc repositioning surgery (MMA-ADR).

Group 1 consisted of patients without TMJ symptoms, with or without disc displacement. Group 2 consisted of patients with TMJ disc displacement and TMJ symptoms, indicating internal joint pathology. Group 2 patients had moderate to severe pain, limited mouth opening, and no response to conservative treatment (physical therapy, medications, or splint therapy). Articular disc repositioning was performed before MMA with a mini-anchor technique.

Orthognathic surgery included standard BSSO and Le Fort I osteotomies, counterclockwise rotation, and internal rigid fixation. The maxilla was stabilized with 4 bone plates and at least 4 screws of 2-mm diameter each, and the sagittal split osteotomies were fixed with 1 or 2 bone plates, followed by 2 or 3 bicortical positional 2-mm screws in the retromolar region on each side.

Thirty-seven patients (74 TMJs) met the inclusion criteria (32 women, 5 men; mean age, 29.86 years; age range, 15-50 years). Postoperative MRIs were made after a mean 16.2 months (range, 6-51 months). Group 1 (18 patients) had no identified TMJ clinical symptoms or abnormalities, although some of the MRIs showed changes in disc position. Group 2 (19 patients) generally demonstrated TMJ disc displacement, pain, and limited mandibular movement.

The mean advancement of the pogonion was 13.72 mm (SD=5.77) for group 1 and 14.92 mm (SD=5.31) for group 2. The average counterclockwise rotation and change in the occlusal plane was 7.38 degrees (SD=4.47 degrees) for group 1 and 7.76 degrees (SD=4.24 degrees) for group 2. For group 1, 13 joints (36%) demonstrated normal disc position, and 23 joints (64%) had disc displacement (15 reducing, 8 nonreducing) preoperatively, whereas in group 2, 35 joints (92%) had anterior disc displacement, and 3 joints (8%) had a lateral displacement that was consider normal variation.

After orthognathic and TMJ surgery, the postoperative disc position for group 1 was normal in 12 joints (33%) with disc displacement in 24 joints (67%) (12 reducing, 12 nonreducing). For group 2, 30 joints (79%) had normal disc position after surgery, 7 had displaced disc with reduction (18%), and 1 was nonreducing (3%). A statistically significant improvement in disc position after surgery was observed.

Comparing preoperative and postoperative disc positions, group 1 demonstrated that 36.1% of TMJs had normally preoperative disc positions, 38.5% of TMJs had normal postoperative disc positions, 33.3% of displaced discs with reduction had worsening of position, and there was a 50% increase in discs displaced without reduction. However, changes in disc position in group 1 were not statistically significant (P=.515).

In group 2, comparison of MRI scans of disc positions in the preoperative and postoperative phases showed that 97.3% of TMJs exhibited improved disc position. Of the TMJs that had exhibited disc displacement with reduction, 88.2% displayed normal position, and none deteriorated after surgery. As for patients with disc displacement without reduction, 94.5% showed improvement in their condition, with 66.7% showing

normal position and 27.8% showing displacement with reduction. Only 1 patient in this group (5.6%) maintained disc displacement without reduction. Changes in group 2 were statistically significant.

Twenty-six patients (70.3%) had complete absence of postoperative TMJ pain, compared with only 9 (24.3%) preoperatively. A significant reduction of TMJ pain was observed in group 2 (P=.001). Twenty-six patients (70.3%) had myofascial pain and headaches preoperatively, while only 6 (16.2%) had symptoms postoperatively. A significant reduction in the severity of myofascial pain and headaches (P<.001) and myalgia (P=.001) was observed in group 2. With regard to jaw function in group 2, the median preoperative VAS score was 5, and the median postoperative score was 0, demonstrating significant difference (P=.003) and indicating an improvement in subjective assessment of postoperative jaw function.

For group 1, median lateral excursion values were as follows: left=9 mm (preoperative) and 7.5 mm (postoperative); right=9 mm (preoperative) and 6.5 mm (postoperative). For group 2, median lateral excursion values were as follows: left=8 mm (preoperative) and 4.2 mm (postoperative); right=10 mm (preoperative) and 4 mm (postoperative). The differences in the lateral excursion for preoperative and postoperative values were statistically significant on both sides and for both groups (P<.005).

Regarding TMJ sounds, in group 1, 11 patients (61.1%) had preoperative TMJ sounds and 7 (38.9%) did not. In this group, only 1 subject had postoperative sounds. However, no patients with joint sounds in the preoperative phase presented with this sign postoperatively. In group 2, 14 patients (73.6%) had preoperative TMJ sounds, and 5 (26.4%) did not. After surgery, of the 14 patients who presented TMJ sounds preoperatively, the symptoms persisted postoperatively only in 4; of the 5 patients who did not have TMJ sounds, 3 had joint sounds in the postoperative period. Nonsignificant differences were observed for both groups.

The authors concluded that TMJ articular disc repositioning surgery appears to have benefits for patients with pain symptoms that do not respond to conventional treatments and for those with disc displacement with reduction. By comparison, many of the displaced discs worsen when only orthognathic surgery is performed. The significant improvement of symptoms in group 2 patients was not seen in group 1. Authors recommend joint surgery only be performed on patients with TMJ pain and displaced discs with good disc morphology as demonstrated on MRI.

Liu et al[356] examined the effect of arthroscopic disc repositioning on facial growth in juvenile patients with unilateral anterior disc displacement. Anterior disc displacement (ADD) of the TMJ is relatively common in both teenagers and adults and associated with joint sounds, joint pain, and limited mouth opening. ADD may also be associated with condylar resorption and osteoarthritis (OA), as well as impair growth in juvenile patients. Animal experiments have shown that unilateral ADD can result in mandibular asymmetry (MA). There is ample evidence that the incidence of ADD is higher in patients with facial skeletal asymmetry than in the general population. Orthodontists and orthognathic surgeons generally believe that ADD can affect jaw development, which might lead to MA or retrusion.

More importantly, ADD occurring in juvenile patients has a more significant effect on facial symmetry than that in adult patients. The incidence of MA was much higher (72.12%) in patients with unilateral juvenile anterior disc displacement (UJADD) than that in the general population. Degenerative changes in the affected joint became worse with disease progression and deviation of the submental point increases.

It has been reported that the disruption of condylar morphology in cases of ADD can be arrested and condylar growth reinitiated upon successful repositioning of the displaced articular disc. It is therefore expected that the correction of disc position in adolescence may provide a better prognosis than surgery in adulthood. However, surgical repositioning of the articular disc has been a matter of considerable controversy. Some practitioners believe that TMJ disc displacement is a self-limited disease that does not require manipulation of disc position during treatment. Others argue that disc repositioning surgery is neither good for TMJ function nor stable in long term. The purpose of this study was to investigate whether compromised condylar development on the affected side and subsequent mandibular asymmetry can be alleviated in UJADD patients who received arthroscopic TMJ disc repositioning.

A retrospective cohort design was implemented. Inclusion criteria consisted of first clinical evaluation between January 2010 and December 2017, age 10 to 20 years, UJADD diagnosed by MRI, and follow-up period longer than 6 months. Exclusion criteria included severe medial or lateral rotational disc displacement, orthodontic or orthognathic treatment before or during the follow-up period, a history of joint infection, jaw fracture or congenital and systemic diseases that might affect jaw development, MRI or PAC images unsuitable for measurement because of poor image quality or missing anatomic reference points, and patients with contralateral disc displacement in both groups or patients with recurrence of disc displacement after surgery found by MRI at follow-up. Patients underwent arthroscopic disc repositioning (group 1 or surgery group) or no intervention (group 2 or control group) according to surgical indications and patient choice. The predictor variable was

the TMJ arthroscopic disc repositioning surgery. The primary outcome variable was change in condylar height difference of bilateral TMJ and menton deviation between the groups. The secondary outcome variables included change in condylar height difference on affected/normal side between the groups and change in the length of TMJ disc and the upper joint space.

A total of 108 UJADD patients were reported in this study. The surgery group consisted of 55 patients (40 women, 15 men; age, 17.6 years at diagnosis; follow-up, 12.1 months) while the control group consisted of 53 patients (36 women, 17 men; age, 16.6 years at diagnosis; follow-up, 12.4 months).

Results of assessment indicated that condylar height difference was decreased by 0.61 mm in the surgery group but increased by 1.68 mm in the control group ($P<.001$). Menton deviation was decreased by 1 mm in the surgery group but increased by 1.81 mm in the control group ($P<.001$). The condylar height on the affected side was increased by 1.10 mm in the surgery group but decreased by 1.03 mm in the control group ($P<.001$).

In the surgery group, MRI showed pronounced condylar bone regeneration after follow-up. The average condylar height on the operated side increased from 23.11 mm to 24.21 mm ($P<.05$), with an average growth of 1.10 mm and a maximum increase of 3.90 mm. The contralateral condyle grew with an average increase of 0.49 mm in height. As a result, the difference in the height of bilateral condyles was decreased by 0.61 mm. Also, the upper joint space was significantly increased by 1.23 mm.

In the control group, MRI showed that condylar bone destruction was aggravated after follow-up. The average condylar height was decreased from 24.48 mm to 23.45 mm ($P<.05$), with an average decrease of 1.03 mm for the ipsilateral condyle. However, the contralateral condyle grew with an average increase of 0.65 mm in height. As a result, the difference in the height of bilateral condyles was increased by 1.68 mm. Articular disc length was shortened compared with that before measurement.

In this study, mid- and long-term follow-ups of patients with UJADD were carried out to investigate the effect of the arthroscopic repositioning of the displaced articular disc on condylar development. Results suggested that the stability of disc position was beneficial for the balanced development of bilateral condyles and facial symmetry in patients with UJADD after surgery. Early surgical treatment appears to avoid, perhaps reverse, mandibular asymmetry in adolescent patients. This may lead to face symmetry and a more esthetically acceptable outcome, reducing the possibility of future orthognathic surgery for jaw deformity.

It appears likely that the morphological changes seen here (an increase of condylar height and joint space) are because of bone regeneration after disc repositioning. This morphologic change will play a critical role in the long-term stability of the joint, dental occlusion, and facial shape. Because condylar remodeling is an active process, most studies focus on the growth potential of the condyle. The articular fossa also has the capacity for remodeling and likewise plays an important role in the long-term stability of joint structure. Possible factors affecting condylar bone regeneration include age, sex, method of disc repositioning (open versus endoscopic), length of articular disc, coverage of the condyle, location of the articular disc during the surgery, and so on. The increase of joint space may be attributed to generally thicker dimension of the articular disc compared with the posterior disc ligament located above the condyle when disc displacement occurs. After disc repositioning, there is an increase in the posterior and superior intracapsular spaces with a decrease in the anterior space. Arthroscopic disc repositioning appears to benefit balanced bilateral joint growth and balanced facial appearance. Thus, it seems reasonable that UJADD should be treated as early as possible to optimize condylar development and avoid jaw developmental deformities.

Gakhal et al[357] analyzed outcomes after revision replacement of failed total TMJ prostheses. While end-stage TMJ disease can be managed with alloplastic total joint replacements, these prostheses can fail secondary to allergy, infection, wear, fracture, and heterotopic bone development. Authors prospectively reviewed outcome data for all patients who required revision surgery of previously placed TMJ prostheses between 2004 and 2016. Data included pain and diet VAS scores, as well as interincisal distance recorded prerevision and at 6 weeks, 6 months, and 12 months after revision. Reasons for prosthesis failure and the number of previous interventions were noted. Twenty patients (26 joints) received revisions. The reasons included infection (n=9), reankylosis (n=5), wear of the existing prosthesis (n=2), fracture of the prosthesis (n=2), foreign body reaction (n=1), and allergy to the prosthesis (n=1). The mean age of the patients (15 women, 5 men) was 53.3 years (range, 47 to 68 years). Preoperatively, the mean pain score was 73.1 (SD= ±22.4), mouth opening was 20.9 mm (SD= ±10.2 mm), and diet score 41.7 (SD= ±23.6). At the 12-month follow-up, all the measures improved significantly ($P=.05$), with a pain score of 18.4 (SD= ±25.2), mouth opening 32.2 mm (SD= ±9.3 mm), and diet score 89.4 (SD= ±18.5).

The authors concluded that TMJ prosthesis revision replacements performed by an experienced team can result in considerably improved outcomes with limited complications. However, authors also indicated that

improvements in function and pain may not be as marked as when the prostheses were initially placed.

SLEEP-DISORDERED BREATHING

The most current complete review of morphologic differences contributing to the effectiveness of the oral appliance notes that, "morphologic variations as predictors were usually weak. Biomechanical factors and wide variations in the metrics of appliance use were unclear, pointing out gaps in knowledge and practice of oral appliance therapy (OAT)."[358] Many current studies had suboptimal samples sizes with fewer than 100 participants, with the majority sampling fewer than 50 participants. Of the larger sample sizes, one was a retrospective study, and the other omitted a clear description of the appliance and methods used.[359,360] Other trials sought to determine the phenotype of patients that gain the most benefit from OAT, which is difficult to determine with the methodologies used.[361,362] Without clear practice guidelines, the dental sleep medicine practitioner may be frustrated with direct care of their patients with obstructive sleep apnea (OSA), as the available options for available oral appliances has not significantly expanded in recent years.

Most articles reviewed could be enhanced with expanded detail. Defining specific terms or conditions, such as bruxism, should be clarified (for example, is bruxism considered clenching, lateral movements, or both?).[363] It is important to describe specific details of the oral appliance being investigated other than the name. Laboratory fabrication techniques vary widely among named appliances. A Herbst appliance presents buccal arms for advancement located on the right and left surfaces of the appliance; thickness and extension of acrylic resin, metal and solder composition, and general fitting of the device are not indicated simply by the Herbst designation. Also integral to the treatment sequence are patient instructions, accompanying medications used, method of titration, incidence of appliance breakage, and subjective symptoms such as TMJ pain or dysfunction. Allergic reactions may also arise to the various components. This collective pool of information is critical to the practitioner delivering the individual care to each patient with OSA. Little evidence exists to clearly guide the dental professional to select an oral appliance and effectively titrate it in a straightforward and medical manner.[364]

Moreover, the duration of studies should be lengthened, with an increased number of participating individuals providing clear demographics of the cohort beyond sex. Expanded explanation of reasons for drop out/discontinuation with the therapy would be useful. Ongoing follow-up of patients with OSA undergoing OAT may review gradual and continued improvement over time. Oral appliances are not continuous positive airway pressure (CPAP). CPAP is an instantaneous intervention, whereas the oral appliance is more gradual, allowing for healing over a course of time. Objectively, CPAP will often outperform an oral appliance, but more patients accept and tolerate OAT in the long term. Most studies evaluating OAT and CPAP demonstrate preference for the oral device.

Beyond oral appliance therapy, this review points to the critical nature of OSA treatment for the overall health and well-being of a patient. Each study highlights the unmistakable risk factors associated with increasing severity of OSA. The relative risk of cardiovascular diseases (CVDs) is most prominently defined within the current studies. A systematic review and meta-analysis included 10 cohort studies involving over 36 000 participants and 3362 patients with CVDs and demonstrated that risk of CVD increased incrementally and continuously with an increase of the apnea-hypopnea index (AHI), the measure of OSA severity.[365] Another meta-analysis investigated over 1 million participants, looking at factors such as elevated blood pressure (BP) associated with OSA; oxygen desaturation index (ODI); and short and long sleep duration.[366] Snoring was found to be a risk factor for elevated BP. It was concluded that hypertension (HTN) risk might be decreased by treating OSA, ODI, and snoring and ensuring appropriate sleep duration. A different trial involving over 25 000 participants concluded that risk of acute pulmonary embolism (PE) occurrence and recurrence is significantly elevated with OSA compared with those without.[367] Treatment for OSA might have a modifying effect on PE occurrence.

Continuous positive airway pressure therapy did not fare well in current studies. One trial demonstrated that motor vehicle accident (MVA) incidence did not change after CPAP use.[368] Among those who had an MVA, body mass index (BMI) was the only baseline characteristic that differed between the groups and tended to increase with PAP therapy. Differences in sleep study data or accident conditions were not observed.

A study involving over 2000 participants examined the involvement of sleep bruxism (SB) with insomnia and OSA.[369] It was concluded that insomnia is likely associated with SB, especially in middle-aged women, while OSA appears to be age- and sex-dependent. Such overlap may influence treatment decisions to achieve optimal outcomes. A systematic review and meta-analysis concluded that children and adolescents with a definitive diagnosis of attention-deficit/hyperactivity disorder (ADHD) have an elevated chance of developing sleep and awake bruxism as compared with those without ADHD.[370]

Another project concluded that jaw and neck muscle activation is significantly coherent during SB, and coherence is independent of sleep stage.[371] The results

support the hypothesis of bruxism being a centrally regulated phenomenon. A topical review examines bruxism, tooth clenching, and tooth grinding as controversial topics within dentistry.[363,372] The authors claim that there is no current consensus on the meaning of bruxism, based on assertions of tooth grinding and presence or absence of tooth clenching. They recognize that tooth clenching during sleep seems to have both beneficial and detrimental effects. Previous studies have shown that submaximal tooth clenching is associated with motor-evoked jaw pain for individuals with chronic TMDs. Tooth clenching during sleep may play a role in the perpetuation of TMDs and be a risk for development.

The occlusal pathway as a contributor to TMDs is not showing promise.[373] The implementation of education related to sleep medicine is important, necessary, and advisable for all dental schools at both predoctoral and postdoctoral levels.[374]

In light of the current pandemic because of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, many studies were performed pertaining to aspects of 2019 novel coronavirus disease (COVID-19) and sleep. The relationship between the symptomless Multivariable Apnea Prediction (sMVAP) index and adverse outcomes of patients with COVID-19 was explored.[375] It was concluded that using the sMVAP for OSA risk assessment and then predicting the adverse outcomes of COVID-19 patients is an effective method. The use of sMVAP index should be vigorously touted for screening COVID-19 inpatients for OSA, and high-risk individuals should be appropriately managed. A systematic review suggested that many of the risk factors and comorbidities associated with OSA, including obesity, HTN, and diabetes mellitus are associated with poor COVID-19 outcomes.[376] The reviewers concluded that it may be necessary to examine new diagnosis and treatment pathways for this patient population.

This review illustrates the wide variation in topic, quality, and relevance of current studies.

Oral appliance therapy

A scoping review examined factors contributing to the effectiveness of oral appliance therapy for obstructive sleep apnea (OSA).[358] The reviewers sought to enhance understanding of OAT effectiveness by exploring morphologic interactions in individuals with OSA. Databases including MEDLINE, PubMed, The Cochrane Library, and EBSCO were scanned with the following search terms: OA treatment effectiveness; positive and/or negative outcome predictors. Craniofacial predictors of OAs for OSA and biomechanical factors of anatomic traits associated with OA success were included. The search examined radiographic cephalometric images for morphology/phenotypes and apnea-hypopnea index responses. If the title or abstract was not relevant, or it was a case report, the article was excluded. No age, sex, or language restrictions were used.

The review selected 140 articles that indicated impact on musculature and pharyngeal airway structure because of OAT. The alterations were individually unpredictable with wide variability in AHI (61.81% ±12.29 events/h mean ±standard deviation). Morphologic variations as predictors were usually weak. Biomechanical factors and wide variations in the metrics of appliance use were unclear, pointing out gaps in knowledge and practice of OAT. The authors concluded that current knowledge is heterogeneous and widely variable. They call for an integrated basis to identify morphologic and biomechanical elements of phenotypic expressions of sleep-disordered breathing (SDB) in the design and application of OAs. Furthermore, they are seeking identification of subgroups of individuals with OSA who respond to OAT.

Another study set out to examine the impact of moderate protrusion with a mandibular advancement device (MAD) for OSA could substantially improve upper airway volume and, moreover, what signs and symptoms of OSA can be improved by this therapy.[377] Fifty-eight adults with a diagnosis of OSA were selected for treatment with MAD. The mean AHI was 19.2 ±8.6. Signs and symptoms of OSA (AHI, oxygen saturation, snoring, daytime sleepiness, and health-related quality of life) were evaluated at baseline and after 6 months of OAT. Nasal resistance, airway volume, and cross-sectional areas with and without the device in place were recorded. Based on AHI reduction, the treatment response was classified as complete, partial, or incomplete. Statistical analyses included the chi-square test, *t* tests, Mann-Whitney U tests, and regression analyses (linear and logistic).

Twenty-three patients attained a complete response (AHI$\leq$5 events/h) to MAD therapy. In 13 individuals, the response was partial, and incomplete in 9 patients. The complete responders were significantly younger and had a deeper vertical overlap than the other groups. A convex profile was positively associated, but a vertically restricted throat and increased lower facial height were negatively associated with an airway volume increase. They noted that excellent MAD therapy outcomes were attained in most patients; only age and deep vertical overlap had some influence on AHI reduction, illustrating the multifactorial nature of response to OAT.

A different project analyzed the effect of gradual increments of mandibular advancement on the treatment efficacy of MADs and explored determinants of effective and target mandibular protrusion for OSA.[378] Participants were prospectively recruited; 42 patients aged 41.5 ±9.0 years were involved. The mandible was titrated from 0 mm with 0.5 mm increments until the AHI was decreased to the lowest level. Rhinospirometry, rhinomanometry, and MRI were used to examine the change

of respiratory function and upper airway (UA) morphology. There was a dose-dependent relationship between mandibular protrusion and the AHI improvement rate, success rate, and normalization rate. Curves plateaued after approximately 70% of maximal mandibular protrusion was reached. The correlation between AHI and mandibular protrusion intensified as the OSA severity increased.

The target protrusion for individuals with mild, moderate, and severe OSA was 3.5 ±1.8 mm (38.6 ±19.4% maximal mandibular protrusion [MMP]), 5.8 ±1.9 mm (62.9 ±18.8% MMP), and 5.9 ±2.2 mm (68.8 ±15.6% MMP), respectively. Regression analysis revealed that the factors influencing effective and target protrusion consisted of maximal lateral dimension of the total UA with MADs, mean lateral dimension of the oropharynx, and soft palate length. Additional protrusion brought more lateral expansion of the velopharynx, whereas the change in nasal ventilation was insignificant. It was concluded that the dose-dependent effect of mandibular protrusion on reduction of AHI by using MAD was nonlinear and became more evident with increased severity of OSA. They note that mandibular protrusion should be personalized to each patient.

Another study set out to determine dose-dependent effects of mandibular advancement on optimal continuous positive airway pressure requirements in OSA.[379] Optimal CPAP requirement provides an estimate of airway collapsibility severity, and higher CPAP pressures predict MAD therapy failure in retrospective studies. Therefore, understanding the effects of mandibular advancement on optimal CPAP requirements may enhance the optimization of subject selection for OAT. Patients with OSA (AHI>10 events/h) underwent a research polysomnogram (PSG) in which a remote-controlled mandibular positioner (RCMP) was used to determine dose-response effects of varying mandibular advancement positions (0% "habitual bite," 25, 50, 75, and 100% of maximum mandibular advancement, in random order) on optimal CPAP requirements, before commencing MAD treatment. A separate PSG evaluated treatment outcomes.

Seventeen participants (47 ±9 years; body mass index 26 kg/m^2 (23-27); AHI 18 events/h (14-44); minimal oxygen saturation 84 ±7%) were evaluated. Optimal CPAP requirements were reduced with mandibular advancement in a dose-dependent manner (8.9 ±2.4 versus 7.9 ±2.8, 6.4 ±1.8, 5.7 ±1.9, and 4.9 ±1.8 cm H_2O; respectively, P<.001). Compared with nonresponders, responders to MAD therapy had lower AHI, lower arousal index, and great $MinSaO_2$ at baseline. Optimal CPAP requirements at 0% mandibular advancement (or other positions) were not different among groups. The authors claim that increasing mandibular advancement lowers optimal CPAP in a dose-dependent manner, which supports previous work indicating a beneficial effect of MAD on upper airway collapsibility.

A different group sought to evaluate if variability in mandibular morphology would influence the displacement of the mandible with a MAD.[380] They stated that MADs are designed with standard titration systems, lacking consideration for individual anatomical characteristics of the TMJs and mandibular morphology. They set out to examine if a difference of mandibular shape would influence the displacement of the jaw with a MAD, in search of optimization of mandibular positions with MAD for patients with OSA even when opening the mouth. A mandibular movement model was used to evaluate movement patterns of different points on the chin. The impact of different bony mandibular shapes on these movements was also considered. Differences in movement patterns of the mandibular anterior teeth were discerned based on distance from the center of the condyle, with a more horizontal direction in participants with a greater distance. The investigators note that MADs should be designed according to each individual's anatomy to avoid mandibular protrusion in situations that may narrow the UA. They posit that airway obstruction is more severe in certain untreated individuals with sleep apnea than in others when opening their mouths during sleep based on their findings.

A systematic review and meta-analysis examined the efficacy of CPAP versus MAD in the treatment of OSA.[381] Databases including PubMed, the Cochrane Library, and Embase were searched; key pertinent literature sources were also considered, through October 2019. Odds ratios (ORs), mean difference (MD), and 95% confidence interval (95% CI) were used to assess and synthesize outcomes. Fourteen randomized controlled trials (RCTs) were included, with 249 individuals in the CPAP group and 247 in the MAD group. CPAP was found to significantly reduce AHI (MD: −7.08, 95% CI: −9.06～−5.10) and the percentage of stage 1 and 2 after therapy (MD: −3.728, 95% CI: −6.912～−0.543), compared with MAD. However, CPAP also significantly decreased the short form-36 (SF-36, a health-related quality-of-life measure) social function score (MD: −3.381, 95% CI: −6.607～−0.154). No significant difference in Epworth sleepiness scale score was discerned between the 2 modalities. The analysis concluded that CPAP had better therapeutic efficacy than MAD in OSA patients.

Another project looked at combination therapy with MAD and expiratory positive airway pressure (EPAP) valves to improve outcomes for OSA patients.[382] Twenty-two individuals with OSA (AHI 22 [13-42] events/h) who were incomplete/nonresponders (residual AHI>5/h) on an initial split-night PSG with a novel MAD containing an oral airway completed an additional split-night PSG with MAD+oral EPAP valve and

MAD+oral and nasal EPAP valves (in randomized order). Compared with MAD alone, MAD+oral EPAP significantly reduced the median total AHI, with further reductions with the MAD+oral/nasal EPAP combination (15 [10-34] versus 10 [7-21] versus 7 [3-13] events/h, $P<.01$). OSA resolved (AHI<5/h) with MAD+oral/nasal EPAP in 9 participants and 13 had ≥50% reduction in AHI from baseline. However, sleep efficiency was reduced with MAD+oral/nasal EPAP versus MAD alone or MAD+oral EPAP (78 ±19 versus 87 ±10 and 88 ±10%, respectively, $P<.05$). It was concluded that combination therapy with a novel MAD device and simple oral or oronasal EPAP valves reduced OSA severity to therapeutic levels for a substantial proportion of incomplete/nonresponders to MAD therapy alone.

A different study examined the use of direct-to-consumer prefabricated adjustable thermoplastic mandibular advancement devices (PAT-MADs), its effectiveness in the treatment of OSA, feasibility, and short-term adherence in a Chinese population.[383] Fifty patients diagnosed with mild to moderate OSA on formal PSG were fitted with a PAT-MAD. Level 3 home sleep apnea testing (HSAT) was used at baseline and after treatment to measure sleep indices including AHI, hypopnea index (HI), apnea index (AI), oxygen desaturation index (ODI), and the lowest O_2 saturation (L_{sat}). Quality of life (QOL) of Epworth sleepiness scale (ESS), Pittsburgh sleep quality index (PSQI), functional outcomes of sleep quality-10 (FOSQ10), and satisfaction surveys were administered.

Over 3 months, indices demonstrated a trend toward improvement. Results were statistically significant when stratified into groups who achieved cure and success. Furthermore, they found a mean improvement in AHI, −12.7 ±9.3; AI, −5.7 ±8.2; HI, −6.3 ±3.7; ODI, −11.2 ±8.6 for responders, with a success rate of 41%. Out of the QOL measure, ESS showed a decrease of −1.41 (−2.52, −0.3) ($P=.017$) when controlled for age and BMI. Up to 68.8% of patients found that the device was useful in alleviating snoring. Adherence was reported at 59%. The authors concluded that titratable PAT-MAD is an economical and effective option for OSA patients of Chinese descent. It has potential to serve as a trial device and method of selection before proceeding with bespoke MADs. Further studies are warranted to substantiate other factors which influence the recommendation of MADs for patients within this demographic.

A randomized controlled crossover trial sought to explore the effects of MAD on jaw-closing muscle activity (JCMA) time-related to respiratory arousals and on JCMA time-related to nonrespiratory arousals in patients with OSA.[384] Eighteen individuals with OSA (mean ±standard deviation=49.4 ±9.8 years) with a mean ±standard deviation AHI of 22.0 ±16.0 events/h of sleep participated. Two ambulatory PSG recordings, one with a MAD in situ and another without the MAD in place, were performed. JCMA was quantified as the sum of rhythmic masticatory muscle activities (RMMAs) and other orofacial activities. Significant reductions in AHI ($Z=-2.984$; $P=.003$), in the respiratory arousal index ($Z=-2.896$; $P=.004$), and in the JCMA time-related to respiratory arousal index ($Z=-3.434$; $P=.001$) were found with MAD in use. On the nonrespiratory arousal index, and on the JCMA time-related to nonrespiratory arousal index, MAD had no significant effect ($T=2.23$, $P=.82$; and $Z=-0.66$, $P=.51$, respectively). They noted that the study demonstrated that effective MAD therapy significantly reduced jaw-closing muscle activities time-related to respiratory arousals in OSA patients. Further studies are warranted to confirm the results in OSA patients with comorbid sleep bruxism.

A single-center, prospective study evaluated anatomic alterations during MAD therapy.[385] TMJs of patients undergoing MAD treatment were evaluated with MRI and electrical alterations in masticatory muscle surfaces before and after treatment for patients with mild to moderate obstructive sleep apnea-hypopnea syndrome (OSAHS). MRIs were performed at baseline and after 18 months of therapy in the first cohort. Electrical changes in mandibular movement and masticatory muscle surface were monitored in the second cohort before and after 6 months of MAD therapy.

In cohort 1, MRI analyses of TMJs discerned no significant deviation in the angle of joint disc position. A minor change in the position relationship between condylar process, articular disc, and fossa was noted, but was not found to be significant. There was no significant change in the shape and magnitude of mandibular incisal edge movement; percussion movement; masticatory movement; and condylar central trajectory among the involved participants, before and after treatment with MAD after 6 months as evaluated with electromyography. The study concluded that the effect of MAD therapy for OSA on the stomatognathic system is nominal.

A cross-sectional trial sought to examine the success rate of OA for patients with OSA, as the efficacy of OAT varies widely among this patient population.[386] This Japanese multisite project was carried out at 10 medical facilities. A total of 442 participants met the inclusion criteria, in which participants used a MAD and underwent PSG to assess baseline and posttreatment parameters. Age, sex, BMI, and AHI at the time of diagnosis and at follow-up were determined. After OAT, the average AHI was reduced from 22.6 ±13.8 to 10.0 ±10.2/h, and mean rate of decrease in the AHI was 52.5 ±38.4%. Considering therapeutic success rates, criterion 1 (AHI<5/h), criterion 2 (AHI<10/h), criterion 3 (AHI<15/h), and criterion 4 (AHI reduction ≥50%) accounted for 33.5%, 66.3%, 80.5%, and 63.3%, respectively. Oral

appliance success was reduced according to increase in OSA severity, increasing BMI, and increasing age. They concluded that variability of OAT based on multiple criteria may support the clinician to evaluate treatment options for patients with OSA.

Another project explored the effects of posture and mandibular advancement on nasal resistance in OSA and the efficacy of a novel OA in patients with OSA and high nasal resistance.[387] High nasal resistance is associated with OAT failure in sleep apnea therapy. The novel device in consideration has a built-in oral airway and has been shown to decrease pharyngeal pressure swings during sleep and may be successful in those with high nasal resistance. Thirty-nine patients with OSA (7 women, AHI=29 ±21 events/h) underwent split-night PSG with and without OA in random order. Before sleep, participants were fitted with a nasal mask, pneumotachograph, and a choanal pressure catheter for standard nasal resistance measurement seated, supine, and lateral (with and without OA in random order).

Awake nasal resistance increased from seated, to supine, to lateral posture ($P<.001$). Corresponding measures of nasal resistance did not change with mandibular advancement ($P=.388$). OAT decreased the median AHI by 47% (29 ±21 versus 18 ±15 events/h, $P=.002$). Participants with high nasal resistance (>3 cm H_2O/L/s) had similar reductions in AHI versus those with normal resistance (61% [−8, 82] versus 40% [−5, 62], $P=.244$). The investigators stated that nasal resistance changes with posture in participants with OSA. The novel OA with a built-in oral airway reduced OSA severity in people with OSA, including those with high nasal resistance.

A different study evaluated MAD to discern changes in the position of dental and skeletal structures between CBCT images obtained from individuals currently undergoing MAD for OSA.[388] Eighteen patients participated. Landmarks were deployed in different structures and allowed for calculation of distances and angles. Reliability was established based on reevaluation of CBCT imaging for 5 participants 3 times. Statistical analysis involved descriptive statistics, repeated-measures analysis of variance, and paired *t* tests.

Landmarks presented excellent reliability, the lowest being the z-axis of the rightmost anterior-superior part of the coronoid process (intraclass correlation coefficient=0.854). The greatest average change in distance was from the buccal furcation of 17 to 47 (−6.66 ±6.66 mm). The largest mean difference was 27 degrees buccal furcation-left lingula-left hyoid bone (−16.83 ±27.30 degrees). A mean distance change of 0.55 mm and mean angular change of 13.11 degrees of all linear distances and assessed angles were noted. The authors concluded that vertical linear skeletal changes with MAD in situ include a vertical increase of the mandible relative to the maxilla and a superior displacement of the hyoid bone relative to the mandible. Anterioposterior linear changes included mandibular protrusion and anterior movement of the hyoid bone relative to the cervical vertebrae and an anterior migration of the hyoid relative to the maxilla. Angular movements included the rotation of the hyoid anterosuperiorly. Skeletal repositionings should be correlated with individual symptoms to discern whether short- or long-term use of MAD is indicated for patients. Evaluating specific tendencies with MAD therapy will assist clinicians to predict outcomes of skeletal changes to definitively decide the best participants for this treatment modality.

A single-center prospective cohort study sought to analyze agreement in degree of configuration and obstruction of the UA with jaw thrust compared with an OA in situ during drug-induced sleep endoscopy (DISE) examination of patients with OSA, as well as to study clinical decision-making with jaw thrust or an interim MAD.[389] Sixty-three patients participated. Agreement among observations in supine position for degree of obstruction was 60% (n=36, κ=0.41) at the level of the velum, 68.3% (n=41, κ=0.35) for oropharynx, 58.3% (n=35, κ=0.28) for tongue base, and 56.7% (n=34, κ=0.14) for epiglottis; in lateral position, agreement was 81.7% (n=49, κ=0.32), 71.7% (n=43, κ=0.36), 90.0% (n=54, κ=0.23), and 96.7% (n=58, κ=could not be determined), respectively. In the supine position, agreement for configuration of obstruction at the level of soft palate was found in 20 of 29 individuals (69.0%, κ=0.41), and in the lateral position, it was 100%. Thirty patients would have been prescribed OAT relying on jaw thrust, and 34 by using the boil-and-bite device as a screening tool. The primary reason for being labeled as unsuitable was complete retropalatal collapse during jaw thrust; with the temporary MAD, this was caused by complete retropalatal or hypopharyngeal collapse. It was concluded that there is only slight to moderate agreement in degree of obstruction for jaw thrust and a boil-and-bite oral device during DISE examination. Greater improvement of UA patency at the hypopharyngeal level was observed during jaw thrust, but this maneuver was less effective in improving UA obstruction at the retropalatal level.

A randomized placebo-controlled trial examined the long-term effects of a MAD on stress symptoms and cognitive function in participants with upper airway resistance syndrome (UARS) versus placebo.[390] Thirty individuals with UARS were randomized into 2 groups: placebo and therapy with MAD. UARS was confirmed with the presence of sleepiness (ESS $\geq$10) and/or fatigue (Modified Fatigue Impact Scale $\geq$38) associated with an AHI$\leq$5 events/h and a respiratory disturbance index (RDI) >5 events/h of sleep and/or flow limitation >30% of total sleep time. All participants completed the Rey

Auditory-Verbal Learning Test, the Logical Memory test, the Stroop Color Test, the Trail Making Test, the Digit Symbol Substitution Test, and Inventory of Stress Symptoms. Cognition protocol was defined based on the most used neuropsychological tests in the literature. Evaluations were provided at baseline and after 1.5 years of therapy.

Mean adherence to placebo was 6.6 ±2.6 h/night, and to MAD, 6.1 ±2.4 h/night. MAD group reported side effects that were minor and short term. There was no statistically significant difference in Rey Auditory-Verbal Learning Test, Logical Memory test, Stroop Color Test, Trail Making Test, and Digit Symbol Substitution Test at baseline and 1.5 years of treatment between the groups. Inventory of Stress score decreased at the alert phase and the resistance phase after 1.5 years of MAD therapy compared with placebo. It was concluded that MAD treatment was effective in reducing stress symptoms in patients with UARS after 18 months of therapy.

A different randomized controlled trial evaluated a direct comparison of the objective adherence between MAD and CPAP use in participants with moderate OSA, based on the premise that comparable health effects of MAD and CPAP treatment have been attributed to higher adherence to oral appliance as compared with CPAP.[391] Fifty-nine individuals with AHI 15-30 events/h underwent adherence monitoring for 12 months. MAD adherence was registered with the TheraMon microsensor; CPAP adherence was assessed with the built-in registration software program and SD card output. Subjective adherence with both modalities was compiled by using a questionnaire.

Forty participants (68%) completed the study with the therapy to which they were randomly assigned. Median (interquartile range) objective adherence (h/night) in the third month was 7.4 (5.2-8.2) for MAD and 6.8 (5.7-7.6) for CPAP (P=.41), compared with 6.9 (3.5-7.0) with MAD and 6.8 (5.2-7.6) with CPAP (P=.85) at 1 year. There were no significant changes between the third and twelfth month for both MAD (P=.21) and CPAP (P=.46). Changes in adherence were not significantly different between MAD and CPAP (P=.51). Self-reported adherence was significantly greater with MAD than with CPAP at all follow-up intervals; self-reported adherence with CPAP was less than the objective CPAP adherence at the sixth and twelfth month (P=.02). The investigators concluded that objective adherence with MAD and CPAP is comparable and stable over time. Subjective adherence is greater with MAD than with CPAP, lending to interesting discrepancy between objective and subjective adherence with CPAP.

A longitudinal follow-up study involving a subset of patients initially enrolled in a randomized controlled clinical trial (RCT) looked at long-term follow-up and comparison regarding efficacy of MAD and CPAP therapy, patient adherence, and satisfaction over a 10-year period.[392] The initial cohort was 103 participants with OSA; the subset included 51 MAD users and 52 CPAP users, randomized. After the 10-year follow-up interval, 14 patients with MAD and 17 CPAP patients were eligible. Data were analyzed at baseline, 3-month, 1-, 2-, and 10-year follow-up. All 31 participants underwent PSG and self-reported metrics.

PSG demonstrated a favorable outcome of both treatments at 10-year follow-up. Baseline included those in both groups who did not differ in AHI. At the decade follow-up, both MAD and CPAP groups demonstrated a significant decrease in AHI. At baseline, the mean AHI in MAD was 31.7 ±20.6 events/h versus the CPAP group (49.2 ±26.1 events/h). At 10-year follow-up, the average AHI in MAD was 9.9 ±10.3 events/h, and in CPAP group, it was 3.4 ±5.4 events/h. Both modalities resulted in a substantial improvement in subjective neurobehavioral outcomes at the 10-year follow-up. Both treatment modalities exhibited good and stable effects after a 10-year follow-up interval. Either therapy is indicated for the long-term management of OSA.

Another project examined individual differences in efficacy of MAD therapy among OSA patients.[361] The trail set out to elucidate underlying individual differences in efficacy with OSA endotypic traits calculated from baseline PSG, including collapsibility (airflow at normal ventilatory drive, $V_{passive}$), loop gain (drive response to reduced airflow), arousal threshold (drive preceding arousal), compensation (increase in airflow as drive increases), and the ventilatory response to arousal (VRA, increase in drive because of arousal). Responders to MAD therapy have a lower loop gain and milder collapsibility (according to previous knowledge). Thirty-six participants (AHI, 23.5 [IQR: 19.7-29.8]/h) underwent pretreatment testing and at 3 months with full PSG, with MAD fixed at 75% of maximal protrusion. Traits were estimated at baseline by using preestablished parameters and PSG. Response was defined as AHI reduction $\geq$50%.

MAD therapy significantly decreased AHI (49.7% [23.9-63.6] from baseline, median [IQR]). Responders exhibited decreased loop gain (mean [95% CI], 0.53 [0.48-0.58] versus 0.65 [0.57-0.73]; P=.020) at baseline compared with nonresponders, which persisted after adjustment for pretreatment AHI and BMI. Increased loop gain remained associated with nonresponse after adjustment for collapsibility (OR, 3.03 [1.16-7.88]/1 SD increase in LG [SD=0.15]; P=.023). The authors noted that MAD nonresponders exhibited greater ventilatory instability, demonstrated as elevated LG. Evaluation of baseline degree of ventilatory instability by using this approach may enhance upfront MAD therapy participant selection.

The wide variation of MAD therapy for OSA contributes to a need for accessible and accurate methods for patient selection; the impact of awake nasopharyngoscopy for this process is unreliable. A prospective trial introduced an assessment method based on anatomical UA features during tidal respiration for nasopharyngoscopy to relate these features to OAT outcome.[362] One hundred participants with diagnosed OSA were enlisted for MAD therapy with a fixed 75% of maximal protrusion. Nasopharyngoscopic observations during Müller's maneuver and tidal breathing were evaluated both with and without an OA. Treatment outcome, verified by 3-month follow-up PSG with MAD, was classified as (1) AHI reduction ≥50%, (2) treatment AHI <5 events/h, and (3) ≥0% increase in AHI compared with baseline or treatment deterioration.

Sixty-five patients completed the treatment regime. After adjusting for baseline AHI, BMI, and supine positioning, the location of the velum (odds ratio [OR], 4.0; 95% CI: 1.3-11.8; *P*=.013) and crowding of the oropharynx (OR, 7.7; 95% CI: 1.4-41.4; *P*=.017) were correlated to treatment deterioration. Addition of both features significantly (*P*=.031) increased the accuracy of baseline models based on clinical measurements alone. Furthermore, with the MAD in place, a posteriorly located soft palate (OR, 9.8; 94% CI, 1.7-56-3; *P*=.010) and a posteriorly situated tongue base (OR, 7.4; 95% CI: 1.5-35-9; *P*=.013) were associated with treatment deterioration. It was concluded that awake nasopharyngoscopy might be a useful office-based evaluation to exclude the risk of treatment deterioration and improve patient selection for MAD therapy.

A different RCT sought to evaluate self-reported sleep quality, treatment compliance, and respiratory event index (REI) after 4 months of therapy with MAD or CPAP in patients with mild and moderate OSA.[360] One hundred-four individuals participated and were randomly assigned to the treatment modalities. The CPAP software program, clinical examination, Pittsburgh Sleep Quality Index (PSQI), and type 3 polygraphic sleep tests contributed to the relevant data. Chi-square test, *t* test, and Mann-Whitney U test were used to analyze compliance, PSQI global score, and REI, respectively. Reliable change index (RCI) evaluated change in PSQI global score.

Six patients did not complete follow-up. More participants were compliant with MAD therapy (79.5%) than CPAP (38.9%) at 4 months (*P*=.001). Both groups had improved PSQI global scores: MAD (8.0 ±3.1 to 5.7 ±2.5, *P*<.001) and CPAP (7.7 ±3.5 to 6.7 ±3.4, *P*=.01). More individuals exhibited improved PSQI global score according to the RCI in the MAD arm (38.6%) than in the CPAP group (16.7%) (*P*=.01). Both modalities decreased REI (*P*<.001), but CPAP (REI=1.1) more so than MAD (REI=7.9) (*P*<.001). The investigators stated that sleep quality is improved in mild-moderate OSA with both therapies. More patients complied with MAD, which improved sleep quality in more patients than CPAP, even with lower REI for the PAP group. In terms of sleep quality, MAD therapy should be regarded as superior therapy over CPAP for mild-moderate OSA.

Occlusal changes during long-term OAT for OSA are common; this project set out to compare subjective versus objective occlusal alterations.[393] Consecutive patients who were adherent to MAD therapy were recruited. The participants responded to 2 questionnaires using numeric visual analog scales (VASs), ranging from 0 (not at all) to 10 (very much). The first questionnaire used open-ended questions, and the second questionnaire asked specific questions about side effects. Plaster casts at baseline and follow-up were used to evaluate horizontal overlap, vertical overlap, and space for the teeth. Thirty-eight patients (12 women) with a median age of 64 years (interquartile range or IQR of 57 to 69 years) and median treatment duration of 9.5 years (IQR, 5.8 to 14.3 years) were involved.

Horizontal and vertical overlap, molar relationship, and the irregularity of mandibular anterior teeth changed significantly during treatment. No associations were found between any of the participants' responses and the objectively measured occlusal changes. Younger patients, those with a small baseline horizontal or vertical overlap, and those who developed an anterior reverse articulation were more likely to report occlusal alterations. The author stated that patients undergoing long-term OAT for OSA are unaware of various types of occlusal changes, which will progressively increase in magnitude and be more difficult to treat, if warranted. Therefore, regular follow-up with MAD patients is warranted to monitor potential side effects.

A retrospective cohort study explored success rates for MAD therapy for OSA patients in a single provider private practice setting.[359] Patients with pretreatment and posttreatment sleep studies were included over a 14-year period; AHI <10 events/h with therapy was deemed treatment success. Of 2419 patient records analyzed, 544 (22%) had pretreatment and posttreatment sleep studies (89% PSG). Of 510 participants with complete data, 459 (90%) attained posttreatment AHI <10 events/h, indicating treatment success. Fifty-one patients (10%) had a final AHI ≥10 events/h, constituting treatment failure. Among the1921 who did not undergo an efficacy sleep study, 66 (3%) discontinued therapy because of adverse side effects. Considering these individuals as treatment failures as well, the overall treatment failures were 117 of 576 (20%). Of the treatment successes, OSA was categorized by using baseline AHI as mild in 170 (34%), moderate in 181 (36%), and severe in 138 (28%). In patients with baseline and efficacy sleep studies, there was an 80% success rate for treatment of OSA with a

custom-fabricated adjustable MAD for all disease severity levels.

A random crossover study compared the efficacy of tongue-retaining device (TRD) versus CPAP for treatment of OSA.[394] Thirty-six participants with a mean age of 52.7 ±10.6 years were enrolled. Inclusion criteria were age ≥18 years, AHI ≥5 events/h, and minimum oxygen saturation (SO_2) ≥70% determined with PSG. Severe periodontal disease, unstable cardiopulmonary or neurological disease, and/or total sleep time <2 h excluded participation. A 1-week wash-in period was followed by questionnaires and randomization into 2 groups: TRD/CPAP and CPAP/TRD (18 patients each). After 3 weeks of intervention, questionnaires were readministered, and WatchPAT home sleep test was performed. After a 1-week wash out period, participants were switched to the other therapy. Primary outcome was AHI; secondary outcomes were SO_2, Functional Outcomes of Sleep Questionnaire (FOSQ), ESS scores, treatment side effects, and adherence. Nine patients withdrew, leaving 27 participants included in the final analysis. Mean AHI dropped from 38.7 ±24.0 to 2.5 ±0.5 and 12.7 ±2.6 events/h for CPAP and TRD, respectively (95% CI mean differences: 4.65-15.62; P<.001). No significant difference was found in ESS and FOSQ scores between treatments. Common adverse side effects were drooling, tongue numbness, pain for TRD, nasal blockage, mask compression, and cumbersome nature of CPAP with travel. It was concluded that CPAP was superior to TRD for resolving PSG indices; however, both similarly improved QOL and daytime sleepiness. TRD might be considered a short-term alternative treatment for OSA.

Pathophysiology and medical implications

An updated systematic review and meta-analysis sought to summarize the evidence concerning the relationship between obstructive sleep apnea syndrome (OSAS) and the risk of cardiovascular diseases.[365] The search was performed by using PubMed and Web of Science up to September 10, 2019. Categorical as well as linear and nonlinear dose-response meta-analyses were respectively conducted to evaluate the association between the severity of OSAS and the risk of CVDs. AHI was designated as an indicator of OSAS severity. Ten cohort studies involving 36 347 participants and 3362 patients with CVDs were included. The pooled RRs of overall CVDs were 1.13 (95% CI: 1.02-1.24) for mild versus non/normal OSAS; 1.16 (95% CI: 1.02-1.32) for moderate versus non/normal OSAS; 1.26 (95% CI: 1.15-1.39) for moderate-severe versus non/normal OSAS; and 1.41 (95% CI: 1.22-1.63) for severe versus non/normal OSAS. The linear dose-response meta-analysis demonstrated that every 10 events/h increment in AHI value was associated with a 9% increased risk of suffering from CVDs. The nonlinear dose-response meta-analysis showed that the risk of CVDs increased continuously with the increment in AHI. The investigators concluded that this review and meta-analysis provided evidence for a positive association between OSAS and the risk of CVDs, despite the severity of OSAS. The relative risk of CVDs increases continuously with the increment in AHI.

Another meta-analysis thoroughly investigated the correlation between sleep status and hypertension, noting that HTN is a global health issue, with sleep status as a risk factor.[366] Electronic databases including Cochrane Library, PubMed, and Embase were searched through May 31, 2019. Studies were selected according to predefined screening criteria, and their qualities were evaluated by using quality check scales. By using the Stata 15.1 software program, the associations between sleep status and hypertension were analyzed by meta-analyses, with odds ratio and 95% CIs as effect indexes. Moreover, publication bias and small study bias was assessed by using the Begg and Egger test. Furthermore, a sensitivity analysis was conducted through ignoring one study per time and then observing its influences on the pooled results.

Fifty-four studies involving 1 074 207 participants were eligible for the meta-analysis. Several factors were included in the analysis: Elevated blood pressure was associated with OSA; oxygen desaturation index; short sleep duration; and long sleep duration. The differences in ≤5-h, 6-h, ≥9-h, and 10-h groups had statistical significances, while there was no significant difference in ≥8-h group. Snoring is a risk factor for elevated BP (OR, 1.94; 95% CI: 1.41-2.67). Subgroup analysis was conducted, and results were varied. They concluded that HTN risk might be decreased by treating OSA, ODI, and snoring, as well as by appropriate sleep duration. Future studies with large sample sizes and high quality should take place to further support the findings.

A different study explored the effects of various intermittent hypoxemia (IH) properties on BP and short-term blood pressure variability (BPV) in patients with severe OSA.[395] Nocturnal BP was continuously monitored with pulse transit time (PTT). Apnea-related systolic BP elevation values were used to reflect BPV. Beat-to-beat R-R interval data were incorporated in PSG for heart rate variability (HRV) analysis. The low-frequency/high-frequency band ratio was used to reflect sympathovagal balance. The rate of pulse oxyhemoglobin saturation (SpO_2) decrease was counted as the change in percentage of SpO_2/second after obstructive apnea and expressed as the oxygen desaturation rate (ODR). Individuals with severe OSA (n=102) were divided into 2 groups according to the median ODR: faster ODR (FODR group: ODR>37, n=50) and slower ODR (ODR≤37, n=52).

Comparisons between the 2 groups exhibited significantly higher diastolic BP (SBP) values in the FODR group than in the slower ODR group (awake SBP 149.9 ±18.3 versus 131.8 ±15.6 mm Hg; asleep SBP: 149.6 ±19.9 versus 128.7 ±15.6 mm Hg; both $P<.001$); in the short-term BPV (15.0 ±4.8 versus 11.6 ±3.6 mm Hg; $P<.001$); and the prevalence of HTN (74.0% versus 26.9%; $P<.001$). Multiple linear regression analyses revealed that after adjusting for BMI, functional residual capacity, expiratory reserve volume, and baseline SpO_2, ODR, as assessed by using $\Delta SpO_2/\Delta t$, had the strongest association with both BP and short-term BPV. Correlation analysis showed that ODR was positively correlated with the low-frequency band ratio (r=0.288, $P=.003$). It was concluded that ODR, as a novel hypoxemia profile, was more accurately associated with the elevation of BP and BPV in patients with severe OSA; FODR might be associated with elevated sympathetic activity.

A multicenter sample of 4732 participants examined the association between mild OSA and systemic arterial hypertension (SAH) in the European Sleep Apnea Database cohort, to determine the impact of mild OSA on the important clinical outcome of HTN.[396] The risk of mild OSA was subclassified into 2 groups, mild $_{\text{AHI } 5<11/h}$ (AHI 5 to <11 events/h) and mild $_{\text{AHI } 11\leq 15 \text{ events/h}}$ (AHI ≥11 to <15 events/h), and compared with nonapneic snorers for prevalent SAH after adjustment for relevant confounding variables including sex, age, smoking, obesity, daytime sleepiness, dyslipidemia, chronic obstructive pulmonary disease, type 2 diabetes, and sleep test methodology (polygraphy or PSG).

SAH was found to be greater in the mild $_{\text{AHI } 11<15/h}$ OSA group than that in the mild $_{\text{AHI } 5\leq 11/h}$ group and nonapneic snorers (52% versus 45% versus 30%; $P<.001$). Corresponding adjusted odds ratios for SAH were 1.789 (mild $_{\text{AHI } 11\leq 15/h}$; 95% CI: 1.49-2.15) and 1.558 (mild $_{\text{AHI } 5\leq 11/h}$; 95% CI: 1.34-1.82), respectively ($P<.001$). In sensitivity analysis, mild $_{\text{AHI } 11\leq 15/h}$ OSA remained a significant predictor for SAH for the polygraphy (OR, 1.779; 95% CI: 1.403-2.256; $P<.001$) as well as the PSG groups (OR, 1.424; 95% CI: 1.047-0.939; $P=.025$). The data suggest a dose-response relationship between mild OSA and SAH risk, beginning from 5 events/h in polygraphy recordings and continuing with a further risk elevation in the 11 to <15 events/h range. These results potentially introduce a challenge to traditional thresholds of OSA severity and may assist in stratifying patients with OSA according to CV risk.

The impact of sleep apnea (SA) on survival subsequent to cancer diagnosis is unknown, even though previous studies suggest that intermittent hypoxia associated with OSA contributes to accelerated cancer progression.[397] This investigation identified a cohort of 1575 individuals diagnosed with SA over a 9-year interval with a subsequent cancer diagnosis by using a connection of the University of Washington Medicine system and a population-based cancer registry serving the same Seattle-Puget Sound region. They computed age-standardized 5-year relative survival after cancer diagnosis for all cancers combined, and for specific cancer sites, for both the SA group and the general Seattle-Puget Sound population, and US life tables were employed as the reference population. Relative survival was estimated by sex, cancer stage, and health-care encounters.

Five-year overall relative survival for cancer was more favorable in the SA cohort than in the general population (83.6%; 95% CI: 79.6% to 86.8% versus 71.6%; 95% CI: 71.3% to 71.9%); this pattern applied to most specific cancer sites. However, 5-year relative survival was slightly less favorable in the SA group among patients with melanoma (97.7%; 95% CI: 84.6% to 99.7% versus 99.2%; 95% CI: 98.8% to 99.5%) and cancer of the corpus uteri (84.0%; 95% CI: 58.2% to 94.5% versus 84.6%; 95% CI: 83.1% to 86.0%). The investigators concluded that the fact that survival after cancer, overall and for most cancer sites, was more favorable in SA patients warrants larger community-based studies to further tease out impact of SA and treatment on site-specific survival for various cancer types, especially in patients with melanoma or uterine cancer.

Another study explored the impact of OSA on the risk of acute pulmonary embolism, hospital outcomes including mortality, and PE recurrence.[367] Adult patients from a single hospital system (Mayo Clinic, Rochester, Minn) were retrospectively enrolled over a 5-year period. Frequency of PE, hospital mortality, and secondary outcomes were evaluated in participants with versus without OSA. PE occurrence risk was evaluated in relation to compliance with OSA therapy. Of 25 038 patients, 3184 (13%) had OSA and 283 (1.1%) exhibited PE. Frequency of PE in patients with and without OSA was 2.4% versus 0.9% (OR, 2.51; 95% CI: 1.9-3.3; $P<.001$). OSA was independently associated with elevated risk of PE after adjusting for demographics and comorbidities (OR, 1.44; 95% CI: 1.07-1.9; $P=.017$). Adjusted hospital mortality was elevated in patients who experienced a PE (OR, 2.88; 95% CI: 1.7-4.9; $P<.001$) but not in patients with OSA (OR, 0.98; 95% CI: 0.7-1.4, $P=.92$). OSA was not a significant deciding factor for mortality in those who experienced a PE (OR, 0.56; 95% CI: 1.1-2.78; $P=.47$), accounting for demographics, PE severity, and Charlson comorbidity index. Adjusted risk of PE recurrence was elevated in participants with OSA compared with those without OSA (OR, 2.21; 95% CI: 1.05-4.68; $P<.04$). The participants compliant with OSA treatment exhibited a lower rate of PE occurrence (16% versus 32%; P=not significant). It was concluded that risk of acute PE occurrence and recurrence is significantly elevated with OSA

compared with those without; treatment for OSA might have a modifying effect on PE occurrence.

A different clinical cohort was orchestrated to examine the association between lipid profiles and OSA during REM or NREM sleep.[398] A total of 2619 participants with at least 30 minutes of REM sleep were included. Sleep variables and fasting lipid profiles (total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein [HDL-C], apolipoprotein [apo] A-I, apoB, apoE, and lipoprotein (a) [Lp (a)]) were determined for each individual. AHI in REM and NREM sleep (AHI_{REM} and AHI_{NREM}, respectively) were recorded. Linear regression analysis was used to assess the associations of AHI_{REM} and AHI_{NREM} with lipid profiles.

When stratified by AHI_{REM} severity of sleep apnea, all demographics, clinical variables, and sleep parameters differed between the groups except for apoA-I. In fully adjusted multivariable linear regression models, AHI_{REM} was independently associated with elevating levels of TG, HDL-C, and apoE (P=.04, P=.01, and P=.01, respectively). AHI_{NREM} was independently associated with increasing levels of TC, TG, LDL, and apoB and lower level of HDL-C (all P<.05). In sensitivity analyses by only pursuing associations in patients who had an AHI_{NREM} or AHI_{REM} <5 events/h in separate regression models, AHI_{REM} was not associated with all-lipid profile in almost all adjusted models (P>.05), whereas AHI_{NREM} was associated with raised TC, LDL-C, and apoB (P=.03, P=.01, and P=.01, respectively). The researchers noted that AHI_{NREM} was independently associated with the largest alterations in serum lipids, including TC, LDL-C, and apoB.

OSA is associated with elevated CVD risk but has not been shown to increase recurrent CV events in patients with acute coronary syndrome (ACS). This study sought to examine the effect of OSA on CV risk for patients with different ACS phenotypes.[399] Post hoc analysis of the ISAACC (Continuous Positive Airway Pressure in Patients with ACS and OSA) study included 1701 individuals admitted for ACS. To determine the presence of OSA (AHI ≥15 events/h), all patients underwent polygraphy; follow-up continued for 1 year. Unsupervised clustering by using latent class analysis identified subgroups of patients on the basis of 12 clinical factors associated with CV risk. The effect of OSA on recurrent CV event risk was examined for each phenotype identified.

Two phenotypes were identified: individuals without previous heart disease and without previous ACS ("no-previous-CVD" phenotype, 81%) and patients with previous heart disease and previous ACS ("previous-CVD" phenotype, 19%). The median IQR at follow-up was 2.67 (3.8) years. For the no-previous-CVD phenotype, the effect of OSA exhibited an adjusted hazard ratio (95% CI) of 1.54 (1.06-2.24; P=.02), whereas for the previous-CVD phenotype, the effect of OSA showed an adjusted hazard ratio of 0.69 (0.46-1.04; P=.08). It was concluded that OSA is associated with an increased risk of recurrent CV events for patients with ACS and a specific phenotype. These individuals are primarily characterized by no previous heart disease and admission for a first ACS event.

Sleep apnea is prevalent among those with coronary artery disease (CAD) and increases CV risk. It was demonstrated previously that one month of cardiac rehabilitation (CR) decreased severity of SA in patients with CAD by reducing fluid accumulation in the legs during the day and the volume of fluid shifting rostrally into the neck during sleep. This study set out to determine wither CR will lead to longer term attenuation of SA in patients with CAD.[400] Fifteen patients with SA and CAD who had participated in a 1-month randomized trial on the impact of exercise training on SA were followed up until they completed 6 months of CR (age: 65 ±0 years; BMI: 27 ±3.9 kg/m^2; AHI: 39.0 ±16.7 events/h). The AHI was evaluated at baseline by PSG and then at 6 months by portable monitoring at home. Cardiorespiratory fitness (VO_{2peak}) was evaluated with a graded cardiopulmonary exercise test at baseline and 6 months. The 6-month CR program included once weekly, 90-minute, in-facility exercise sessions, and 4 d/wk at-home exercise regimens. After 6 months of CR, there was a 54% decrease in the AHI (30.5 ±15.2 to 14.1 ±7.5, P<.001). BMI remained unchanged, but VO_{2peak} increased by 27% (20.0 ±6.1 to 26.0 ±8.9 mL/kg/min, P=.04). The investigators concluded that participation in CR is associated with a significant long-term reduction in OSA severity, which suggests that the attenuation of SA by exercise could be a mechanism underlying reduced mortality after participation in CR in patients with CAD and sleep apnea.

OSA has been associated with a 2- to 7-fold risk of motor vehicle accidents; CPAP therapy may decrease MVA risk. This issue was further evaluated in long-term CPAP users and untreated controls.[368] Case-control and before-after study designs were used. The observational cohort consisted of CPAP-treated and untreated individuals matched for sex, age, and AHI. All MVAs reported to the police were identified. Two thousand-sixty patients (75.8% men; mean age, 56.0 ±10.5 years) were included. The median CPAP usage was 6.4 h/d. The control participants (N=1030) were screened for MVAs for a median of 6.5 years after discontinuation of CPAP. No significant differences were found between the incidences of MVAs per 1000 person years before treatment (3.2), after treatment (3.9), or in controls (2.6). Individuals who had MVAs after treatment had a higher BMI but did not differ in terms of other baseline characteristics, sleep study variables, or accident conditions as

compared with controls. In the majority of these patients, daytime sleepiness was decreased, whereas BMI tended to increase during treatment. The authors noted that MVA incidence did not change after CPAP therapy; among individuals who had MVA, BMI was the only baseline characteristic that differed between the groups and tended to increase with PAP therapy. Differences in sleep study data or accident conditions were not observed.

A twin study investigated the heritability of the relationship between OSA and its comorbidities such as HTN, diabetes, and dyslipidemia.[401] Forty-seven monozygotic and 22 dizygotic adult twin pairs recruited from the Hungarian Twin Registry (mean age, 51 ±15 years) underwent an overnight diagnostic sleep study. A medical history was obtained, BP was measured, and blood samples were drawn for fasting glucose, total cholesterol, triglyceride, high-density lipoprotein and low-density lipoprotein cholesterol, and lipoprotein (a). To examine the heritability of OSA and its comorbidities, a bivariate analysis was performed with an adjustment for age, sex, BMI, and smoking after false discovery rate correction and after exclusion of participants on lipid-lowering and antidiabetic medications. There was a significant correlation between indices of OSA severity, such as AHI, ODI, and percentage of sleep time spent with oxygen saturation <90%, as well as BP, serum triglyceride, lipoprotein (a), and glucose levels (all $P<.05$). The bivariate analysis revealed a common genetic background for the correlations between serum triglyceride and ODI ($\tau=0.63$, $P=.03$), as well as percentage of sleep time spent with oxygen saturation <90% ($\tau=0.58$, $P=.03$). None of the other correlations were found to be significantly determined based on genetics or environment. It was concluded that this twin study illustrated the co-occurrence of OSA with hypertriglyceridemia has a genetic influence and heritable factors contribute to the pathogenesis of dyslipidemia in OSA.

OSA has been described as a risk factor for cardiac arrhythmias, with an established association with atrial fibrillation (AF). Relationships with other arrhythmias and conduction disorders have not been fully investigated and were explored with this review.[402] The National Inpatient Sample database from 2009 to 2011 was used to examine this relationship. The presence of diagnosis was determined based on the International Classification of Disease-9 (ICD-9) codes. Univariate and multivariate logistic regressions were used to establish mortality risks among all groups. Multivariate logistic regression demonstrated increased mortality in patients with OSA in comparison to individuals without OSA and patients across all categories of arrhythmias and conduction disorders. One significant finding was the increased association between cardiac arrest and those with OSA compared with patients without OSA (OR, 95.72; 95% CI: 89.13-105.81, $P<.001$). The authors concluded that OSA is significantly associated with non-AF arrhythmias, conduction disorders, and sudden cardiac arrest. Awareness of this association is important for early screening for OSA in obese patients to prevent CV morbidity and mortality. They posit that CPAP might be beneficial against all types of arrhythmias and sudden cardiac death.

The presence of OSA contributes to the development of peripheral arterial diseases (PAD). There is a lack of data demonstrating how often these conditions coexist; this study sought to determine the prevalence of OSA in patients with PAD.[403] Patients previously qualified for first revascularization because of PAD were included in this project. All patients underwent an overnight sleep study to detect OSA, which was diagnosed when the AHI was ≥5 events/h. From 141 patients (60% men; mean age, 69.6 ±9.5 years), OSA was diagnosed in 68 individuals (48%). Thirty-nine (28%) had mild OSA (AHI 5-14 events/h); 21 patients (15%) moderate OSA (AHI 15-29 events/h); and 8 patients (6%) had severe OSA (AHI ≥30 events/h). Participants without OSA had significantly lower BMI (26.9 ±5.5 versus 27.7 ±5.3 kg/m^2, $P=.01$) and lower hip circumference (97.4 ±11.7 versus 98.7 ±7.4, $P=.04$). There were no differences in the distribution of other known CV risk factors and diseases among the groups. There were no significant differences in OSA distribution or its severity between patients with lower extremity artery disease and carotid artery disease. They stated that the prevalence of OSA in patients with PAD is very high, affecting nearly 50% of the studied patients.

Characterizing associations of sleep variables with blood-glucose-level factors among African-Americans may clarify the underlying mechanisms of impaired glucose metabolism and help determine treatment targets to prevent diabetes mellitus (DM) in blacks.[404] Cross-sectional analyses were conducted in 789 blacks who underwent home sleep apnea testing and 7-day wrist actigraphy in 2012-2016 as part of the Jackson Heart Study. Sleep-disordered breathing variables included respiratory event index (REI) associated with 4% oxygen desaturation and minimum oxygen saturation. Sleep patterns on actigraphy included fragmented sleep markers. Associations between sleep characteristics (8 exposures) and measures of glucose metabolism (3 outcomes) were determined by using multivariate linear regression. Mean (SD) age of the participants was 63 (11) years; 581 (74%) were women; 198 (25%) had DM; and 158 (20%) were taking antihyperglycemic medication. After multivariate adjustment, including antihyperglycemic medication use, the betas (95% CI) for fasting glucose and A1c, respectively, for each SD higher level were 0.13 (0.02, 0.24) mmol/L and 1.11 (0.42, 1.79) mmol/mol for REI associated with 4% oxygen

desaturation and 0.16 (0.05, 0.27) mmol/L and 0.77 (0.10, 1.43) mmol/mol for fragmented sleep indices. Among 589 individuals without DM, the betas (95% CI) for homeostatic model assessment of insulin resistance for each SD higher level were 1.09 (1.03, 1.16) for REI associated with 4% oxygen desaturation, 0.09 (0.85, 0.96) for minimum oxygen saturation, and 1.07 (1.01, 1.13) for fragmented sleep variables. It was concluded that SDB, overnight hypoxemia, and sleep fragmentation were associated with higher blood glucose values among African-Americans.

Sleep bruxism and temporomandibular disorders (TMDs)

A statement article was generated to give an overview of a general project and to present the overall structure of a thorough multidimensional toolkit for the assessment of bruxism, that is, a bruxism evaluation system.[405] This intermediate step will be further elucidated in a future extended publication and will ultimately assist in defining a Standardized Tool for the Assessment of Bruxism (STAB) as the end result. Two invitation-only sessions were held during the 2018 and 2019 General Session and Exhibition of the International Association for Dental Research (IADR) meetings. Participants of these closed meetings were separated into 2 groups, to form the basis for a multidimensional evaluation system comprising 2 main axes: an evaluation axis A with 3 assessment domains (subject-based, clinically based, and instrumentally based assessment) and an etiological/risk factors axis B evaluating different groups of factors and conditions (psychosocial assessment; concurrent sleep and nonsleep conditions; drug and substance use or abuse; and additional factors). The efforts of the 2 groups that led to the identification of different domains for assessment are summarized in this article, along with a roadmap for future research directions. This approach will allow clinicians and researchers to modulate evaluation of bruxism patients with a comprehensive look at the clinical impact of the various bruxism activities and etiologies. The ultimate goal of the system is to assist the refinement of decision-making processes in the clinical setting.

A systematic review examined current knowledge on possible association and causality between sleep bruxism and OSA by using full-night PSG.[406] Databases including PubMed, Web of Science, Cochrane, LILACS, MEDLINE, and BBO-ODO were searched through May 2019. The methodological rigor was evaluated with the QuATEBS tool. Two hundred seventy articles were gathered, and after independent inspection of abstracts by 2 authors, 17 articles underwent full-text reading. Ten articles failed to meet inclusion criteria, leaving 7 included in qualitative synthesis. Four studies supported the association between OSA and SB: (1) A subtype of patients with OSA may have SB as a protective response to respiratory events; (2) most episodes of bruxism take place shortly after the termination of apnea/hypopnea (AH) events; (3) bruxism episodes occur secondary to arousals arising from AH events; and (4) there is a correlation between the frequency of SB and AH events, and 3 studies did not support; (5) AH episodes are related to nonspecific SB oromotor movements; (6) SB episodes are not directly associated with the end of AH events; and (7) individuals with OSA did not experience more SB events than control group. The authors concluded that there is no scientific evidence supporting a conclusive relationship between SB and OSA. Moreover, well-designed and randomized trials with control groups are warranted to examine whether possible mechanisms common to SB and OSA exist and whether OSA therapy could improve SB negative oral health outcomes in patients with SB and OSA.

Electromyography (EMG) biofeedback (BF) training is possibly an effective cognitive behavioral approach to modulate bruxism. This trial explored SB regulation by daytime clenching control by using a single-channel auditory EMG BF device.[407] Seventeen male participants (mean age, 24.4 ±3.1 years) with self-reported awake/sleep bruxism were enlisted and divided into a BF (n=10) and control (CO) group (n=7). All participants underwent 4 EMG recording sessions during both daytime and sleep over 3 weeks. During the daytime in the second week, the BF received feedback alert signals when excessive EMG activity with certain burst duration was detected while the participants went about regular daily activities. The CO group underwent EMG evaluation sessions without receiving any notifications of parafunctional activities. The number of phasic burst events during sleep was compared between the 2 groups.

While the number of phasic EMG events was not significantly different between the BF and CO groups at baseline, significantly reduced phasic events were observed in the BF group as compared with controls at the follow-up (week 3) (P=.006, Tukey HSD). Since daytime BF training is focused on raising awareness of awake bruxism, it does not interrupt the sleep sequence or involve associated side effects. They suggested that the reported results with EMG BF targeting for tonic EMG events during the daytime can be an effective strategy to regulate phasic EMG events during sleep.

A different study sought to determine the accuracy of scoring masticatory muscle activity (MMA) events in 7 different PSG arrays.[408] Nineteen participants (13 women; mean age, 31.1 ±12.9 years, 12 self-reported bruxers) underwent 1-night PSG testing, augmented with audio, video, and a separate front electroencephalography set (FES). The same examiner scored the MMA events with 7 different setups, with varying number of channels available: (1) one, (2) two, and (3) four EMG

channels, (4) PSG without audio or video (PSG-N), (5) home PSG with FES and audio (FES-A), (6) PSG with audio (PSG-A), and (7) PSG with audio and video (PSG-AV). A subset (n=10) of recordings were scored twice to assess intrascorer reliability. MMA indices and accuracy of scoring the events in various setups were compared against PSG-AV.

The intraclass correlation coefficient (ICC) between PSG-AV and PSG-A was high (0.940, $P<.001$) as well as for FES-A (0.927, $P<.001$); it was lower for PSG-N (0.835, $P<.001$). For setups with only EMG channels, coefficients were very low (ICC<0.100 for all). Intraexaminer reliability was high (ICC>0.939 for all setups), with the exception of PSG-N (ICC=0.764, $P=.002$). When comparing against MMA events recorded in PSG-AV, the sensitivity of MMA event recognition for PSG-A was 78.5% and specificity 95.5%, which were substantially greater than sensitivity (52.0%) and specificity (87.2%) of PSG-N. It was concluded that MMA event scoring accuracy with PSG-A or FES-A is almost comparable to that with PSG-AV. As precise event recognition is essential for accurate MMA scoring, they noted that one cannot reliably depend on EMG alone.

A cross-sectional clinical study investigated the associations between sociodemographic, occupational, clinical conditions, psychological, and sleep quality variables on definite SB.[409] Records from a private medical outpatients' clinic were reviewed for adults (aged 20-60 years) and the elderly (>60 years) who had undergone PSG from July 2017 to February 2018. A questionnaire based on criteria of the AASM was also administered. Definite SB data pattern distribution was analyzed, and multivariate Poisson regression with robust variance was used to evaluate the associations between definite SB diagnosis, established with PSG recordings, and the independent variables (A significance level of 5% was adopted.). Two hundred forty participants were included in the study, and the SB prevalence was 7.08% (n=17). The adjusted Poisson regression analysis divulged association between definitive SB and individuals with respiratory allergy (PR=3.63; 95% CI: 1.01-13; $P=.047$) and restless sleep (PR=2.97; 95% CI: 1.04-8.50; $P=.042$). This project revealed associations between definite SB and clinical conditions (respiratory allergy) and sleep behavior (restless sleep). Knowledge involving factors associated with definite SB can lead to decision-making in the clinical setting and management strategies involving a multidisciplinary approach.

Another project looked at the first-night effect on PSG diagnosis of sleep bruxism.[410] Overnight PSG studies were performed for 2 consecutive nights in 43 participants (mean age, 23.7 ±0.32 years; range, 20.0-33.0). Sleep indices and rhythmic masticatory muscle activity (RMMA) were recorded for 2 nights. The diagnosis of SB was scored by the frequency of RMMA with cutoff values of 2 and 4 times/h of sleep. Participants were designated into control (n=15), low (n=13), and moderate-high (n=15) groups. Among the 3 groups, the agreement of the SB diagnosis was compared between the 2 nights. Sleep variables exhibited a significant first-night effect with reduced sleep efficiency, greater sleep latency, and higher occurrence of arousals. The frequency of RMMA significantly increased from the first to the second night in the moderate to high SB group only. The concordance rate of the severity between the 2 nights was 93.3% (14/15) in the controls; 76.9% (10/13) in the low SB group; and 60% (9/15) in the moderate to high SB group. When the severity was established on the first night, it remained the same on the second night in 77.8% (14/18) of the controls, 66.7% (10/15) of the low SB group, and 90.0% (9/10) of the moderate-high SB group. The results demonstrated that the first night effect on the occurrence of RMMA varied among the different degrees of RMMA frequency and suggest that, because of the first night effect, single-night PSG may underestimate the moderate-high level of SB but separate out low levels of SB from controls.

Sleep bruxism can occur with sleep apnea, although the association of SB with insomnia is not as well known. This study set out to evaluate the strength of the associations between SB, insomnia, and OSA in a general population.[369] Data from the 2007 EPISONO general population study (n=2041; Sao Paulo, Brazil) were reanalyzed for this project. The data were gathered from PSG and from a questionnaire. SB could only be assessed as "possible" with self-report questionnaires, but as "definitive" with both self-report and PSG. Logistic regression and decision tree analyses were used, which revealed that being a man, overweight, obese, having an AHI>30, and insomnia syndrome (IS) are among the risk factors for SB (prevalence ratio or PR, 1.5-3.3). A high AHI and insomnia syndrome had similar PRs (2.7 and 2.8, respectively). Decision tree analysis demonstrated that IS contributed to the predictive accuracy of SB self-report (88%). A similar estimate (91%) was noticed with SB PSG data. Correspondence analysis illustrated 3 age profiles in participants: (1) good sleepers aged 20-35 years; (2) women aged 35-50 years with SB and concomitant IS; and (3) participants aged ≥50 years with obesity and SA. The investigators concluded that insomnia is likely a condition associated with SB, especially in middle-aged women, while SA appears to be age and sex dependent. Such overlap may influence the treatment decision to achieve best outcomes.

A systematic review and meta-analysis examined whether children and adolescents with attention-deficit/hyperactivity disorder (ADHD) are at elevated risk of developing bruxism compared with those with ADHD.[370] Observational studies that evaluated the occurrence of bruxism in participants with ADHD were included.

Evidence quality was determined with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria. Thirty-two studies involving 2629 children/adolescents with ADHD and 1739 with bruxism (1629 with SB and 110 with awake bruxism [AB]) were included. The prevalence of bruxism, irrespective of type, in the children/adolescents was 31% (95% CI: 0.22-0.41, I^2=93%). ADHD was associated with an elevated chance of bruxism (OR, 2.94; 95% CI: 0.41, I^2=61%), independent of the type (SB [OR, 2.77; 95% CI: 2.12-4.07, I^2=61%) or AB [OR, 10.64; 95% CI: 2.41-47.03, I^2=65%]). The presence of signs of ADHD without a diagnosis was not associated with a greater chance of bruxism (OR, 3.26; 95% CI: 0.76-14.04, I^2=61%). Children and adolescents with a definitive diagnosis of ADHD have a greater chance of developing sleep and awake bruxism than those without ADHD.

A cross-sectional observational study sought to evaluate the coherence between jaw and neck muscle activity during sleep bruxism.[371] The electromyographic (EMG) activity of jaw (masseter, temporalis) and neck (sternocleidomastoid [SCM], trapezius) muscles in participants with "definite" SB was measured by using ambulatory PSG. Coherence for masseter-temporalis, masseter-sternocleidomastoid, and masseter-trapezius was quantified during phasic and mixed RMMA episodes with a coherence-analyzing software program. Outcome measures included presence or absence of significant coherence per episode (in percentages); frequency of peak coherence (FPC) per episode; and sleep stage. A total of 632 episodes during 16 PSGs of eight participants were analyzed. Significant coherence was found between the jaw and neck muscles in 84.9% of the episodes. FPCs of masseter-temporalis were significantly positively correlated with those of masseter-SCM or masseter-trapezius (P<.001). Sleep stages did not significantly impact coherence of these muscles. It was concluded that jaw and neck muscle activation is significantly coherent during SB; coherence is independent of sleep stage. These findings support the hypothesis of bruxism being a centrally regulated phenomenon.

Another systematic review and meta-analysis set out to gather scientific evidence to support the relationship between dental malocclusion and bruxism.[411] The study was guided by the PECO strategy (P=general population; E=dental malocclusion; C=no dental malocclusion; O=bruxism). Literature searches were performed without language or date restrictions in the following databases: PubMed, Scopus, the Web of Science, the Cochrane Library, LILACS/BBO through VHL, and the gray literature. Search parameters included Medical Subject Headings/DECs, synonyms, and free terms relevant to each database, with no age restrictions applied. Once the relevant data were gathered from the articles, the Fowkes and Fulton guidelines were followed to assess quality and risk of bias. For quantitative analysis, dental malocclusions were categorized into groups according to their type to perform OR meta-analysis with 95% CIs by using the Review Manager software program (Cochrane). GRADE was used to demonstrate the level of certainty of evidence.

Out of 1502 eligible studies, 10 were included for qualitative analysis and 9 for quantitative synthesis. Four studies presented high methodological quality. Five meta-analyses alluded to a nonassociation between bruxism and Angle class I (OR, 1.05; 95% CI: 0.41-2.69; P=.92; I^2=84%), Angle class II (OR, 1.49; 95% CI: 0.77-2.87; P=.23; I^2=27%), or Angle class III (OR, 0.77; 95% CI: 0.31-1.93; P=.58; I^2=0%). Bruxism was associated with children who did not present with a posterior reverse articulation (OR, 0.70; 95% CI: 0.51-0.96; P=.03; I^2=27%) and present crowding (OR, 1.53; 95% CI: 1.03-2.26; P=.03; I^2=0%). The GRADE analysis classified a very low quality of evidence. The authors concluded that individuals who present with bruxism have a greater chance of crowding; however, bruxism is not associated with the presence of any of the other malocclusions evaluated.

A nationwide twin cohort examined the degree of co-occurrence of sleep bruxism and awake bruxism and whether they have common correlates and also twin similarity of SB and AB traits by zygosity and sex.[412] A questionnaire was mailed to all twins born in Finland from 1945 to 1957, in 2012 (n=11 766). Age- and sex-adjusted logistic regression models were used. Twin similarity was evaluated with polychoric correlations, and crosstwin-crosstrait correlations were calculated. The response rate was 72% (n=8410). Any SB was reported by 14.8% and ≥3 nights weekly by 5.0%. Percentages for any AB were 18.4% and 6.3%, respectively. There was substantial co-occurrence (29.5%) between SB and AB, and several shared correlates manifested. For SB, the polychoric intraclass correlation was 0.366 in monozygotic (MZ) and 0.200 in dizygotic (DZ) pairs, without sex difference. A 2-fold crosstwin-crosstrait correlation was observed in MZ twins compared with DZ twins. It was concluded that risk factor profiles of SB and AB were greatly but not entirely similar. The higher correlation in MZ than in DZ pairs suggests the influence of genetic factors on both SB and AB. The greater crosstwin-crosstrait correlation in MZ than in DZ pairs suggests some degree of genetic influences shared by SB and AB.

Numerous theories associate emotional factors with the initiation of SB. Few studies have incorporated validated instruments to assess psychological characteristics and SB in children. This cross-sectional study sought to evaluate the prevalence of parent-reported SB in children and its association with social, emotional, and behavioral problems.[413] A school-based sample at 20 public schools in Brazil was examined. Parents or caregivers provided

information related to tooth-grinding sounds during sleep and about children's social, emotional, and behavioral problems with the Strength and Difficulties Questionnaire. Analyses were conducted considering each subscale of the Strength and Difficulties Questionnaire and the total score. Prevalence ratios were estimated with a Poisson regression model. Statistical inferences were based on 95% CIs. A total of 556 eight-year-old children were assessed. Prevalence of SB was 30.83%. Results of an adjusted analysis demonstrated a significant association of SB with higher scores on total difficulties (overall score) ($P<.001$), emotional symptoms ($P<.001$), and peer relationship problems ($P=.010$) subscales. The authors concluded that parental reports of emotional and behavioral problems were associated with a greater prevalence of SB in schoolchildren and note that interdisciplinary research involving dentistry and psychology may enhance the understanding of bruxism.

Sleep disorders frequently co-occur in patients with epilepsy (PWE), but SDB and insomnia are better studied than others. This study set out to evaluate sleep-related movement disorders in epilepsy.[414] One hundred seventy-five PWE (47.4% women; mean age, 35.4 years; range, 18-71 years) and 130 controls (47.7% women; mean age, 33.6 years; age range, 18-72 years) were interviewed. Restless leg syndrome (RLS) and sleep bruxism were diagnosed in International RLS Study Group's diagnostic criteria and International Classification of Sleep Disorders, third Edition, criteria, respectively. Pittsburgh Sleep Quality Index (PSQI), ESS, and Berlin Questionnaire (BQ) were also used. The findings suggested that RLS and SB are encountered more frequently in PWE than in controls: 20.6% versus 6.1% for RLS and 23.7% versus 5.4% for SB ($P<.05$). Insomnia was more prevalent in epilepsy (46.2% versus 24.6%, $P<.05$), whereas poor sleep hygiene occurred more frequently in controls (28.3% versus 53.8%, $P<.05$). PWE exhibited poorer sleep by PSQI (61.7% versus 41.5%, $P<.05$). Sleepiness (38.7% versus 39.2%) and snoring (42.8% versus 40.8%) were distributed equally among both groups; ESS and BQ lacked significant differences ($P>.05$). It was concluded that sleep disorders comprise an important share of epilepsy comorbidity. Unselected PWE had greater prevalence of RLS; higher prevalence of SB in the epilepsy population shown for the first time; and elevated complaints of insomnia.

The role of oxidative stress (im)balance and its potential involvement in the onset and/or progression of TMD has been studied by looking at synovial fluid. A narrative review evaluated the association between oxidative stress markers in synovial fluid and the etiopathogenesis of TMJ dysfunction.[415] Two independent investigators searched the following electronic databases from inception to March 2019: PubMed/MEDLINE, LILACS, SciELO, EMBASE, TRIPDATABASE, SCOPUS, and Google Scholar. Key search terms included: "temporomandibular joint disorders" OR "temporomandibular joint disc" OR "temporomandibular joint dysfunction syndrome" OR "temporomandibular joint" OR "facial pain" AND "free radicals" OR "oxidative stress." Data extracted from the selected articles included study design, sample profile, TMJ disease reported, diagnostic method, reactive oxygen and nitrogen species evaluated, enzymatic and nonenzymatic antioxidants examined, and techniques used to assess free radicals and antioxidants.

After title and abstract screening of 6974 articles and full-text reading, 19 studies were included. All selected articles were cross-sectional observational studies. Enzymatic and nonenzymatic antioxidant defenses seemed to be diminished in these participants, leading to the establishment of the oxidative stress process. Furthermore, the studies exhibited a positive correlation between the severity of the intra-articular TMD and the increase in oxidative damage. The reviewers concluded that the development of oxidative stress, whether through increased reactive oxygen/nitrogen species, a reduction in antioxidant defenses, or a combination of both, may be associated with initiation and maintenance of intra-articular damage.

The diagnosis of TMDs is complex, and it is unclear in the literature whether the clinical changes associated with them are also reflected in the EMG activity of the muscles of mastication (MM). A systematic review and meta-analysis investigated whether there is a difference between patients with TMD and healthy controls with EMG activity of MM.[416] ScienceDirect, EMBASE, MEDLINE, PEDro, SciELO, CINAHL, and LILACS databases were searched from January 2000 to February 2019. Cross-sectional studies, crossover studies, and RCTs evaluating EMG activity of right and left masseter and anterior temporal muscles in participants with TMD and healthy controls were selected. Two independent reviewers gathered data from the articles. The risk of bias was evaluated with a checklist for assessing methodological quality created based on the Strengthening the Reporting of Observational Studies in Epidemiology and International Society of Electrophysiology and Kinesiology guidelines. Mean differences and 95% CIs were calculated and combined in meta-analyses. A total of 51 267 articles were selected, and 12 were included in the review. Only 2 studies allowed for the comparative analysis of results. The different EMG signal capturing, processing, and analysis methods used constitute a substantial limitation to the comparative analyses of the results reported in the studies for this review. It was concluded that the systematic review failed to demonstrate evidence of significant differences in EMG activity of masticatory muscles between individuals with and without TMD.

Another systematic review sought to investigate the association between painful TMDs and sleep quality in adults.[417] Observational case-control studies using either Research Diagnostic Criteria for TMD (RDC/TMD) or Diagnostic Criteria for TMD (DC/TMD) for TMD diagnostic and validated questionnaires for sleep quality were selected by 2 investigators in a 2-phase protocol. A systematic review was conducted in accordance with the PRISMA statement. Databases include PubMed/MEDLINE, LILACS, SCOPUS, PsycINFO, Web of Science, and gray literature (ProQuest, Google Scholar, and OpenGrey). To qualify, studies had to include adults (>18 years old), with no language, sex, or time of publication restrictions. The quality of the studies was evaluated with the Newcastle-Ottawa Scale (NOS). Eight case-control studies were included, with high (4) and moderate (4) quality assessment. Seven studies exhibited a significant association between the presence of painful TMD and sleep quality ($P<.05$); the other demonstrated impaired sleep in participants with higher sensitivity to heat pain ($P<.001$). Different pain scales were used to evaluate pain levels; 6 studies found differences as compared with controls. One study demonstrated that in nonpainful TMD, the PSQI values were not different when compared to the control group. The reviewers concluded that an association exists between painful TMD and sleep quality; the presence of pain appears to strongly impact sleep quality in those with TMD.

Bruxism is frequently indicated as a risk factor for the occurrence of TMDs. Despite their common co-occurrence, the precise relationship between the 2 entities has not been thoroughly explained, and their causal relationship is still suspected. This project explored the distribution of TMD among those with SB and nonbruxers.[418] Seventy-seven patients of the Clinic of Prosthetic Dentistry at Wroclaw Medical University who had been diagnosed with TMD and probable SB participated. They underwent video-polysomnography to evaluate the intensity of SB by using the Bruxism Episode Index (BEI). TMD diagnoses included local myalgia; temporal tendinitis; myofascial pain; myofascial pain with referral; hypertrophy; osteoarthrosis; disc displacement with reduction; disc displacement without reduction with limited opening; subluxation; adhesions/adherence; arthralgia; headache attributed to TMD; and oromandibular dystonia. None of these conditions occurred statistically significantly more often in the studied individuals (bruxers; BEI $\geq$2) as compared with the controls (nonbruxers; BEI <2) ($P>.05$ for all comparisons). This study concluded that the distribution of TMD among those with and without SB was similar; therefore, the prevalence of SB appears to not be a certain risk factor for TMD occurrence.

A topical review examines bruxism (and related phrasing "tooth clenching" and "tooth grinding," which describe common oral parafunctional behavior) as a controversial topic within dentistry.[363] Different authors define bruxism in different ways; this article strives to clarify the misunderstandings associated with the various definitions. They claim that there is no current consensus on the meaning of bruxism, based on assertions of tooth grinding and presence or absence of tooth clenching. Moreover, the parafunction may be comprised of AB and/or SB, despite the unclear interrelationship between the 2 entities. Oral parafunctions of tooth clenching and grinding seem to have characteristic differences, even though AB and SB may coexist in the same person. Based on a systematic literature review, the authors presented evidence-based research and expert opinion pertaining to tooth clenching that may assist the practicing clinician elevate the level of care provided for individuals experiencing TMDs.

A continuation of the previously discussed topical review explores the consequences of tooth clenching, including long-term impact on the central nervous system.[372] They recognize that tooth clenching during sleep seems to have both beneficial and deleterious effects. Previous studies have shown that submaximal tooth clenching is associated with motor-evoked jaw pain for individuals with chronic TMD. Tooth clenching during sleep may play a role in the perpetuation of TMD and also be a risk factor for its development. Another study posited that elevated background MMA during sleep protrudes and stabilizes the mandible and decreases upper airway resistance. Although the majority of evidence suggests the diagnosis of clenching during sleep or while awake is associated with the presence of linea alba and/or scalloped tongue, the cause-and-effect relationship has not been demonstrated. It was concluded that avoiding the ambiguous term "bruxing" and separating clenching from grinding, patients diagnosed with TMD have a better understanding of explanation of causes and proper treatment(s). Future study on clenching should include a rigorously performed statistical meta-analysis, which may elucidate an alternate conclusion.

Coronavirus-19 disease and sleep issues

Because of the 2019 novel coronavirus disease pandemic, social distancing measures were enforced to control the spread of the virus. However, isolation may adversely impact the psychological well-being and impair sleep quality. This study sought to evaluate the sleep quality of respiratory patients during the COVID-19 outbreak lockdown.[419] All individuals who attended a telemedicine appointment from March 30 to April 30 of 2020 were asked to participate in the survey. Sleep difficulties were assessed with the Jenkins Sleep Scale. The cohort consisted of 365 patients (55.6% men; mean age, 63.9 years; 50.1% with SDB). During the lockdown, 78.9% of participants were confined at home without working. Most

individuals (69.6%) reported ≥1 sleep difficulty, and frequent awakening was the most prevalent issue. Reporting at least one sleep difficulty was associated with women, home confinement without working, diagnosed or suspected SDB, after adjusting for cohabitation status, and the use of anxiolytic medication. Home confinement without working was associated with difficulties falling asleep and waking up prematurely in the morning. Older age was found to be protective for difficulties falling asleep, waking too early, and nonrestorative sleep. Interestingly, those with SDB with good compliance to PAP therapy were less likely to report sleep difficulties. The authors concluded that being a woman, home confinement without working, and SDB may predict an elevated risk of reporting sleep difficulties. Medical support during major crises should be bolstered and potentially made available through telemedicine, which might contribute to reducing psychological distress and improve sleep quality.

A different project examined the relationship between the symptomless Multi-Variable Apnea Prediction index and adverse outcomes of patients with COVID-19.[375] Following the sMVAP quartiles, participants were divided into 4 groups. The clinical electronic medical records, nursing records, laboratory results, and radiological findings for all patients with laboratory-diagnosed Severe Acute Respiratory Syndrome Coronavirus 2 infection were assessed. Cox proportional hazard ratio (HR) models were used to determine the risk factors associated with in-hospital death. Ninety-seven patients were included in this study. The transfer rate of the "Quartile 4" group was significantly greater than that of the "Quartile 1" group. Coronary heart disease high d-dimer and sMVAP at admission were associated with greater odds of death. It was concluded that using the sMVAP index for OSAHS risk assessment and then predicting the adverse outcomes of COVID-19 patients is an effective method. The use of sMVAP index for OSAHS screening for inpatients with COVID-19 should be vigorously touted, and high-risk individuals should be effectively managed.

A systematic review investigated the rapidly emerging COVID-19 literature to determine (1) the relationship between OSA and adverse COVID-19 outcomes; (2) potential causal mechanisms; (3) what effect COVID-19 has had on OSA diagnosis; and (4) what impact COVID-19 has had on treatment and management of OSA during this period.[376] PubMed was searched from 1966 to June 2, 2020; studies were selected if they had explored the relationship between COVID-10 and OSA, were in English, and had full text available. The findings of the review suggest that many of the risk factors and comorbidities associated with OSA, which include obesity, HTN, and DM are associated with poor COVID-19 outcomes. There are plausible mechanisms by which OSA may independently elevate risk of morbidity and mortality associated with COVID-19, and data from the newly published CORONADO study imply that OSA-treated individuals may be at greater risk of death from COVID-19. The reviewers concluded that it was clear that the pandemic has majorly impacted the treatment management and diagnosis of OSA, and in the future, it may be necessary to examine new diagnosis and treatment pathways for this patient population.

A unique systematic review and meta-analysis was undertaken to evaluate the impact and prevalence of sleep problems among the general population, healthcare workers (HCWs), or COVID-19 patients.[420] Electronic databases searched from November 1, 2019, to July 5, 2020, included APA PsycINFO; Cochrane; Cumulative Index to Nursing and Allied Health Literature (CINAHL); EBSCOhost; EMBASE; Google Scholar; MEDLINE; ProQuest Medical; ScienceDirect; Scopus; and Web of Science. Five preprint servers were also scanned for articles accepted after peer review but not yet published (medRxiv.org; Preprints.org; psyarxiv.com; arXiv.org; biorxiv.org). All languages were included. Random-effect models and meta-analysis models were used with the DerSimonian and Laird methodology.

Forty-four articles including a total of 54 231 participants from 13 countries were deemed relevant and contributed to the systematic review and meta-analysis of sleep problems during COVID-19. The global pooled prevalence rate of sleep problems among all populations was 35.7% (95% CI: 29.4% to 42.4%). Patients with COVID-19 seemed to be the most impacted group, with a pooled rate of 74.8% (95% CI: 28.7% to 95.6%). HCWs and the general population had comparable rates of sleep problems with rates of 36.0% (95% CI: 21.1% to 54.2%) and 32.3% (95% CI: 25.3% to 40.2%), respectively. The reviewers concluded that the prevalence of sleep problems during the COVID-19 pandemic is high and impacts nearly 40% of individuals from the general population and HCWs. Those with a COVID-19 diagnosis exhibited even greater rates of sleep difficulties.

Another study evaluated the impact of COVID-19 on treatment adherence and self-reported sleep duration among patients with OSA on CPAP therapy.[421] A retrospective review of medical records of individuals seen in the Sleep and Circadian Clinic at Brigham Health during the immediate period of 1 month after the national lockdown was announced on March 15, 2020, was performed. Participants with OSA were included only if PAP adherence data were available in the 12 months before and in the month after the stay-at-home orders. Patients with other sleep disorders and patients with OSA lacking adherence data were excluded. The mean age of patients was 63.5 ±13.9 years (55% men), with mean BMI being 31.8 ±7.9 kg/m^2. Severe OSA was diagnosed in 59.5%, moderate OSA in 29.3%, and mild

OSA in 11.2%. A greater number of patients reported insomnia after the lockdown (41% versus 48%, *P*=.02). Sex stratification demonstrated worsening insomnia only among women. There was no significant difference in PAP adherence as measured by hours of use, self-reported sleep duration, or use of sleep medications. It was concluded that post-COVID-19 stay-at-home orders had a negative impact on sleep as evidenced by increased reporting of insomnia, especially among women, but no impact on PAP adherence or self-reported sleep duration.

A review article summarized practical recommendations from a task force of the European cognitive behavioral therapy for insomnia (CBT-I) academy addressing issues of sleep problems during lockdowns during the COVID-19 pandemic.[422] Most individuals were exposed to an unprecedented stressful situation of unknown duration with home confinement, which could increase daytime stress, anxiety, depression, and disrupt sleep. Given the fundamental role that sleep plays in emotional regulation, sleep interruption can directly impact next-day emotional functioning. The review summarizes the body of knowledge about the stress-sleep link and confinement as well as effective treatments for insomnia. The effects of the current home confinement that can disrupt sleep are discussed, as well as those that could improve sleep quality. Suggestions are offered for adaptations of CBT elements that are feasible to implement for those facing altered work schedules and obligations; those with health anxiety; those dealing with childcare and home-schooling; and recognition of general limitations imposed on physical exercise and social involvement. Managing sleep issues as best as possible during home confinement can minimize stress and possibly prevent disruptions of social connections.

A retrospective cohort study in Finland examined baseline characteristics of 28 patients admitted to the hospital for COVID-19 during the early phase of the pandemic, to identify risk for severe disease and critical care admission.[423] Data were derived from hospital records. Basic descriptive statistics were used to characterize patients, including medians, percentiles, and frequencies. Differences were tested with Mann-Whitney U-test and Pearson chi-square test. Preexisting OSA was present in 29% of individuals admitted to the hospital for COVID-19. Overall, other conditions on admission were comparable with those reported elsewhere. C-reactive protein (CRP) and procalcitonin (PCT) were elevated in patients who were eventually transferred to critical care as compared with those who were not (median CRP 187 mg/L versus 52 mg/L, *P*<.005; median PCT 0.46 versus 0.12, *P*=.047). It was concluded that preexisting OSA was in a disproportionately large group of patients, suggesting that OSA is an important risk factor for severe COVID-19. Moreover, elevated CRP, PCT, and possibly native oxygen saturation were identified as useful clinical measures to designate individuals at risk for critical care.

Sleep status can impact the body's immune status and mental health. This study sought to examine the sleep status of Chinese residents during the outbreak of COVID-19 and to investigate related risk factors.[424] A cross-sectional survey was conducted in February 2020 to evaluate the sleep status of residents nationwide in the form of an online questionnaire. Of the 8151 respondents, 6437 were ultimately included in the analysis. Logistic regression was applied to analyze the associated factors impacting residents' sleep quality. During the COVID-19 pandemic, the incidence of sleep disturbances in residents was 17.65%. Elevated risk of sleep disturbances was found to be associated with women (OR, 1.35; 95% CI: 1.16-1.59), older age (OR, 1.42; 95% CI: 1.1-2.64), and poor self-reported health status (OR, 5.59; 95% CI: 4.32-7.23). Those individuals who believed COVID-19 had caused a high number of deaths or who thought COVID-19 was difficult to cure were more likely to experience sleep disorders, and the ORs were 1.73 (95% CI: 1.43-2.09) and 1.57 (95% CI: 1.29-1.91), respectively. Regular exercise was found to be protective for sleep disturbance (OR, 0.77; 95% CI: 0.63-0.93). The investigators concluded that during the COVID-19 pandemic, nearly 20% of participants exhibited sleep disorders. During the outbreak, it is important to pay close attention to those at high risk for sleep disturbances; adopt effective risk communication strategies; enhance residents' rational understanding of COVID-19; and develop practical indoor physical activity programs for the general public to enhance sleep quality.

The COVID-19 outbreak led to significant alterations in lifestyle, responsibilities, and stressors. Such dramatic societal changes might lead to overall sleep health decreasing (stress view), remaining unaltered (resilience view), or even improving (reduced work/schedule burden view). This issue was explored with longitudinal, cross-sectional, and retrospective recall methods.[425] In late March 2020, 699 American adults were engaged 2 weeks after the installation of social distancing and stay-at-home directives in the United States. Relative to baseline data from mid-February 2020, cross-sectional and longitudinal analyses showed that average sleep quality was unchanged, or even improved, early in the pandemic. Clear individual differences were noted: Approximately 25% of individuals reported that their sleep quality had degraded, which was explained by stress vulnerability, caregiving, adverse life impact, shift work, and the presence of COVID-19 symptoms. The researchers concluded that the pandemic has negatively impacted some individuals' sleep health while paradoxically improving others' sleep health by decreasing rigid work/school obligations.

ORAL MEDICINE AND ORAL AND MAXILLOFACIAL SURGERY

The aim of the oral medicine and oral and maxillofacial surgery (OMFS) section of this year's annual literature review is to identify topics from the field with special relevance for the practicing general and restorative dentist. It is obvious that the implications of the ongoing "**co**rona**v**irus **di**sease" (COVID)-19 pandemic have impacted head and neck medicine and dentistry in an unprecedented manner. Therefore, the oral medicine/OMFS section will provide a comprehensive review of the "**s**evere **a**cute **r**espiratory **s**yndrome-**co**rona**v**irus-2" (SARS-CoV-2) and COVID-19 that is relevant to dentists.

The uncontrolled transmission of SARS-CoV-2 had to be curbed by global restrictions that were imposed on the public, the economy, medicine, and dentistry.[426] Within the first surge of COVID-19 cases in early 2020, the World Health Organization (WHO) recommended to defer nonemergency medical and dental treatment until after the pandemic; an undefined point in time.[426] Over time, these recommendations had to be adjusted when more knowledge about COVID-19 became available to prevent withholding nonemergency urgent care from patients in need.[427] Lockdown measures led to a significant increase of severe courses of potentially unproblematic diseases of odontogenic origin (for example, odontogenic infections).[428] Continued accessibility to routine dental care during sustained pandemic conditions can avoid such events. The lasting success of this approach can only be achieved if dental health-care providers have sufficient knowledge in relevant pathophysiology, transmission routes, infection risk reduction precautions, and clinical oral signs of COVID-19.

SARS-CoV-2 infection: Pathophysiological basics

The novel coronavirus, SARS-CoV-2, belongs to the family of the regular coronaviruses that have been familiar to the scientific world for quite some time.[429] Coronaviruses are known to cause an extensive variety of mostly mild infections of different organ systems, for example, respiratory tract, liver, and nervous system.[429] As zoonotic diseases, coronaviruses can migrate between animal and human hosts and have a special adaptive affinity for specific environments in new hosts.[430] The potential of coronavirus transmissions to escalate to pandemic status has previously been recognized, and the related coronaviruses SARS-CoV-1 and "**m**iddle **e**astern **r**espiratory **s**yndrome" (MERS)−CoV are already associated with extensive outbreaks of epidemic proportions in various parts of the wold.[429]

SARS-CoV-2 is an enveloped RNA-virus.[429] The main binding protein to human cells is called the spike protein which is embedded within the viral envelope.[429,430] The main receptor for the spike viral protein on human cells is the angiotensin converting enzyme-2 (ACE2) which is virtually omnipresent in the human body.[430] Viral entry into the cell is facilitated by another widely expressed protein, the transmembrane protease serine 2 (TMPRSS2).[430] After cellular entry, the viral RNA is released, and an abundance of viral particles are produced, assembled, and finally expelled by inherent cellular mechanisms.[429,430] Oral tissues, salivary glands, and upper respiratory tract (nasopharynx and oropharynx) cells display a very high expression rate of ACE2 and TMPRSS2 and are suspected to function as the main viral entry port.[431-433]

SARS-CoV-2 infection: Transmission

Very early COVID-19 research identified virus-laden droplets as the main route of SARS-CoV-2 transmission.[434] The dynamic behavior of the COVID-19 pandemic led to the awareness that there might be the risk of airborne viral transmission provable by in vitro and in vivo studies.[435-438] Furthermore, infections from contaminated surfaces and fecal-oral routes have been described.[430] While the true infection risk associated with aerosols is debatable as the critical viral inoculum for infection is unknown, oral health-care providers and their assistants are considered to be at an increased risk for exposure to any infectious fluids because of close approximation to the upper aerodigestive tract where the highest viral concentrations are expected.[439] The use of aerosol-generating dental instruments may further enhance vulnerability.

In-office transmission of SARS-CoV-2 and the infections of oral health-care providers have been reported, particularly at the beginning of the SARS-CoV-2 pandemic.[440] These reports led to the mandatory use of strict hygiene protocols and the meticulous application of personal protective equipment.[441] Only a few investigations have examined in-office virus transmission as a source of COVID-19 spread. Studies reported by Estrich et al[442] and S. H. Froum and S. J. Froum[443] revealed that the number of dentists and dental assistants in the United States with proven COVID-19 infections was very low (<1%) during the follow-up period (>6 months) within the active pandemic. In-office transmissions of COVID-19 could not be proven by contact tracing.[442,443] These findings can be explained by the efficacy of enhanced hygiene protocols.

SARS-CoV-2 infection: Risk reduction

Effective infection control has always been based on meticulous adherence to hygiene protocols. COVID-19 must be considered highly contagious, although the exact mechanisms of transmission have yet to be elucidated.[429] It is unknown whether asymptomatic patients can transmit the disease through virus-laden droplets.[444-446] Furthermore, it remains unclear whether oral health-care

providers performing aerosol-generating procedures are at risk of infection during treatment of asymptomatic patients.[444-447] Our lack of understanding in this area highlights the importance of transmission-prevention algorithms.

The identification of tentative SARS-CoV-2-positive patients as a mainstay of infection control and contact tracing remains a challenge in everyday practice. Patient interviews exploring COVID-19 symptoms combined with body temperature measurements may help to identify patients with minimally symptomatic COVID-19.[448-450] The reported loss of smell and taste are significantly associated with SARS-CoV-2 positivity.[450]

The detection of asymptomatic patients may be facilitated by the prudent use of rapid antigen tests, the ubiquitous application of which is still hampered by legal and economic obstacles.[451] Despite high sensitivity and specificity, these tests will still not detect every COVID-19 patient.[452] Because of these uncertainties, conscientious implementation of hygiene protocols and correct use of personal protective equipment remain mandatory.

The practicing dentists protective gear should consists of a FFP2/N95 mask, eye protection and/or face shield, a protective gown, and gloves.[453] Training dentists and their staff in proper PPE use is compulsory.[453] There is increasing evidence that the permanent use of masks is associated with a decreased risk for SARS-CoV-2 infection in health-care personnel.[454,455] Although there are initial hints for the superior protective effects of N95 respirators, the level of evidence in this subject matter remains low.[454]

Disinfectant mouth rinses may reduce viral load in the oral cavity and oropharynx of SARS-CoV-2-positive patients and may decrease their infectivity.[456] Initial in vitro and in vivo results indicate efficacy of povidone iodine (0.5%) and chlorhexidine (0.12%) mouth rinses.[456]

Sufficient airing of the dental office to dilute potentially infectious aerosols is considered an important factor in reducing SARS-CoV-2 transmission. There is increasing evidence that mechanical air purifiers with special filters can increase dental office ventilation and reduce the aerosol burden when treating patients.[457]

Commonly available hand disinfectants in use in the majority of the dental practices were shown to be effective against SARS-CoV-2.[458] Health-care providers are urged to comply with strict hand hygiene protocols.[441]

SARS-CoV-2 infection: Clinical appearance and therapy

COVID-19 is a diverse disease. Most patients exhibit mild to moderate symptoms (cough, chills, fever) or neurological disorders (loss of taste and smell). A small percentage of patients experience rapid exacerbation of these symptoms which can culminate in severe pneumonia, respiratory distress syndrome, septic events, and death.[459] The main risk factors identified for an unfavorable course of the disease include male sex, advanced age, cardiovascular disease, and hypertension.[460] Despite major research efforts to discover drugs effective against COVID-19, none were available at the time this review was written (January 2021). The much-praised drugs hydroxychloroquine, azithromycin, and remdesivir failed to reduce mortality in large-scale randomized trials.[461] The use of steroids seems to have a beneficial effect on the course of the disease in critically ill patients.[461] Because of promising study results, the initiation of the global vaccination against COVID-19 provides hope for future control of pandemic conditions.[462]

COVID-19-associated oral lesions

Case studies reporting oral mucosal alterations, aphthous lesions, erosions, and ulcers have emerged.[338,463,464] These efflorescences are nonspecific for COVID-19 and might be associated with superinfections or immune system dysfunction in the wake of active COVID-19 disease.[338] The onset of oral mucosal lesions can be expected about 7-14 days after the first symptoms appear and usually does not require any specific treatment.[338] Pretreatment patient interrogation for COVID-19 symptoms will likely unveil affected patients. Practicing dentists without special training, equipment, and facilities for the treatment of COVID-19 patients are urged to defer appointments for these patients until after their recovery.[426] Widespread recognition of oral mucosal lesions associated with COVID-19 is unlikely. Prolonged SARS-CoV-2 shedding from the oral cavity after resolution of COVID-19 symptom cannot be assumed based on the currently available evidence.[465] Thus, it is likely safe to continue dental treatment in patients who have overcome COVID-19.

DENTAL CARIES AND CARIOLOGY

Dentists are generally the target of this annual review. However, over the past 10 to 20 years, the focus of understanding and managing dental caries has shifted from a purely dental approach to a more molecular biological approach. Here, readers will gain an appreciation for where dental caries research is going while taking a manageable bite out of the challenging topic of molecular biology as it pertains to caries.

With this goal in mind, we will start with 2 very interesting reports on quorum sensing (QS), the means of dental bacterial communication within the biofilm community. Given the impact of the COVID-19 pandemic, a detailed understanding how this biological system work seems even more meaningful. The British government recently estimated that by 2050, antimicrobial resistance could result in 10 million deaths each year and cause cumulative losses in GDP of $100 trillion (US)

worldwide.[466] That said, bacteria will remain a public health threat for the years to come. In published reports by Zhao et al[467] and Muras et al,[468] authors describe the mechanism of QS and how a better understanding of this sophisticated cell-to-cell interspecies communication could be useful in the development of new antibacterial strategies. In the first article, [467] focus primarily directed to the description of QS promotes antibiotic resistance. The reader is encouraged to read this article to gain a complete understanding of the process. In the second article, [468] Spanish researchers concentrated on the signaling molecules that may render a target of intervention and treatment. QS is a cell-to-cell chemical communication system that is density dependent. When a bacterium enters the human body, its capacity to produce a successful virulent attack is limited by the immune system of the host. With expansion, a critical bacteria population size may be achieved increasing the likelihood of a successful virulent attack. In QS, specific signaling molecules (autoinducers) are secreted allowing the bacterial community to develop coordinated social behavior starting with aggregation that leads to biofilm matrix formation.

Zhao et al[467] described how QS contributes to antibiotic resistance. Generally, there are 3 possible ways for bacteria to achieve antibiotic resistance: chemical modification, efflux pump systems, and modification of drug-targeting genes. Chemical modification involves bacterial production of enzymes that inactivate antibiotic chemical groups. Antibiotics typically enter bacteria through the cell membrane. Once internalized, the antibiotic may be effective. Antibiotic drug efflux resistance uses a cell membrane efflux pump protein to eject antibiotic molecules from the cell, thus negating its effect. Last, bacteria have evolved strategies to interfere with the antibiotics target site. By activating and deactivating portions of their DNA to modify the drug targets, bacteria reduce antibiotic binding ability rendering the drug inefficient. Using these resistance mechanisms, evolution toward "super bacteria" has occurred. As an example, *Staphylococcus aureus* (*S. aureus*) can directly degrade penicillin by producing β-lactamase and deprive methicillin of its capacity to bind cell wall mucin synthase by producing PBP2a protein. Additionally, *Pseudomonas aeruginosa* (*P. aeruginosa*) can produce different drug efflux pumps to eliminate multiple antibiotics and can modify its body shape and biofilm density to become resistant to almost all antibiotics on the market. It has also been proven that *P. aeruginosa* can obtain and transmit resistance through horizontal gene transfer from other microorganisms. Horizontal gene transfer is the passing of one or more genes through routes other than parent-to-offspring, and sometimes between different species.[469,470] Fairly common in bacteria, the phenomenon occurs by microorganism attachment leading to gene sharing. Some bacteria are capable of "collecting" genes that have leaked out from cells, incorporating the genes, and pass these foreign genes to their next generation upon reproduction.

Muras et al[468] analyzed the critical role of the QS signals AI-2, AIPs, and AHLs in several oral biofilms in vitro. Limited information is available on microbe-to-microbe interactions within multispecies oral biofilms in vivo and how QS molecules can affect equilibrium between commensal and pathogenic oral bacteria. Based on available in vitro studies, manipulation of QS to interfere with dental plaque formation is a promising strategy for the control of oral biofilm-related diseases. A secondary benefit of this strategy is that the odds of inducing bacterial resistance or tolerance are less than those when other interventions are used. However, additional studies involving multispecies-biofilm models and oral sample-derived biofilms are needed before QS compounds can be applied in oral health practice. The development of efficient treatments against the most common oral diseases will require additional targeted research.

Remineralization

Casein phosphopeptide-amorphous calcium fluoride phosphate (CPP-ACFP) is the most widely used compound to achieve the worthwhile goal of tooth remineralization. However, its efficacy has been both supported[471] and questioned,[472] and a significant amount of research has been published on this topic. Bochun et al[473] investigated the effects that a conventional glass ionomer cement (GIC), modified by the addition of CPP-ACFP, had on the composition of a caries-related biofilm. While the physical properties of the material generally remained unaltered, all experimental groups exhibited a significant increase in ion release and reduction of microhardness. Approximately 39% reduction in the bacterial biofilm volume was observed with 5% CPP-ACP group. This regulatory ability is mainly manifested in the inhibition of *Streptococcus mutans* (*S. mutans*) and the promotion of *Streptococcus gordonii* (*S. gordonii*). By displaying an anti-demineralization ability, these modified GICs theoretically lead to a reduction in the cariogenic potential of plaque and may function as a promising remineralization system possessing both enriched antimicrobial and remineralization properties.

Although CCP-ACFP is the most studied compound, the biomimetic synthesis of enamel-like apatite structures under physiological conditions is an appealing alternative to the repair of demineralized enamel with restorative material. Recent advancements have occurred in the development of biomimetic enamel remineralization systems. Some are already available for clinical use, such as the self-assembling peptide (SAP) P_{11}-4 and

nanohydroxyapatite, while others remain in development, such as the dentin phospho-protein 8DSS peptides, Leucine-rich amelogenin peptides, and poly(amidoamine) dendrimers.[474] SAP P_{11}-4 creates a biomimetic scaffold within the initial enamel caries lesion resembling the enamel peptide matrix and represents a most promising clinical product. Two very interesting reviews on SAPs were published by Mohamed et al[474] and Bonchev et al.[475] Both concluded that this material is effective in remineralizing enamel caries. Although both these systematic reviews were based primarily on in vitro studies, they provide perfect background reading for 2 additional clinical randomized controlled studies published on this topic in 2020.[476,477]

The SAP can be used in its monomeric form (P_{11}-4) or as a polymeric self-assembling peptide matrix (SAPM). In a controlled clinical trial from Kosovo, Doberdoli et al[476] compared the effectiveness of monomeric SAP P_{11}-4 in combination with fluoride varnish to SAMP for the treatment of noncavitated occlusal caries. Ninety children and adolescents were enrolled. Group 1 (test) received SAP P_{11}-4 and 2 fluoride varnish applications (baseline and day 180). Group 2 (test) received SAP P_{11}-4 at baseline and 2 SAPM home applications weekly. Finally, the control group received fluoride varnish at baseline and day 180. Caries progression was measured by laser fluorescence, Nyvad caries activity, ICDAS-II-codes, and investigator assessments. Laser fluorescence demonstrated superior results for groups 1 and 2 as values significantly decreased compared with the control group ($P<.001$). ICDAS-II codes at day 360 showed partial regression for group 1 (6.7%) and group 2 (20.0%) and partial progression for the control group (23.3%) ($P<.01$). Nyvad caries activity yielded superior caries inactivation for groups 1 and 2 compared with the control group ($P=.002$). These results demonstrated that SAP P_{11}-4, applied, either in combination with fluoride varnish or twice weekly SAPM, was a superior treatment for early caries compared with fluoride varnish alone.

In a randomized split mouth clinical trial, Bröseler et al[477] compared the efficacy of SAP P_{11}-4 to that of fluoride varnish in the treatment of early facial surface carious lesions. Participants presenting at least 2 clinically affected teeth were treated at day 0 and day 90 with P_{11}-4 (test) or fluoride varnish (control). At day 180, fluoride varnish was applied on all study lesions. Standardized pictures were made at days 0, 30, 90, 180, and 360 and blindly assessed. Hierarchical linear models (HLM) under allowance of confounders were used to compare the decrease in size between test and control groups. The visual analog scale (VAS) and Global Impression of Change Questionnaire (GICQ) were used as clinical assessments. Overall, 37 participants from age 13 to 37 years with 90 early carious lesions were involved in the research. HLM analysis showed a significant difference between test and control groups, indicating a decrease in test lesions and stabilization of control lesion size ($P=.001$). The mean size (SD) relative to baseline for test lesions progressively decreased from day 30 to day 360, while control lesions remained stable at the same time intervals. Within the limits of this study, it was shown that the size of early carious lesions treated with P_{11}-4 was significantly reduced and superior to the effects of fluoride varnish treatment alone. SAP P_{11}-4 is the first caries treatment with the potential to regenerate decayed enamel by forming de novo hydroxyapatite in the depth of early carious lesions, providing a new advanced therapeutic option for preventive dentistry.

Antimicrobial peptides

Antimicrobial peptides are usually referred to as specifically targeted antimicrobial peptides (STAMPs). These are small peptides, typically 6 to 8 amino acids, that selectively bind to specific microorganisms resulting in cell death. While waiting for the completion of clinical phase III trials on the very promising antimicrobial peptide C16G2,[478] developed in the United States, interesting data were published in 2020[479,480] on GH12, another antimicrobial peptide developed in China. Because of the multifaceted microenvironment of dental plaque, new caries-prevention strategies must ecologically modulate bacterial communities to successfully reduce cariogenic potential. This means that new strategies must focus not only on the pure elimination of all the bacteria but also on a shifting of the entire microbial community from one that is pathologic to one characterized by ecologic balance.

The antimicrobial peptide GH12 has been shown to reduce lactic acid production and exopolysaccharide synthesis from an *S. mutans* biofilm and a 3-species biofilm in vitro in studies presented in last year's AARD review. Nevertheless, the anticaries and microecological effects of GH12 must still be investigated in an in vitro complex biofilm model and in an in vivo animal caries model. Jiang et al[479] studied GH12 at a concentration of 64 mg/L (previously determined to be clinically efficacious) to determine the cariogenic properties on human biofilms in vitro, the effects on the microbiota in vivo, and the anticaries and microecological regulation effects in an animal caries model. GH12 at 64 mg/L was selected for use in subsequent in vitro and in vivo assays. When treated with GH12 at 64 mg/L, a biofilm sample from healthy volunteers maintained its microbial variety and displayed a microbial community structure similar to that of controls. In the rat model with a caries-promoting diet, GH12 at 64 mg/L regulated the microbiologic community by decreasing caries-associated bacteria and increasing commensal bacteria. Additionally, GH12 at 64 mg/L significantly reduced caries scores for sulcus and smooth surface caries in all locations. In conclusion, GH12

strongly influenced the cariogenic ability of dental plaque by reducing it and maintaining a dental plaque composition typical of healthy individuals. GH12 essentially suppressed both the incidence and gravity of dental caries in vivo.

In a second article by the same research group, the cationic amphipathic alpha-helical antimicrobial peptide GH12 also demonstrated good stability, low cytotoxicity, and excellent antibacterial effects.[480] Considering its strong antibacterial activity against the acidogenic microorganisms and its histidine-rich sequence, it was hypothesized that GH12 might show greater antimicrobial effects at an acidic pH. Therefore, this study evaluated if GH12 was activated directly by acid. In fact, GH12 possessed much lower minimal inhibitory and bactericidal concentrations against various bacteria at pH 5.5 than at pH 7.2. This result was confirmed on both planktonic *S. mutans* and *S. mutans* embedded in the biofilm; the effect was more powerful at a pH 5.5. Additionally, short-term treatment with GH12 effectively inhibited the synthesis of water-insoluble exopolysaccharides and lactic acid production of preformed *S. mutans* biofilm at pH 5.5. The authors concluded that acidic pH improved the antibacterial and antibiofilm activities of GH12, thus making it an "intelligent" anticaries agent with improved targeting ability in a cariogenic acidic microenvironment.

Caries removal strategies

A systematic review of RCTs focused on the efficacy of 3 caries-removal techniques: complete caries removal (CCR), selective caries removal (SCR), and stepwise caries removal (SWR).[481] Ten articles describing 8 studies were included in the review. Possible outcomes were pulp exposure, endoperiodontal complication, or restorative failure. The overall risk of pulp exposure was significantly reduced with SCR and SWR compared with CCR. However, the risk of endoperiodontal complications appeared similar across all 3 methods. The authors concluded that RCTs with lower risk of bias, higher power, and longer follow-up are required to identify the best caries-removal techniques for deep carious lesions in vital teeth.

A similar systematic review was published by Barros et al.[482] Out of more than 2000 articles initially identified, only 10 could be used in the review, 4 of which were meta-analyses. The purpose of the systematic review was to compare selective removal, stepwise removal, and nonselective removal of carious tissue in permanent teeth. Only controlled clinical trials and cohort studies involving patients with dental caries in permanent teeth were included. The test group included patients undergoing selective removal of carious tissues, while controls included patients undergoing nonselective removal and/or stepwise carious tissue removal. The primary outcome considered was preservation of pulp health as measured clinically and radiographically. The quality of restorative treatment, pulp exposure, dentine deposition, and microbiologic status were also assessed.

The meta-analysis indicated that when pulp health is the goal, selective removal of carious tissues is the treatment of choice. Secondary outcomes, such as microbiologic status, quality of restorative treatment, and deposition of dentin, could not differentiate treatments. It was concluded that pulp exposure occurs more frequently with nonselective removal of carious tissue than selective removal. Furthermore, one article in the review concluded that multiple surface restorations, glass ionomer restorations, and poor oral hygiene are risk factors for failure regardless of caries-removal technique. Two noteworthy considerations emerged. In previous systematic reviews, no differentiation was made between deciduous and permanent teeth, even though it is well-known that deciduous teeth have greater potential for regeneration and conclusions here should not be generalized to permanent teeth. Additionally, this was the first review to incorporate nonselective caries removal and stepwise excavation treatments in the same group (the control group) because they are considered 1- and 2-step nonselective caries removal techniques.

A problem frequently encountered in caries-removal studies is the inability to standardize the degree of caries excavation making direct comparisons between teeth treated quite challenging. In addition, it is uncertain if leaving carious dentin is advantageous or harmful. Does remaining caries result in less pulp exposure and fewer symptoms, or is it more closely associated with increased risk of restorative failure?

In the included studies, follow-ups ranged from 3 months to 5 years, making comparison of pulp health maintenance impossible. It was also not possible to carry out a complete meta-analysis of microbiologic data in this review because carious dentin was assessed at different times. Despite methodological differences, 2 studies reported reduced microbial loads for all groups evaluated, without statistical differences between groups of selective removal, nonselective removal, or stepwise excavation of carious tissues.

Selective removal and stepwise excavation presented similar results with respect to the maintenance of pulp health. Selective removal has several advantages, such as maintenance of part of the affected dentin, reduced risk of pulp exposure, no need for cavity reopening, less time wasted, reduction in material used, and no need for the patient to return. Disinfecting the cavity with chlorhexidine before applying the restorative material is important in reducing the bacterial contamination.[483]

Compared with more invasive caries-removal techniques, the systematic review indicates advantages of selective caries removal to be cost-effectiveness and

improved maintenance of teeth with deep caries. All included articles confirmed the safety and efficacy associated with selective caries removal for permanent teeth because of reduced pulp exposure. However, the authors emphasized that the selective removal procedure is not a popular choice among clinicians. Literature shows that many clinicians prefer more aggressive techniques, even if they are associated with greater risk of pulpal exposure, than more evidence-based carious tissue removal strategies. Readers are encouraged to consider these conclusions when clinical circumstances dictate. Selective caries removal should be considered for all permanent teeth because it is performed in a single appointment and preserves a greater volume of dental tissue, including the dental pulp.

Probiotics

Probiotics are an effective therapeutic agent for dental diseases, and several interesting aticles were published in 2020 on this topic.[484-488] Probiotics are live microorganisms that, once administered in appropriate quantities, confer health benefits on the host. Probiotics may also be used as alternative or adjuvant therapeutic agents for numerous diseases. They positively influence the microbial composition of the gastrointestinal tract, directly counteract dental plaque biofilm formation, and improve the host's immune system against cariogenic microbiota. Although it is not a systematic review, an interesting review article by Sivamaruthi et al[489] discusses the roles of probiotics in dentistry for children and adult populations, indicates possible mechanisms of action, and discusses anticaries effects.

In children, the following probiotic interventions have been reported to be effective in reducing *S. mutans* counts:

- consumption of milk containing *Lactobacillus rhamnosus* (*L. rhamnosus*) 5 d/wk for 7 months;
- consumption of tablets containing 3 microorganisms including *Bifidobacterium longum*, *Saccharomyces cerevisiae*, and *L. rhamnosus*, or a single organism *Bacillus coagulans*, both administered for 14 days;
- supplementation of *Streptococcus salivarius* M18 (*S. salivarius*) for 3 months;
- probiotic lozenges of *L. reuteri* for 28 days, or chewing tablet containing *Streptococcus uberis* KJ2, *Streptococcus oralis* KJ3, *Streptococcus rattus* JH145 for 30 days;
- supplementation of *L. reuteri* ATCC 55730 during the last months of gestation for mothers and 1 year for newborns;
- probiotic milk containing *L. rhamnosus* LB21 and fluoride for 21 months;
- supplementation of *S. salivarius* M18 tablet for 90 days;
- intervention with 150 ml of probiotic milk containing *L. rhamnosus* SP1 for 40 weeks;
- consumption of *Lactobacillus casei* Shirota (*L. casei*) in milk formulation for 7 days; and
- milk containing *Lactobacillus paracasei* SD1 (*L. paracasei*).

The following probiotic interventions have been reported to reduce *S. mutans* counts in adults:

- 3-week consumption of probiotic cheese containing *L. rhamnosus* LC705;
- the consumption of probiotic yogurt containing *Bifidobacterium* DN-173010 for 2 weeks;
- 4-week consumption of fermented milk containing *L. casei* Shirota;
- consumption of probiotic tablets containing *L. paracasei* GMNL-33 3 times/d for 2 weeks;
- consumption of condensed milk containing *L. paracasei* SD1 for 4 weeks; and
- *S. salivarius* WB21 or *S. salivarius* T12711 tablets for 2 weeks.

The mechanisms behind the positive effect of probiotics on caries and dental plaque are exclusive to each strain and are the consequence of a combination of actions. For example, the probiotic *Streptococcus* A12 strain competes with the cariogenic *S. mutans* by raising the plaque pH through the arginolytic pathway, colonizing tooth surfaces, and producing challisin-like protease, a specific enzyme that can interfere with the bacteriocin production of *S. mutans*. Analogously, *Streptococcus dentisani* produce bacteriocin that both directly kills the cariogenic bacteria and buffers the pH of dental plaque through the arginolytic pathway.

S. salivarius, one the most frequently used probiotic microorganisms, competes with cariogenic bacteria by colonizing soft tissue. The bacteriocin of *S. salivarius* M18 inhibits dental plaque population. *S. salivarius* M18 also produces urease and dextranase enzymes, which buffer the acidity of saliva and reduce plaque formation.

Overall, the literature implies that the mechanisms of anticaries probiotic action are related to 3 main factors, including antagonism for colonization in the mouth, neutralization of the acidity of saliva and plaque pH, and the direct action of bacteriocins and other enzymes (dextranase and urease) on cariogenic bacteria.

Manmontri et al[490] published a multicenter controlled clinical trial investigating the effects of the probiotic *L. paracasei* SD1 on quantities of *S. mutans* in saliva and plaque samples from preschool children. The probiotic was administered as a milk powder with a placebo provided to a control group. The 487 participants participating in this study were divided into 3 groups: Group I

received placebo milk daily, group II was given probiotic milk daily, and group III consumed probiotic 3 times per week. DNA analysis was performed to quantify the presence of bacteria after the treatment, but only 268 children provided adequate quantity of saliva for quantitative PCR analysis. The results indicated that the quantity of *S. mutans* significantly decreased in groups II and III compared with that in group I, while the total amount of *Lactobacilli* was significantly increased. There was no difference in quantities of *S. mutans* or total *Lactobacilli* when comparing groups II and III at any period. A clinically substantial findings were that changes in the quantities of *S. mutans* and total *Lactobacilli* lasted for 6 months after discontinuation of saliva and blood sampling in the preschool children included in the study.

Another interesting article was published by de Alvarenga et al[491] on the effect of the probiotic *L. paracasei* 28.4 on *S. mutans*. This probiotic was delivered in a gellan hydrogel form to inhibit *S. mutans* in both planktonic and biofilm states. The investigators were interested to test the probiotic's ability to interfere with extracellular polysaccharides (EPS) production and to alter the gene expression of several cariogenic virulence factors. *L. paracasei* 28.4 strain was isolated from a caries-free individual, incorporated in a 3 gellan hydrogel, and tested on *S. mutans*. Initially, the preventive effects of probiotic-impregnated gellan gum formulations were evaluated on *S. mutans* growth in planktonic cultures. In these assays, 3 different formulations of progressively increasing concertation of probiotics *L. paracasei* 28.4 (0.5%, 0.75%, and 0.1%) were tested on different *S. mutans* strains, including a reference strain (UA 159) and 5 clinical strains. Pretreatment with the probiotic formulations produced complete inhibition of *S. mutans* growth, independent of the gellan concentrations analyzed. In general, the final data indicated that gellan gum formulations were capable of releasing *L. paracasei* cells into the media that consequently prevented *S. mutans* growth.

To verify a possible influence of acids produced by *Lactobacillus* on *S. mutans* growth, authors measured pH values of the culture medium. Findings indicated that after pretreatment with *Lactobacillus* formulations at 0.75% and 1% of gellan, the pH value remained stable compared with the control group (pH=7.0). These outcomes show that pH variation did not interfere with the inhibitory activity of probiotic formulation on *S. mutans* growth.

The next step was to evaluate effects on *S. mutans* biofilms, an important consideration since dental caries can be associated with the biofilm state. A probiotic formulation containing 1% gellan gum was selected for the biofilms test because of its pH stability and gel-like consistency, which facilitates application in the oral cavity. A significant decrease of *S. mutans* cells in biofilms was observed for all 3 strains after pretreatment with the probiotic-impregnated gellan. Pretreatment with *L. paracasei* 28.4 gellan formulation caused a 68.8% (at 4 hours) and 71.3% (at 24 hours) reduction of the *S. mutans* biofilm biomass. After observing that *L. paracasei* 28.4 released from gellan inhibited *S. mutans* in both planktonic and biofilm states, it was also observed to be capable of reducing *S. mutans* EPS by 75% at 4 hours and 85% at 24 hours. Finally, authors reported that the expression of *S. mutans* genes, important for adhesion, biofilm formation, and polysaccharide production, was downregulated (6.6-fold degrease) by *L. paracasei* 28.4.

This article was selected for review to emphasize that the mechanisms of probiotics function are varied. The literature indicates that the most effective probiotics for preventing pathogen growth must both occupy the same ecological position as the pathogens and produce compounds that directly antagonize the pathogen. As this study demonstrated, bacterial species with a high likelihood of outcompeting *S. mutans* are already present in the oral cavity. Therefore, probiotics from the oral cavities of healthy individuals can effectively antagonize cariogenic species such as *S. mutans*. As EPS in *S. mutans* incorporates important virulence factors involved in adhesion, biofilm formation, and the suppression of pathogenicity, it is indicated as an important means of controlling dental caries. The control group in this study showed high production of EPS at 24 hours. After pretreatment with *L. paracasei* 28.4, there was a decrease of 85% in the production of EPS with simultaneous downregulation of several genes involved in biofilm formation and virulence.

Within the limitations of the study, gellan gum proved to be an encouraging biomaterial for encapsulation of probiotic cells maintaining the viability of *L. paracasei* 28.4 in suitable quantities to impart antimicrobial effects on *S. mutans*. Compared with probiotic suspensions, the use of gellan gum formulations has the advantages of being a topical agent, easy to store, and capacity for prolonged exposure to microbial cells within the oral cavity.

Additional well-designed and rigorous research was authored by Javid et al[492] who addressed the effectiveness of a probiotic yogurt that contains *Bifidobacterium lactis* Bb12 (*B. lactis* Bb12) on salivary *S. mutans* and *Lactobacilli* in students with early-stage dental caries. In this double-blind randomized placebo-controlled clinical trial, 66 students (age 18–30 years) with early-stage dental caries were selected and randomly assigned to 2 groups: The intervention group received 300 g/d of probiotic yogurt for 2 weeks, and the control group received 300 g/d of regular yogurt for 2 weeks. Saliva samples were collected before and after yogurt consumption. Results demonstrated that the consumption of the probiotic yogurt containing *B. lactis* Bb12 significantly reduced *S. mutans* counts in saliva. The authors

concluded that probiotic yogurt may prevent dental caries progression by reducing populations of *S. mutans* and *Lactobacilli* (cariogenic bacteria) in saliva. This study had several strengths, including analysis of unstimulated saliva which is a more sensitive indicator than the analysis of stimulated saliva. The study was also adequately powered to confidently identify mean differences in bacteria numbers between groups. However, as indicated by the authors, there were few limitations. First, the small sample size used hinders the extension of study conclusion to other populations. Second, the duration of the study was relatively short. Third, the effects of probiotic microorganisms, after a period without probiotic consumption, were not considered. Obviously, more clinical trials of longer duration and greater sample size should be conducted on high-caries-risk subjects to assess the efficacy of these alternative probiotic caries-preventive therapies. Finally, future research into the effectiveness of probiotic products should consider only the saliva-buffering capacity, which was not the case in this research report.

Several oral and systemic diseases, such as periodontitis, dental caries, recurrent endodontic infections, and even head and neck cancer (HNC), may result from an imbalance in the oral microbiome. While antibiotics may help in controlling the dysbiosis, they can also lead to superinfections. Consequently, new approaches must be found to address this shortcoming. One approach involves the use of bacteriocins and probiotics.

Recently, the possible use of nisin bacteriocin and nisin probiotic in biomedical applications was proposed.[493] Nisin is a lantibiotic (a class I bacteriocin) produced by the gram-positive *Lactococcus lactis* (*L. lactis*) active against both gram-positive and gram-negative bacteria, including *S. aureus*, *Listeria monocytogenes*, *F. nucleatum*, *P. gingivalis*, and *T. denticola*. Nisin has been used successfully for infections associated with drug-resistant pathogens, gastrointestinal and respiratory tract infections, skin and soft-tissue infections, mastitis, HNC, and other oral diseases tested by using both in vitro and in vivo models.[494] Studies support the use of nisin as an antitumor agent for HNC and in managing biofilms that contain disease-associated bacteria.[495] Nisin has been shown to be effective against both pathogenic bacteria in a planktonic state and bacteria present in oral biofilms associated with caries, periodontal disease, and persistent endodontic infections. However, nisin has also been shown to be innocuous to human cells. Although very promising results have been obtained with nisin, a nisin-producing probiotic has not been examined for effectiveness on biofilms related to oral diseases. Therefore, Radaic et al[496] reported on an application of nisin, a very promising antimicrobial agent, as probiotic in dentistry. The purpose of this investigation was to identify the capacity of the nisin-producing probiotic *L. lactis* to stimulate the formation of healthy oral biofilms that counteract disease-associated oral biofilms.

We know that the bacterial composition of the oral microbiome distinctly shifts when oral disease is present. Bacteria that have been associated with this shift include *F. nucleatum*, *T. forsythia*, *Haemophilus influenzae*, and *Klebsiella pneumoniae*. Data suggest that nisin and a nisin probiotic can decrease the presence of these pathogens to control levels, while simultaneously promoting commensal bacteria, such as *Neisseria flava*. Hence, nisin-producing probiotic *L. lactis* and its purified bacteriocin (nisin) can prevent and disrupt oral biofilms, reduce the oral pathogens within oral biofilms, and return the diversity of oral biofilms to physiological levels. Therefore, both these agents may be considered for the indirect prevention of caries because they do not directly intervene in caries formation, but they promote healthier oral biofilms that improve general oral health.

Silver and silver diamine fluoride

The use of silver as an antiseptic and antimicrobial agent has been known since 600 B.C.E. It has been used in dentistry for the treatment of dental caries since the mid-19th century. Today, the use of silver in dentistry, beside dental amalgam, is mainly in the form of silver diamine fluoride (SDF). SDF is a liquid chemical agent, usually transparent (tinted blue in the US the commercial market), made up of silver, ammonia, and fluoride. Highly effective formulations of SDF are formulated at 38% concentration with 44 800 ppm fluoride ions. If placed on carious hard tissue, a sequence of chemical reactions occur that lead to (1) blockage of dentin tubules, (2) reduced dentin sensitivity, (3) arrested caries formation, (4) bacterial death, (5) tooth structure remineralization, and (6) inhibited dentinal collagen degradation. One adverse side effect of SDF application is the dark staining of carious lesions on both enamel and dentin surfaces. Sound enamel does not stain. Therefore, this may be useful as a caries-detection procedure. The use of potassium iodide (KI), after SDF application, is reported to reduce this darkening side effect, although not all the available research agrees on this point.[497]

For many years, SDF has been used in parts of the world (particularly in Japan since 1960) to manage both tooth sensitivity and dental caries. It was not until 2014 the SDF was generally introduced in the United States. Because of its recent rise in popularity, SDF is the object of a great number of dental investigations and subsequent publications.

Traditionally, dental caries has been treated by using a "drill and fill" approach involving complete carious tissue removal to sound enamel and dentine and placement of restorative material. This invasive approach is no longer recommended. Decayed tooth tissue does not always require removal to halt caries progression. A minimally

invasive approach can be a more successful strategy in the long term. Stepwise carious tissue removal, selective caries removal, and the Hall Technique are new techniques recommended in most clinical situations, rather than the classic total caries removal approach.[498] Additionally, it is not always necessary to restore the excavated tooth structure. A nonrestorative cavity control (NRCC) option may be indicated for managing excavated lesions, especially for deciduous teeth.[499] The advantages of SDF in clinical dentistry are its ease of use, possible application without local anesthetic, and virtually instantaneous results. It also facilitates delayed definitive treatment for patients that have difficulty undergoing restorative treatment because of age, anxiety, or financial restrictions.[500]

The clinical efficacy of SDF has been widely documented, but its mechanism of action remains only partly understood. One theory is that silver ions interfere with bacterial proteins and DNA preventing cell wall synthesis, bacterial DNA synthesis, and mitochondrial failure. These bactericidal properties lead to disruption of the biofilm. Compared with untreated dentin surfaces, dentin surfaces demineralized by caries and treated with SDF are associated with only minimal cariogenic species growth.[501]

A second theory for the mechanism of SDF action suggests that remineralization of the demineralized inorganic portion of the tooth is supported by the fluoride ions in SDF and fluorapatite. Silver phosphate and calcium fluoride are subsequently formed, resulting in surfaces more resistant to acid dissolution.

Finally, a third theory indicates that silver precipitants and calcium fluoride reduce the patency of dentinal tubules. In doing so, SDF may inhibit matrix metalloproteinases and cathepsins, the enzymes responsible for collagen degradation within dentin when caries is progressing.

SDF has been reported to reduce *S. mutans* counts.[502] Therefore, microorganisms killed by silver may function in biofilm disruption through a "zombie effect," previously described also for chlorhexidine, whereby local bacteria are killed on contact with silver-affected bacteria.[498,503]

SDF may be used as a single targeted treatment to arrest caries, to manage tooth hypersensitivity, or as an adjunct to another clinical procedures. Atraumatic restorative treatment (ART) can be performed as silver-modified ART (SMART). The Hall technique is sometimes referred to as SMART Hall. This can be achieved in 2 ways: (1) by applying SDF immediately before restoration placement, or (2) by waiting several days or weeks after SDF application for caries progression to arrest before placing restorative material. In both approaches, SDF does not affect the bond strength of composite resin restorations but may affect the bond strength of glass ionomer restorations.[504-509]

Arginine

Arginine is a semi-essential amino acid available as salivary substrates. It is metabolized by the arginolytic bacteria, through the arginine deiminase system (ADS), into substances able to promote enamel fluoride uptake into demineralized enamel lesions and to stimulate an alkaline environment.[510] The caries-preventive effect of arginine has been compared in multiple in vitro studies and randomized clinical trials and has been further analyzed in systematic reviews and meta-analysis. Arginine-based products remain "preclinical" even though extensive data are available supporting its clinical value.

Bijle et al[511] published a scoping review on arginine to identify the extent, range, and type of evidence on the role of arginine and arginine formulations in dental caries prevention. Readers are encouraged to thoroughly review this publication to better understand where the profession currently stands with arginine research and development. A very useful set of tables summarize all available articles on the topic, with synthesized conclusions.

Commercial dentifrices currently available for caries prevention are limited to 1.5% arginine-fluoride toothpaste, 8% arginine-fluoride toothpaste, and 1.5% arginine-zinc-fluoride toothpaste. After reviewing available English publication, authors drew the following conclusions: (1) Available evidence indicates both high risk of bias and (2) high-quality clinical trials are needed for all commercial formulations, and (3) the role of L-arginine monohydrochloride in caries prevention can be enhanced by incorporating it in self-deliverable and professionally applied products. The authors indicated, "This scoping review clearly represents an illustration of how results of primary studies and narrative reviews can be contrasting to systematic reviews, which include rigorous evidence synthesis. Also, the present review emphasizes the need of undertaking further systematic reviews based on new evidence that has not been included in previous systematic reviews." Two additional articles on arginine address associations of current products with other compounds to improve clinical efficacy. It has been suggested that arginine be incorporated into fluoride products (particularly a mixture of 2% L-arginine with 5% NaF varnish) to improve physical properties, enhance fluoride uptake and remineralization potential, and render a stable matrix with higher fluoride/arginine long-term release compared with controls.[511,512]

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