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ANNUAL 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

This comprehensive review of the 2019 restorative dental literature is offered to inform busy dentists regarding remarkable publications and noteworthy progress made in the profession. Developed by the Scientific Investigation Committee of the American Academy of Restorative Dentistry, each author brings discipline-specific expertise to 1 of 8 sections of the report: (1) prosthodontics; (2) periodontics, alveolar bone, and peri-implant tissues; (3) implant dentistry; (4) dental materials and therapeutics; (5) occlusion and temporomandibular disorders; (6) sleep-related breathing disorders; (7) oral medicine and oral and maxillofacial surgery; and (8) dental caries and cariology. The report targets important information likely to influence day-to-day dental treatment decisions. Each review is not intended to stand alone but to update interested readers so that they may visit source material when greater detail is desired. As the profession moves toward evidence-based clinical decision-making, an incredible volume of potentially valuable dental literature continues to increase. It is the intention of this review and its authors to provide assistance in negotiating the extensive dental literature published in 2019. It is our hope that readers find this work useful in the clinical management of dental patients. (J Prosthet Dent 2020;124:274-349)

PROSTHODONTICS

Again in 2019, the professional literature pertinent to the clinical practice of prosthodontics was substantial. Carefully selected articles from well over 50 professional journals were searched to develop this review, which is intended to provide readers with a practical clinical update in prosthodontics and restorative dentistry. For convenience, this extensive subject has been divided into 8 more 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. 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 commentary on all of this

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bulk of material, it is listed here for the reader's convenience: restorative dentistry clinical descriptions,[1-19] dental caries,[20] dental biomechanics,[21,22] bruxism,[23-27] conventional complete dentures,[28-31] conventional fixed prosthodontics,[32-39] conventional removable partial dentures,[40] digital dentistry,[41-45] dental esthetics,[46-50] evidence-based dentistry and research methods,[51-54] general topics in implant dentistry,[55,56] general topics in prosthodontics,[57-63] geriatrics,[64] implant fixed prosthodontics,[65-74] implant occlusion,[75] implant removable prosthodontics,[76-78] implant surgery,[79-92] implant treatment planning,[93-107] implant complications,[108-111] impressions,[112] mastication,[113] material science,[114-124] maxillofacial prosthetics,[125] oncology,[126] osseointegration,[110,127-130] pharmacology,[131] pathology,[132-135] periimplant tissues,[136-138] periodontics and restorative dentistry,[139-142] endodontics and restorative dentistry,[143,144] pediatric restorative dentistry,[145,146] forensic dentistry,[147] prosthodontic practice,[148,149] quality of life,[150] radiology,[151] statistics,[152-154] dental wear loss,[155-157] and xerostomia.[158]

General prosthodontic considerations

At the very foundation of prosthodontics is diagnosis and treatment of patients that are missing teeth. It is expected that the functional and esthetic deficits associated with missing teeth will be improved upon their replacement. Although expected, this improvement may not always be achieved. To quantify patient-reported effects of oral prosthodontics rehabilitation and to investigate associated aspects, Øzhayat and Gotfredsen[159] applied several methods to a dental school cohort.

Patients treated between 2013 and 2018 with either fixed partial dentures (FPDs; n=72) or removable partial dentures (RPDs; n=58) by students at the University of Copenhagen were enrolled. Patients affected by acute pain, significant periodontal or caries disease, or temporomandibular joint disorders were excluded. Patients in need of implant-assisted complete denture therapy were also excluded. The clinical variables recorded were sex, age, prosthodontic treatment received, number of teeth replaced, and position of prostheses (esthetic zone versus masticatory zone).

Patient-reported effect of treatment on oral health related quality of life (OHRQoL) was assessed before and 1-4 months after treatment. Measurements involved the use of the Oral Health Impact Profile 14 (OHIP-14) and global oral ratings (GOR) of esthetics, mastication, and comfort before and after treatment and global transition judgements (GTJ) of esthetics, mastication, and comfort after treatment.

Results indicated that both FPDs and RPDs significantly improved OHIP-14 scores and that most participants reported good effect of treatment. While using the OHIP-14 and GOR measures, the number of participants with good effect of treatment was found to be greater in the RPD group than that in the FPD group. However, while using the GTJ measure, the effect of treatment was higher in the FPD group. Multiple regression analyses showed the association between poor pretreatment mastication ability and good effect of treatment measured by the OHIP-14 and GOR. For the RPD group, poor effect of treatment in mastication ability was associated with poor effect of treatment in comfort as measured by GTJ. Functional problems after treatment were associated with no or poor effect of treatment.

The authors concluded that a large number of patients reported good effect of oral rehabilitation with fixed or removable partial prostheses. Masticatory aspects highly influence the patient-reported effect of treatment, and treatment with an RPD was associated with poor effect in oral comfort.

Currently, most digital design software programs in dentistry includes virtual articulation designed to replicate the customary functions of more familiar mechanical articulators. Similar to mechanical articulators, virtual articulators will accept input of patient-specific determinants of mandibular movement and maxillomandibular relationships. For many, virtual and mechanical articulators are assumed to be identical with respect to the output of trueness and precision. However, independent verification is lacking. Hsu et al[160] reported on such a comparison hypothesizing that there is no significant difference in the trueness and precision of prostheses designed by using virtual or mechanical articulators when incisal pin opening is altered and sagittal condylar inclination is varied.

Maxillary and mandibular dental models with fiducial markers were mounted in a mechanical articulator. Teeth were adjusted to permit guidance solely by condylar housings and the incisal pin/table. Analog relationships were scanned, and replicate virtual articulation was generated (Dental Designer Software v17.2.1; 3Shape A/S). Pattern resin, eccentric, interocclusal records (mandibular right central incisor to first molar area) were made in the mechanical articulator by using 3 sagittal condylar inclinations (10, 30, and 45 degrees; n=12/inclination) and at 3 incisal pin openings (2, 5, and 10 mm; n=12/opening) keeping all other articulator settings constant. Acrylic resin records and models were immediately scanned and saved. A fixed partial denture (mandibular right central incisor to first molar) was designed on the virtual articulator (set to identical parameters) by using virtual movements to sculpt the design. Design files were saved. Mechanical and virtual file were overlaid and aligned, and interocclusal separation was measured at an incisor location (mesiolabioincisal point angle maxillary right central incisor) and a molar location (mesiobuccoocclusal point angle maxillary right first molar).

When an incisal pin opening was altered, there was no significant difference in trueness (F=0.202; *P*=.37) or precision (F=3.134; *P*=.09), except at 5-mm incisal opening, and only at the incisor measurement point (F=15.134, *P*<.001). These differences were less than 100 μm. When sagittal condylar inclination was altered, there was no significant difference (F=3.624, *P*>.05) between virtual and mechanical articulators in trueness for 5 of the 6 measurements (F=3.624, *P*=.07) or for all precision measurements (F=3.529, *P*=.07). The single significantly different trueness measurement (F=9.237, *P*=.006) occurred at 10 degrees and was less than 100 μm.

Eccentric movements on the virtual articulator were generally as true and precise as to the mechanical articulator it sought to replicate. When deviations were noted, they measured less than 100 μm and were judged clinically irrelevant. The authors indicated that, although any discrepancy between mechanical and virtual articulation may be unacceptable, the resultant error for either system remains within the range of correction at the time of placement. It is noteworthy that the trueness and precision of other adjustable settings on the mechanical articulator investigated remain untested. Additionally, other articulator systems and their associated settings remain untested as well. Despite basic movement results presented here, complete reliance on virtual articulation, particularly with complex prosthodontic rehabilitations, is likely unwarranted at this time.

Resolution of temporomandibular dysfunction may be required before complex prosthodontic rehabilitation and often involves the use of occlusal devices during clinical management. Historically, polymethylmethacrylate (PMMA)-based resins have been used to manufacture occlusal devices. PMMA material properties and ease of manipulation have come to represent the gold standard. More recently, computer-aided design and computer-aided manufacturing (CAD-CAM) and additive manufacturing process have gained popularity but lack sufficient scientific validation for clinical use. Prpic et al[161] conducted an in vitro study to investigate critical properties (flexural strength and surface hardness) of different materials and technologies used to produce modern occlusal devices.

One hundred forty rectangular specimens were fabricated from 2 3D-printed light-activated materials (a nonacrylic and an acrylic resin), 2 CAD-CAM materials (a PMMA and a crosslinked polyamide), and 3 conventional chemical-activated PMMA resins according to ISO 20795-1:2013. Flexural strength and surface hardness were determined for 10 specimens of each material by using the 3-point bend test and the Brinell method.

Results indicated surface hardness values ranging from 28.5 ±2.5 MPa to 116.2 ±1.6 MPa. During flexural testing, neither the polyamide CAD-CAM nor the nonacrylic 3D printed specimens fractured during loading within possible penetrant translation. Flexural strengths for other groups ranged from 75.0 ±12.0 MPa to 104.9 ±6.2 MPa. Significant differences including higher flexural strengths for the CAD-CAM materials than for chemical-activated resins (*P*=.042) and 3D printed materials (*P*=.011) and lower surface hardness values for 3D printing materials than for chemical-activated resins (*P*<.001) and CAD-CAM materials (*P*=.004) were identified.

The authors concluded that mechanical properties differed significantly among occlusal device materials investigated and depended more on the material than the manufacturing technology. In general, acrylic resins were less flexible than polyamide and nonacrylic 3D printed materials but demonstrated greater surface hardness values. Clinicians must consider these mechanical property differences when fabricating occlusal devices, particularly for patients with high occlusal load generation or bruxism.

Conventional complete dentures

Complete denture (CD) retention is critical to prosthesis acceptance and successful patient function. Surface tension associated with a thin layer of saliva interposed between the denture base and supporting tissues contributes to effective prosthesis retention. The quality and quantity of saliva play a significant role in retention of adequately constructed dentures. Saliva of suboptimal quality or quantity is likely to adversely influence denture retention.

Patients affected by xerostomia are at risk of suboptimal denture retention and stability. A denture adhesive that performs well in a relatively dry environment is desirable. Ohno et al[162] conducted an in vitro investigation to evaluate the properties of a newly developed denture adhesive for patients with dry mouth and compare these properties with those of a currently available adhesive and oral moisturizing agent.

Authors developed a new gel-type denture adhesive (NDA), specifically for patients with xerostomia, with the following objectives: improved retention force, ease of dispensing, ease of cleanup, adequate moisturizing capacity, and absence of flavor. In vitro comparisons between NDA and New Poligrip (NP; GlaxoSmithKline) and Biotene Oralbalance Gel (BT; GlaxoSmithKline) were conducted to assess retention force, resistance to squeezing from a tube or syringe, and ease of removal.

In accordance with ISO10873:2010, retention force was measured for circular denture base specimens (Ø22×1 mm) under the following conditions: dry specimens (severe dry mouth model), 1-minute water exposure specimens (moderate dry mouth model), and 10-minute water exposure specimens (normal condition model). The specimens were loaded (9.8 ±0.2 N) and separated (5 mm/min crosshead speed) in a test frame.

The maximum value on the pressure-sensitive axis was recorded, and force per unit area represented adhesive strength. The resistance to squeezing was evaluated by pushing the specimens out of syringes, while the ease of removal was evaluated by measuring the time required to wash the material from a polymethylmethacrylate plate.

In the severe dry mouth model, the newly developed adhesive (NDA) resulted in greater retention force than NP and BT. Moreover, the resistance to squeezing was significantly less for NDA than that for NP, indicating the new material's relative ease of dispensing from a tube. Both BT and NDA were easier to remove from a denture base resin surface than NP, indicating good relative cleansability. Given these results, the authors concluded that the newly developed denture adhesive is suitable for use in patients with xerostomia.

The choice of the most appropriate occlusal scheme for conventional CDs remains controversial with respect to patient satisfaction, biological benefits, degree of residual ridge resorption, denture stability and retention, force transmission to the denture foundation, masticatory muscle activity, temporomandibular joint health, maximum occlusal force generation, and masticatory function. To investigate this controversy, Pero et al[163] carried out a crossover clinical trial evaluating the masticatory function and maximum occlusal force of edentulous participants wearing conventional CDs with bilateral balanced occlusion (BBO) and canine guidance (CG), with normal (NR) and resorbed mandibular ridges (RR).

Thirty edentulous patients (mean age 71.5 years) seeking treatment with maxillary and mandibular conventional CDs completed the trial. Inclusion criteria included female sex, mentally receptive, older than 45 years, edentulous for at least 1 year, previous denture experienced, good understanding of the common language, normal or resorbed mandibular ridge, and normal salivary flow (unstimulated saliva $\geq$0.3 mL/min). Exclusion criteria included debilitating systemic conditions, pathological alterations of the alveolar ridges, parafunctional habits, self-reported pain, and movement limitations that may interfere with testing. Participants received 2 sets of new CDs, one incorporating BBO (33-degree cusp angle) and the other CG. After a period of adaptation, each new denture was worn for 30 days. Denture stability, mandibular denture-bearing area, soft-tissue resiliency, and muscle attachment where evaluated, and participants were subsequently assigned to NR and RR groups. Masticatory function was measured by using masticatory performance (sieving method; 5 almonds at 20 cycles); masticatory ability—questionnaire method, with visual analog scale (VAS)—and maximum occlusal force (gnathodynamometer; right and left first molar regions for 5 seconds). Data were analyzed by using repeated-measure ANOVA or Generalized Estimating Equations (GEEs) (α=.05).

The results demonstrated that the height of mandibular ridge was significant for the masticatory performance (NR>RR, P<.001) regardless of occlusion. The occlusion had a significant effect on maximum occlusal force (CG>BBO, P=.021) but was not significant for the masticatory performance (P=.156). The mandibular ridge height did not influence occlusal force (P=.060). The interaction of the factors (occlusion+ridge) was not significant for masticatory performance (P=.184) or occlusal force (P=.236). VAS scores showed a significant effect of the mandibular ridge on masticating lettuce, resulting in greater ease (P=.016) and mastication quality (P=.028) for participants with resorbed ridges. Participants with CG reported greater ease of masticating fresh bread and beef while indicating greater mastication quality for raw carrots. Participants with CG and normal ridges exhibited the highest overall mastication ability, as compared with BBO (P<.05).

The authors suggested that the CG occlusal scheme for conventional CDs represented a reasonable alternative to the classical BBO scheme. In this crossover clinical trial, CG occlusion was associated with significant occlusal force generation and the participants' self-perception of mastication and occlusal force. The height of the mandibular ridge influenced the general ability to masticate with CG and improved the masticatory performance, both for participants with normal mandibular ridges. Findings presented here support the notion that CG complete denture occlusion, as an alternative to BBO, is clinically acceptable requiring less complicated clinical and laboratory processes without compromising patient function.

Long-term, unsupervised wear of a conventional maxillary CD opposing a bilateral, distal extension, removable partial denture may result in aggressive maxillary anterior residual ridge resorption (RRR), as described by Kelly[164] almost 50 years ago. This condition became known as combination syndrome. It has been suggested that placement of dental implants in the anterior mandible restored with an implant-retained overdenture (IRO) may present similar loading conditions to the maxilla potentially leading to combination syndrome over the long run. To objectively quantify maxillary anterior RRR given this clinical scenario, Alsrouji et al[165] applied 3D cone beam computed tomography (CBCT) and quantitative software program to investigate bone loss over time.

For this clinical trial, 2 patient groups were developed. The test patients (n=18, 8 men, 10 women, age 52-79 years) were provided mandibular IROs on 2 interforaminal implants opposing maxillary conventional CDs, while control patients (n=4, all men, age 54-70 years) were provided conventional CDs. All participants received CBCTs before treatment and at follow-up 12 months after treatment. All scans were rendered as 3D

models. RRR was quantified by superimposing and sectioning before and after CBCT models of the anterior maxillary region. Further analysis of sectioned models revealed the predominant region and depth of RRR.

Mean reduction of anterior maxillary bone volume in the CD control group was 2.60% (SD=1.71%) while the mean reduction in the IRO experimental group was almost 3 times greater at 7.25% (SD=3.16%). This difference was significant (P=.011). Pretreatment volume of the anterior maxilla was not a significant covariate, which suggests that change in volume percentage did not depend on anterior maxillary volume before treatment. Predominant areas of RRR were on the buccal and occlusal aspects of the anterior maxillary residual ridge, and the depth of bone resorption was within 0.5 mm over the 12-month course of experimental observation. Within the limits of this study, the authors concluded that mandibular IROs opposing conventional maxillary CDs resulted in significantly greater RRR of the anterior maxilla than conventional CDs.

In an effort to shed etiologic light on the remarkable anterior maxillary RRR associated with combination syndrome, Alsrouji et al[166] conducted a clinical investigation on edentulous participants to measure and compared blood flow in the anterior mucosa supporting maxillary CDs opposed by either mandibular IRO or CDs. Disturbances in blood flow could then be compared with RRR measured 1 year after wearing the prostheses. It was hypothesized that the greater functional pressure exerted by mandibular IROs will cause greater blood flow disturbance in the anterior supporting mucosa beneath maxillary CDs, potentially leading to marked RRR in the anterior maxilla.

The test group for this clinical trial included 9 healthy edentulous individuals (5 men and 4 women, age 57-79 years) restored with maxillary CDs opposing mandibular IRO (interforaminal implants ×2). Controls consisted of 4 healthy edentulous patients (all male, age 54-70 years) provided with conventional CDs. A laser Doppler flowmeter (LDF model INL191; AD Instruments) and a standard robust needle probe (MNP100XP; AD Instruments) were used for noninvasive measurement of capillary blood perfusion in the anterior maxillary mucosa (at 3 standardized locations) after denture removal for 0, 30, 60, and 90 minutes. RRR in the anterior maxilla was quantified using a CBCT superimposition method. RRR was quantified as reduction in bone volume 1 year after treatment. The measurement of blood flow was compared with quantified RRR data. Statistical evaluations were accomplished with significance set at α=.05.

Mean blood flow measure for the IRO group was significantly lower than that for the CD group after immediate denture removal and 30 minutes later. At 60 minutes, mean differences were not significant between groups. At 90 minutes, the mean blood flow equalized to reach a steady state of 377 BPU. The mandibular IRO was associated with the initial reduction of blood flow in the opposing anterior maxilla mucosa to almost a quarter (103 BPU) of the steady state value compared with the mandibular CD, which reduced maxillary anterior blood flow to only about one half (183 BPU). This suggested greater blood flow disturbance in the IRO group. Simultaneous measurement of RRR revealed mean percentage volume change of 7.3 ±1.3% for the IRO group and 2.6 ±1.7% for the CD group within 1 year, representing nearly 3 times greater RRR in the IRO group.

Within the limits of this study, the authors concluded that blood flow disturbance in the anterior maxillary denture-bearing mucosa beneath CDs opposing mandibular IROs was significantly greater than that when opposing mandibular CDs. Additionally, this significant blood flow disturbance seems commensurate with the significantly greater RRR observed in the anterior maxilla of patients with mandibular IRO. The authors expressed disappointment that they failed to measure blood flow before implant insertion and several times over the subsequent year. Had they done so, characterization of blood flow alterations would have been more detailed.

Conventional removable partial dentures

Standard practice when placing survey crowns for RPDs has been the use of complete metal crowns (CMCs) or metal-ceramic crowns (MCCs). The use of tooth-colored ceramic crowns has historically been avoided because of strength and durability concerns. More recently, CAD-CAM technology and monolithic zirconia crowns (MZC) with high bend strength and fracture toughness have opened the door to a viable ceramic survey crown alternative. With this in mind, Tanaka et al[167] investigated the suitability of MZCs for RPD abutments by determining change in retentive force of an Akers clasp (cast metal, tapering, half-round clasp) by using repetitive insertion and removal testing.

A single right mandibular second premolar model was used for in vitro testing. Complete coverage restorations for the model included a distal rest seat, a distal guiding plane, and a 0.25-mm undercut on the mesiofacial surface. A survey MZC and CMC (silver-palladium alloy, Ag-Pd) were fabricated for the premolar model. Ag-Pd and cobalt-chromium (Co-Cr) alloy Akers clasps were fabricated to fit the experimental survey crowns. Extensions projecting from the minor connector-clasp shoulder junction facilitated experimental engagement. On a universal test frame, initial clasp retentive force was measured for all combinations of crown and clasp materials. After initial retentive force measurement, repetitive insertion/removal testing was carried out up to 10 000 cycles. For every 1000 cycles, clasp retentive force was measured. Crown surfaces before and after testing

were observed with optical microscopy and field emission scanning electron microscopy (SEM). Specimens displaying obvious discoloration due to wear were subjected to characteristic X-ray imaging and electron probe microanalysis.

The results indicated that initial retentive force of the Co-Cr clasp was greater than that of the Ag-Pd clasp for both MZCs and CMCs ($P<.05$). Clasp retentive force decreased with increasing number of insertion and removal cycles. The least reduction in force was observed for the Ag-Pd clasp on MZCs. Wear marks were detected where CMCs contacted the clasp. Discoloration of MZC due to wear of the Co-Cr clasp was observed.

The authors concluded that with repetitive insertion/removal of clasps on MZCs, retentive force decreased depending on clasp materials. Of note, the amount of retentive force reduction was similar to or less than that observed with conventional CMCs. Considering only RPD retentive force, the authors suggested that the data presented here may indicate that MZCs could serve as survey crowns for RPD therapy.

A second critical factor when considering CAD-CAM tooth-color survey crowns for RPD abutments is the crown's load-bearing fracture resistance, specifically related to rest seat location and design. This is particularly true when the survey crown restores an anterior abutment that requires a cingulum rest. In consideration of this clinical concern, Manchester et al[168] reported on an in vitro investigation of monolithic CAD-CAM ceramic and composite resin material applied to RPD surveyed crowns with cingulum rest seats restoring a mandibular canine. The authors hypothesized that no differences exist in fracture resistance of the tooth-color materials of interest and that no difference exist in fracture strength afforded by 2 different cingulum rest seat designs (sharp bottom versus round bottom).

One hundred and twenty standardized CAD-CAM crowns were fabricated to fit a standardized composite resin die (mandibular left canine preparation) from 5 different monolithic tooth-color materials (n=24/group): EM/lithium disilicate (IPS e.max CAD CEREC blocks; Ivoclar Vivadent AG); SM/zirconia (NexxZr T; Sagemax Bioceramics Inc); LP/zirconia (Lava Plus High Translucency; 3M); ZC/zirconia (ZirCAD LT; Ivoclar Vivadent AG); and MZ/composite resin (MZ100 CEREC blocks; 3M ESPE) used as a control. Crowns from each group were divided into 2 subgroups representing 2 different shaped cingulum rest seats: round-bottom design subgroup (n=12, 0.5 mm apical radius of curvature) and sharp-bottom design subgroup (n=12, 0.25 mm apical radius of curvature). Crowns were cemented with resin cement to standardized composite resin dies. After water storage (24 hours at 37 °C), the specimens were compressively loaded to failure. Static loading was applied through a shape-matched (sharp bottom or round bottom) nickel-chromium alloy cingulum rest fitted to a universal testing machine (crosshead speed=1.5 mm/min). Failure load was defined as a 10% decrease in load or the visible presence of cracks or bulk loss of ceramics in the rest seat area. Upon failure, representative specimens were examined under optical stereomicroscopy (×10 magnification) and SEM to determine failure patterns and fracture mechanics.

Results demonstrated significant differences by materials and rest seat designs ($P<.001$). The order of materials from greatest to least maximal load capacity was ZC (3200.8 ±416.8 N), SM (2784.1 ±400.5 N), LP (2526.9 ±547.1 N), EM (1124.9 ±283.9 N), and MZ (773.5 ±255.0 N). Round-bottom cingulum rest seat design subgroups had approximately 30% greater mean failure loads than the sharp-bottom design subgroups for all surveyed crowns tested. SEM revealed that fractures initiated near the center of the greatest depth of the rest seat, regardless of round- or sharp-bottom design, and propagated toward mesial and distal proximal surfaces.

Based on the in vitro protocol used, the authors reported that zirconia-based RPD abutment crowns fractured at twice the load compared with lithium disilicate crowns. Of the 3 zirconia-based materials included, ZC (ZirCAD LT) demonstrated significantly greater fracture resistance than the other groups. Designing the cingulum rest seat with a broad round-bottom shape provides significantly greater fracture resistance than a sharp-bottom rest seat design ($P<.05$).

The success of RPD therapy relies, at least in part, on fit of the prosthesis to the denture foundation. Intimate contact between the metal framework and abutments and properly extended denture bases that are well adapted to residual ridges optimize prosthesis support, stability, retention, and ultimately patient comfort and function, for treatment success. Traditional design and manufacturing processes for RPD frameworks can be laborious. Recently, CAD-CAM technology has gained popularity in this arena. To assess the accuracy of CAD-CAM methods in RPD framework production, Soltanzadeh et al[169] conducted an in vitro study evaluating the accuracy and fit of conventional versus CAD-CAM–manufactured RPD frameworks based on standard tessellation language (STL) data analysis and to evaluate the accuracy and fit of each component of the RPD framework.

A maxillary master model (Kennedy class III mod. 1) was developed to include rest seats, guiding planes, appropriate axial contours, and fiducials for subsequent digital reference, alignment, and measurement. The model was duplicated and scanned. The resultant STL file served the experimental reference data set. The model was then used to fabricate 4 groups of similarly designed RPD frameworks (10 specimens/group) in Co-Cr alloy. Group I frameworks were fabricated by using

conventional lost wax methods. Group II specimens were developed from individual master model scans (TRIOS 3; 3Shape A/S), digital framework design, and 3D metal printing. Group III manufacturing involved individual gypsum master model duplicates that were subsequently scanned for digital framework design and 3D metal printing. Group IV framework fabrication consisted of individual master model scans used to print resin models that were then subjected to conventional lost wax processing.

Once complete, all frameworks were scanned. A surface-matching software program (Geomagic Control 2014; 3D Systems) was used to record the gap distance between each digital framework STL file and original master model data set at 8 locations. A gap of 0-50 μm was considered close contact (no gap), and a gap of 50-311 μm was defined as clinically acceptable fit. Color surface mapping provided a visual display of framework adaptation to the model.

When compared with 3D-printed frameworks (groups II and III), conventional cast frameworks fabricated by using dental stone (group I) or printed resin (group IV) models fit significantly better ($P<.05$), particularly in major connector and guide plate areas. Differences between conventional techniques (groups I and IV) were not significant. The greatest gap (0.33 ±0.20 mm) was observed with the major connector anterior strap on printed frameworks (groups II and III). Method of fabrication did not affect the adaptation of rests or reciprocation plates.

The authors concluded that all manufacturing methods appeared to generally provide accurate fit within a clinically acceptable range (50-311 μm), and all methods resulted in good accuracy of fit (<50 μm gap) in rest and reciprocal plates areas. That said, frameworks processed by using conventional methods resulted in better fit and accuracy than 3D printed frameworks processed by using the in vitro protocol presented here. It is interesting to note that significant differences were not detected for fit of 3D printed frameworks based on the scanning methods/sequence applied. Poorest fit was recorded at major connectors, particularly anterior straps when fabricated by using the CAD printing technique (group II).

Conventional fixed prosthodontics

The relatively recent development of CAD-CAM technology in dentistry and the accelerated use of ceramic restorations have revolutionized modern day patient management. A substantial number of clinical reports have established reasonable clinical outcomes, but these data have yet to be pooled. With this in mind, Rodrigues et al[36] accomplished a systematic review and meta-analysis evaluating longevity of tooth-supported ceramic prostheses (partial and complete coverage single-tooth restorations and fixed partial dentures) designed and fabricated by using conventional and CAD-CAM methods.

This investigation used PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and followed PICOT (population, intervention, control, outcome, and time) strategy. The focused question was, *"Is the longevity of tooth-supported ceramic restorations more influenced by conventional or CAD-CAM techniques?"* Two of the authors searched the Web of Science, PubMed, SCOPUS, and LILACS databases between 1966 and October 2017 for publications that compared the survival rate of CAD-CAM against conventional restorations. Initially, 1897 clinical studies were identified. Upon application of exclusion criteria, 11 randomized controlled trials and 3 prospective studies (n=14) were acquired. Date on 3 types of tooth-supported restorations were sought, including partial coverage restorations, complete coverage crowns, and fixed partial dentures. Pooled data revealed that patient follow-ups ranged from 24 to 84 months, 1209 restorations were placed in 957 patients, and 72 restorations failed.

The risk of failure among conventionally manufactured groups (controls) was 8.5% and 14.4% among CAD-CAM groups, indicating a relative risk (RR) of 1.84. When patient dropouts were considered restoration failures, the risk of failure among controls was 22.2% and 28.2% among CAD-CAM groups, resulting in an RR of 1.32. As follow-up periods and patient dropouts varied among studies and groups within studies, incidence rate ratios (IRRs) were calculated based on failures per 100 restoration-years. Multilevel analysis considering dropouts as successes resulted in IRRs of 1.48 and 2.62 failures per 100 restoration-years for the controls and CAD-CAM groups, respectively. Considering dropouts as failures, IRRs of 4.23 and 5.88 failures per 100 restoration-years were calculated for controls and CAD-CAM groups, respectively.

The authors concluded that, based on the meta-analysis conducted, the longevity of a tooth-supported ceramic prosthesis made by CAD-CAM is less than that for restorations made by using conventional fabrication techniques. Authors indicated that the methodological quality of included studies had a low risk of bias in all domains. However, included studies had design limitations, and several involved small sample sizes (ranging from 10 to 163). Evaluation between different CAD-CAM generations and software program limitations should be performed to determine reasons for the higher risk of failure when CAD-CAM processes are used.

Abrasion, attrition, and erosion are major risk factors for destructive occlusal tooth structure loss, particularly when associated with aggressive bruxism. Classical restoration of patients affected by severe wear and reduced occlusal vertical dimension (OVD) typically involves complete-mouth rehabilitation with complete

coverage crowns. A more conservative approach that avoids excessive tooth preparation involves adhesive placement of ceramic occlusal onlays on posterior teeth. At risk in the presence of bruxism is the survival of these structurally conservative restorations. To investigate this rehabilitative approach, Edelhoff et al[170] carried out a prospective nonrandomized clinical trial to analyze and compare the clinical performance, long-term survival, and failure rates of monolithic lithium disilicate occlusal onlays in function up to 11 years in vivo.

The study involved 7 participants (4 men and 3 women; median age 44.3 ±6.56 years) who received complete mouth rehabilitations totaling 103 adhesively bonded lithium disilicate (IPS e.max Press; Ivoclar Vivadent AG) occlusal onlays. Rehabilitation was deemed necessary because of moderate to severe posterior occlusal wear with loss of OVD, dental hypersensitivity, impaired function, or esthetic concerns. Posterior tooth preparations included a circumferential finish line (approximately 1-mm deep) and rounded line angles. The restorations were manufactured by using the monolithic ceramic press technique. The minimum restoration thickness of 1 mm was typically recorded at the central groove. Anterior teeth received veneer or complete-coverage lithium disilicate restorations. All restorations were adhesively luted.

Posterior onlays were evaluated annually (Alfa, Bravo, Charlie ratings) on the following periodontal parameters: marginal discoloration, secondary caries, marginal integrity, surface texture, restoration fracture, and occlusal wear. This patient population was observed for up to 11 years (range 68-139 months; median: 94.9 ±26.1 months). The data were statistically analyzed by using the Kaplan-Meier estimation.

The survival rate for the observed monolithic lithium disilicate occlusal onlays was 100%. Four restorations in 1 participant (3.9%) presented marginal discoloration, 1 after 60 months and 3 after 108 months (all rated Bravo). One restoration (1%) showed a marginal crack formation (a technical complication) after 120 months (rated Bravo). No biological complication, debonding, or secondary caries were identified, and periodontal parameters evaluated showed excellent results.

Within the limits of the study and based on clinical criteria assessed and data collected over the 11-year follow-up period, monolithic lithium disilicate occlusal onlays with a minimum thickness of 1 mm may be considered a reliable treatment option for complete-mouth rehabilitations in patients with severe occlusal wear. However, the authors were quick to point out that according to the monitored USPHS criteria concerning occlusal wear, opposing IPS e.max Press ceramic onlays observed here presented occlusal wear over the follow-up period. This outcome was not further investigated in the current protocol. The authors warned that occlusal surface and functional evaluations must be routine during recall visits. As only 1 restorative material was examined in the present clinical trial, additional randomized studies with a variety of materials may be useful.

Although not reviewed in detail here, 2 noteworthy in vitro investigations into the application and utility of tooth-color occlusal onlays were reported in 2019. The first, published by Heck et al[171] looked at fracture resistance of ultrathin (0.3-0.5 mm) CAD-CAM posterior occlusal onlays subjected to cyclic mechanical loading. Materials tested included IPS EmpressCAD (Ivoclar Vivadent AG) leucite glass-ceramic (as reference), IPS e.max CAD (Ivoclar Vivadent AG) lithium disilicate ceramic, and LavaUltimate CAD/CAM (3M ESPE) nanoceramic composite. The results demonstrated remarkably high fracture strength under cyclic mechanical loading for the lithium disilicate ceramic and nanoceramic composite occlusal onlays. These restorations may present a conservative alternative for patients with posterior occlusal wear.

The second related in vitro investigation (Krummel et al[172]) looked at the effect of bonding substrates (enamel, enamel+dentin, and enamel+composite resin) and the bonding technique (self-etching primer with and without selective enamel etching) on the survival and fracture resistance of thin (0.3-0.6 mm) lithium disilicate ceramic (IPS e.max CAD in Lab HT; Ivoclar Vivadent AG) occlusal onlays. Onlays were luted to extracted human molars, stored in water (21 days), thermocycled (7500 cycles, 5 °C-55 °C, 30 second dwell time), dynamically loaded in a multifunction mastication simulator (Chewing Simulator CS4; SD Mechatronik) for 600 000 cycles, 98 N load, 2.0 Hz, and 0.3-mm lateral slide while thermocycling. The results indicated that self-etching primer with the addition of enamel etching improved the fracture resistance of occlusal onlays when bonding to dentin and enamel and increased survival rate when bonding to enamel. Again, the authors suggested that treatment using occlusal ceramic onlays with a minimum thickness of 0.3-0.6 mm appears to be a promising option for clinical use.

A digital workflow, from intraoral scanning through CAD-CAM of the dental prosthesis, is quickly becoming an accepted alternative to more classical prosthodontic methods. Current literature seems to support a completely digital workflow for the production of single crowns or short-span FPDs, but consensus has yet to be reached with respect to prosthodontic workflows that include complete-arch intraoral scans. With this in mind, Sailer et al[173] investigated whether complete-arch digital scans were similar to or better than complete-arch conventional impressions with respect to time efficiency and perceptions of both patient and clinician. This report represents the first of 3 interesting publications from this

group of authors in 2019. The other reports are mentioned in the following sections.

This randomized controlled clinical trial enrolled 10 participants (6 women and 4 men, mean age 62 years) who were prescribed a posterior zirconia tooth-supported 3-unit FPD. Experimental treatment included registration of tooth preparations by using 3 (test) intraoral digital scanners (Lava C.O.S. [3M]; iTero [Align Technology Inc]; CEREC Bluecam [Dentsply Sirona]) with subsequent workflows and 1 (control) conventional polyether impression method (Permadyne; 3M ESPE) with subsequent conventional prosthesis manufacturing. Each patient received all 4 experimental registration procedures in randomized order to avoid bias. All treatments were rendered by 3 experienced and calibrated clinicians. Registration quality was monitored and repeated as indicated. The time needed for registration procedures, including interarch records, was noted. Patient and clinician perceptions of the comfort and difficulty of registration procedures were rated by using visual analog scales. Statistical analysis targeted differences among registration systems (α=.05).

The total time required for complete-arch registrations was less for the conventional impressions than for the digital scans (conventional 658 ±181 seconds, Lava 1091 ±523 seconds, iTero 1313 ±418 seconds, CEREC 1702 ±558 seconds). The difference was statistically significant for 2 of the 3 scanners (iTero P=.001, CEREC P<.001). For one of the digital scanners (CEREC), significantly more time was needed for the scan than for the other 2 systems (Lava P=.006, iTero P=.005). Scans had to be remade 3 times for Lava and 7 times for iTero, and one conventional impression required remake.

Both patients and clinicians rated digital scans less comfortable than conventional impressions, particularly when scans involving powdering (Lava P=.002 patient rating; CEREC P<.001 clinician rating) were compared with the control. Additionally, scans involving powdering were rated significantly more difficult by clinicians than conventional complete-arch impression (Lava P=.002, iTero P=.010, CEREC P<.001).

The authors concluded that for complete-arch registration, conventional impression procedures were objectively less time-consuming and subjectively preferred by both clinicians and patients over digital scan procedures. Of the scanning systems investigated, those without the need for powdering seem to be preferred to the systems requiring powder.

Part 2 of this worthwhile investigation (Mühlemann et al[174]) involved the same 10 participants treated in part 1 and evaluated the time efficiency of an experienced laboratory technician in fabricating a 3-unit FPD by 3 different CAD-CAM systems (test groups) and a conventional workflow (control). Each patient received an FPD. CAD software systems investigated included Lava C.O.S. CAD (3M), CARES CAD (Institut Straumann AG), and CEREC Connect CAD (Dentsply Sirona). All manufacturing processes were centralized. The conventional workflow consisted of noble metal framework produced by means of traditional lost-wax technique. All frameworks were evaluated clinically before veneering. The time for cast fabrication, framework design and fabrication, and framework veneering was recorded. Chairside time during clinical framework evaluation was also recorded. Statistical analysis targeted differences among workflows (α=.05).

From least to greatest, the mean effective working time for the dental technician was 217 ±23 minutes for CARES, 220 ±29 minutes for Lava, 262 ±22 minutes for CEREC, and 370 ±34 minutes for the conventional workflow. The dental technician spent significantly more time in the conventional workflow than in the digital workflows, independent of the CAD-CAM systems used (P<.001). Centralized manufacturing significantly reduces overall time efficiency of the digital systems (P<.001). The marginal integrity of CAD-CAM–fabricated zirconia frameworks was rated significantly inferior to that of conventionally fabricated noble alloy frameworks (P<.001).

The authors were careful to point out that the veneering process was the most time-consuming fabrication step. With improvements in translucent zirconia materials and the availability of monolithic designs, the total time of technician involvement in manufacturing may soon decrease significantly. As with any digital technology, constant improvement is expected. Results of the present study are limited to software versions and manufacturing processes available at the time of the study.

Part 3 of the current investigatory series (Benic et al[175]) reported on a blinded, randomized controlled clinical trial examining whether marginal and internal fit of 3-unit zirconia FPD frameworks (test) fabricated in fully digital workflows differed from that of metal frameworks (control) fabricated in a conventional workflow. The same 10 participants treated in parts 1 and 2 of this series of reports each received 4 FPD frameworks fabricated for the same abutment teeth (within subject comparisons) according to a randomly generated sequence.

The digital workflows (test) evaluated included the Lava workflow (Lava Chairside Oral Scanner and Laboratory Software v3.0.2 and Lava Zirconia [3M ESPE], Lava Milling Center [Rainer Rominger]), the iTero workflow (iTero scanner [Align Technology Inc], CARES Visual CAD software v6.2 [Institut Straumann AG], Zerion blocks centrally milled [Institut Straumann AG]), and the CEREC infiniDent workflow (CEREC Bluecam, CEREC Connect software v4.0.3, CEREC inLab 3D

software v4.0.3, inCoris ZI blocks centrally milled; Dentsply Sirona). The conventional workflow (control) included a polyether impression (Permadyne; 3M ESPE) and lost-wax casting of a metal framework. Marginal and internal (shoulder, axial, cuspal, and occlusal regions) discrepancies between frameworks and their respective abutments were registered by using the polyvinyl siloxane replica technique assessed by using light microscopy (×200 magnification). Statistical analysis focused on fit discrepancies among workflows (α=.05).

There were no significant differences in marginal discrepancies between workflows studied. Internal fit discrepancy at the shoulder was 96.1 ±61.7 μm for iTero, 106.9 ±96.0 μm for Lava, 112.2 ±76.7 μm for CEREC infiniDent, and 126.5 ±91.0 μm for the conventional workflow (iTero<conventional, P=.029). Internal fit discrepancy in the occlusal region was 148.8 ±66.8 mm for the conventional workflow, 153.5 ±66.8 μm for iTero, 179.7 ±63.1 μm for CEREC infiniDent, and 203.3 ±127.9 μm for Lava (conventional<Lava and CEREC infinDent, P<.01; iTero<Lava and CEREC infinDent, P<.01).

Authors concluded that, within the limitation of this investigation, the digitally fabricated zirconia frameworks studied presented generally similar or better fit than conventionally fabricated metal frameworks. Clinical implications of results reported here have not been sufficiently assessed by using sound scientific methods. Future well-controlled clinical investigations should be carried out to assess the long-term clinical performance of CAD-CAM FPDs.

General implant prosthodontic considerations

As the profession rushes to embrace everything digital, care must be taken to assure the accuracy and appropriateness of new digital equipment, materials, and methods. The use of intraoral scanners in implant-supported fixed prosthodontics may be a good example for digital dentistry application in the absence of sound scientific support. Rigorous evaluation of the accurate manufacturing of intraoral scan bodies (ISBs) may be lacking. To remedy this deficit, Schmidt et al[176] investigated production tolerances of ISBs by using multisensor coordinate measurement with X-ray computed tomography to assess possible influences on transfer accuracy of implant position. The authors hypothesized that ISBs would not differ with regard to the transfer accuracy of the implant position.

Three different ISBs (H1410 [Medentika/Straumann], H9.S3D4.150 [NT-Trading GmbH], caraH10/20 [Kulzer GmbH]; n=4 per group) were digitized (Tomoscope-S; Werth Messtechnik) with a linear accuracy <4 μm. The ISB length, diameter, and angles between the hexagonal interface and scan body structure were determined (GOM Inspect; GOM GmbH). Data were compared with CAD data provided by the manufacturers. The 3D volume describing maximum possible deviations from the true implant position, because of ISB tolerances, was calculated and plotted. Length, diameter, and angle deviations were also plotted and statistically analyzed (α=.05).

Pairwise comparison of all deviations showed significant differences for length and diameter deviations, as well as for the target volume deviation. Angles between the hexagonal interface and scan body structure showed no significant differences between manufacturers. Therefore, the null hypothesis was partially rejected.

The authors concluded that the ISB manufacturing tolerances calculated have the potential to adversely affect transfer accuracy of the implant position recorded intraorally to the final position in the digital cast. The authors indicated that because scanner software algorithms are not known, it is possible that compensation for manufacturing tolerances may be built into the system. If true, this would represent a limitation of the study. An additional limitation might be the low number of specimens measured. This was necessary because of the extremely tedious and costly tomography. As the X-ray 3D-measuring technique used is considered exceptionally precise, the resulting data should be regarded as possible maximum deviations.

As mentioned previously in this review, intraoral scanner systems are generally advocated for dentate arches or short edentulous spans. Mounting interest in extending scanner applications to the longer spans found in the edentulous arches has been met with suboptimal results. Questioning the appropriateness of previous experimental methods used to addressing complete arch implant scanning, Tan et al[177] reported on an in vitro comparison of the 3D accuracy of conventional impressions with digital scan systems (intraoral and dental laboratory scanners) for 2 different interimplant distances in a maxillary edentulous model.

One conventional impression system (Impregum PentaSoft; 3M ESPE) with an open-tray splinted-coping technique, 2 intraoral scanners (TRIOS [3Shape A/S] and True Definition [3M ESPE]), and 3 dental laboratory scanners (Ceramill Map400 [Amann Girrbach AG], inEos X5 [Dentsply Sirona], and D900 [3Shape A/S]) were evaluated on 2 edentulous maxillary master models (A and B) with 6 (interimplant distance=20 mm) and 8 (interimplant distance=13 mm) parallel implants, respectively. Core3D scan bodies (Core3D Centers) were used with TRIOS, True Definition, and D900 intraoral scanners. Range 3 Kit b Scan bodies (Amann Girrbach) were used with the Ceramill Map400 laboratory scanner. 2-CONnect Abutments and inPost scan bodies (Dentsply Sirona) were used with the inEos x5 laboratory scanner. Intraoral scanners registered implant positions on master models, while dental laboratory scanners registered implant positions on casts generated from conventional

impressions. Five virtual or physical replicates (n=5) were generated from each scanner or impression system.

Centroid positions at the implant platform level were derived by using either physical or virtual probe strikes with a coordinate measuring machine (CMM; Global Silver Performance 7.10.7; Brown & Sharpe) with a measurement accuracy of 2 μm. Comparison of centroid positions between master and test models (n=5) defined linear distortions (d_x, d_y, and d_z), global linear distortions (d_R), and 3D reference distance distortions between implants (ΔR). The 2D angles between the central axis of each implant and the x- or y-axis were compared with derive absolute angular distortions ($Absd\theta_x$, $Absd\theta_y$). Linear distortions, absolute angular distortions, 3D reference distance distortions, and model A to B comparisons were calculated. Significance was reported at α=.05. Standard deviations of the measured variables reflect the precision of each system studied.

For model A, the mean d_R ranged from 8.7 ±8.3 to 731.7 ±62.3 μm, mean $Absd\theta_x$ ranged from 0.021 ±0.205 to -2.349 ±0.166 degrees, and mean $Absd\theta_y$ ranged from -0.002 ±0.160 to -0.932 ±0.290 degrees. For model B, mean d_R ranged from 16.3 ±9 to 620.2 ±63.2 μm, mean $Absd\theta_x$ ranged from -0.007 ±0.076 to -0.688 ±0.574 degrees, and mean $Absd\theta_y$ ranged from -0.018 ±0.048 to -1.052 ±0.297 degrees. There was a significant difference among test groups for d_R and ΔR in both models, with True Definition being the least accurate. Independent statistical comparisons for d_R between homologous implant location pairs in model A versus B revealed several significant pairings for intraoral scanner systems, in which instances global linear distortion was larger in model A by 110-150 μm.

Within the limitations of this in vitro investigation, the authors concluded that decreased interimplant distance in an edentulous model is associated with reduced global linear distortions for intraoral scanner systems but had no effect on conventional impressions or dental laboratory scanner systems. Conventional open-tray splinted-coping impressions made with the Impregum material consistently exhibited the best or second-best accuracy at all implant locations, although differences were not significant. The True Definition intraoral scanner consistently exhibited the poorest accuracy for all linear distortions in both models. Finally, impression systems could not be consistently ranked for absolute angular distortions.

Resonance frequency analysis (RFA), introduced to implant dentistry in the 1990s, is used to determine bone-implant complex stiffness, which should represent the initial status and maturation of the bone-implant interface, among other factors. The greater the implant stability, the higher the instrument's frequency measurements, or the higher the implant stability quotients (ISOs) output. The ISO is a calibrated parameter from 1 (low stability) to 100 (high stability). To assess any correlation between RFA and other clinical measurements, specifically changes in marginal bone levels (MBLs), Chen et al[178] accomplished a systematic review of current literature.

Clinical studies published in English up to May 1, 2018, were searched in major electronic databases, including PubMed/MEDLINE, Embase, and Cochrane, by using the medical subject heading (MeSH) resonance frequency analysis, implant stability quotient, RFA, and ISQ, in combination with MBL, marginal bone loss, and marginal bone resorption. A manual search of dental implant-related journals was also conducted. In vitro and animal studies were excluded. After application of inclusion/exclusion criteria to available publications, a total of 62 articles were included in this review.

Investigations reporting both MBL changes and RFA measurements were thoroughly reviewed, and relevant findings regarding relationships between RFA and bone quality or insertion torque were also summarized. Generally, articles reported a trend of increasing ISQs over the observation period, although several indicated an initial dip followed by a steady ISQ increase. These ISQ increases may or may not have been statistically significant. When implants were placed in both arches within the same study, the mean ISQs for mandibular implants were higher than those for maxillary implants. Despite the initially high ISQs, most failed implants demonstrated decreasing ISQs with low ISQs at the time of failure. Contradictory findings were identified regarding relationships between RFA measurements, marginal bone loss, bone quality, insertion torque, and other parameters.

Well-supported, definitive conclusion could not be made, as mixed results were found in the few articles that reported significant associations and correlations between RFA measurements and bone loss. The lack of prospective randomized controlled trials, study heterogeneity, and limited-duration ISQ tracking (typically <2 years) significantly complicated interpretation. Authors suggested that longitudinal RFA measurements may be valuable for evaluating implant stability when supplemented by radiographic assessments and examination of other clinical parameters.

As published reports directly comparing relationships between RFA and change in MBL are generally lacking, contradictory, and relatively obtained in a short term, Chen et al[128] provided a retrospective analysis of ISQs for patients followed up to 10 years between 1998 and 2014 to identify correlations between ISQs and clinical parameters, such as change in MBL.

A total of 173 medically healthy participants (65 men and 108 women; age 21-85 years) with 383 implants (1-5 per patient, diameter 3.5-8.0 mm, length 7-18 mm) restored with any type of prosthesis were enrolled.

Exclusion criteria included heavy smoking, severe bruxing, radiation or bisphosphonate therapy, implants associated with bone grafting, and cement-retained restorations. Implant location, MBL (average of mesial and distal via standardized procedure), and ISO were recorded at surgery and at various recall times for statistical analysis. Statistics were used to evaluate the impact of clinical and demographic variables (time, implant location, patient sex) on ISO and the correlation between ISO and MBL. The level of significance was set at α=.05.

The ISQ values ranged from 19 to 92 across the observation period. The overall mean ISQ at surgery was 62.2 ±10.87. Mean mandibular implant ISQs (71.4 ±11.70) were significantly higher (P<.001) than mean maxillary implant ISQs (57.6 ±6.84). Of the 21 failed implants, 20 failed within the first year, resulting in a 10-year cumulative implant survival estimate of 95%. Failed implants had lower ISOs at surgery (52.3 ±7.03) and baseline (52.5 ±4.20) than surviving implants (63.0 ±10.74 and 62.3 ±8.30). Differences at surgery were significant (P<.05). Mean ISQs generally increased over time. However, there was variation among implants when grouped according to patient sex and implant location. No significant correlation between ISQs and MBL (P=.211) was identified, despite an inverse relationship between ISQ and marginal bone loss.

Variables investigated (observation time, sex, and implant position and arch) and their interactions have significant influences on ISQs. Clinicians should appreciate that low initial ISQs may point to implants at higher risk of failure. Early ISQs many vary for healthy implants in addition to a general increase over time. A correlation between FRA and MBL change could not be identified. Despite its limitations, this report provides an overview of the clinical performance of RFA based on long-term clinical data.

CBCT has been widely adopted in dentistry, particularly with respect to dental implant procedures. Incidental findings within the scanned volume are relatively common and often require medical evaluation, intervention, and/or monitoring. To highlight the need for knowledge-based assessment of the entire scanned volume, Biun et al[179] presented a rare patient with previously undiagnosed, asymptomatic multiple myeloma first identified incidentally on dental CBCT and panoramic radiography. This patient demonstrates the diverse range of lesions that may appear on CBCT and the importance of accurate and timely interpretation.

A 63-year-old man was referred to a private radiology clinic for a panoramic radiograph (PR) and CBCT as part of a preimplant assessment (mandibular first molar site). His medical history was unremarkable. Intraoral examination revealed normal progression of extraction healing in the proposed implant site.

The PR and CBCT demonstrated multiple circular punched-out radiolucencies in the mandibular rami, condyles, cervical spine, and visualized cranial base. The recent first molar extraction site demonstrated peripheral new bone formation on CBCT indicative of normal healing. The radiologic diagnosis of multiple myeloma was confirmed by serum protein electrophoresis.

While CBCT scans are typically prescribed by dentists with specific clinical intent, the dentist maintains responsibility for examining the entire scanned volume. Incidental findings in CBCT are relatively common. Therefore, the referring dentist is challenged to maintain high-level radiologic interpretive skills or refer radiographic interpretation to an appropriately skilled radiologist, such as an oral and maxillofacial radiologist.

The therapeutic implication of this diagnosis is significant. Treatment for multiple myeloma involves high-dose combination chemotherapy followed by autologous stem cell transplantation in tolerant patients. Intravenous bisphosphonates are used to reduce bone pain and slow the progression of bone lesions. Multiple myeloma is currently an incurable condition, with medical therapy aiming to prolong survival.

Implant removable prosthodontics

Placement of a minimum of 2 parallel interforaminal implants in edentulous mandibles is desirable. Implant trajectory approximately perpendicular with the planned occlusal plane or residual ridge crest is typically the surgical objective, although often difficult to achieve given anatomic limitations. The quality of prosthesis retention and stability in the presence of varying implant angulations should be better characterized. ELsyad et al[180] conducted an in vitro study to evaluate the influence of relative labial implant inclinations on the retention and stability of different resilient stud attachments for mandibular implant overdentures.

Four identical edentulous mandibular models, without anatomic undercuts, were fabricated. Each model received 2 dental implants with abutments (LOCATOR; Dentaurum) placed in the canine regions. The implants were inserted parallel to each other and at varying degrees on labial inclination (0, 10, 20, and 30 degrees) relative to a reference set perpendicular to the residual ridge crest. Resilient silicone (1.5-mm layer) was used to simulate ridge mucosa.

Twenty experimental overdentures (5 per model) were constructed. Resilient attachments (LOCATOR; Dentaurum) were picked up in experimental dentures by using chemically activated acrylic resin. For all implant angulation, the following regular attachment inserts were used: extra-light retention (blue, 680 g), light retention (pink, 1365 g), and medium retention (transparent, 2270 g). For the 30-degree implant angulation, the following extended range attachments inserts were used: extra-light retention (red, 680 g) and medium retention (green, 1815 g).

Vertical (retention) and oblique (stability; lateral, anterior, and posterior) dislodging forces were evaluated initially (initial retention) and after overdenture insertion and removal (final retention). Dislodgments were performed in a universal testing machine by using quasi-random sequencing.

After repeated (540 times) insertions and removals, the 30-degree specimens demonstrated the greatest retention and lateral stability, the 0-degree specimens the greatest posterior stability, the 20-degree specimens the least retention, and the 30-degree specimens the least posterior stability ($P<.001$). The greatest stability and retention values were recorded with light and medium regular inserts, and the lowest values were recorded with extra-light regular inserts.

Within the limits of this study, moderate labial implant inclination (10 and 20 degrees) negatively affects retention, as well as anterior and lateral stability. Excessive implant labial inclination (30 degrees) negatively affect posterior stability. Stretching to a clinical conclusion, the authors suggested the use of light and medium regular attachment inserts for implants inclined labially may provide beneficial retention and stability for 2-implant mandibular overdentures.

Various attachments have been used to facilitate retention, support, and stability for complete implant overdentures, including bars, studs, telescopic crowns, and magnets. When appropriately applied and accurately accomplished, most attachment systems perform well. To lend clinical performance data to the evidence-based decision-making process, Lian et al[181] compared intermediate-term clinical outcomes of maxillary implant overdentures supported by 4 implants incorporating stud or bar attachments.

From 2008 to 2014, participants with maxillary edentulism (n=33) were enrolled. Surgical placement of 4 maxillary dental implants was followed by 3-6 months of healing and restoration with either stud-retained (LOCATOR; Zest Anchors, n=18, 12 men and 6 women, mean age 61 years) or bar-retained (Dolder; Cendres+Metaux, n=15, 8 men, 7 women, mean age 59 years) overdentures. Attachment selection was generally based on anatomic conditions and patient preference. Patient and implant characteristics were recorded. Implant and prosthesis performances were examined clinically and radiographically throughout the follow-up period (mean 77 months, range 36-111 months). Implant survival, marginal bone loss, peri-implant clinical parameters, prosthetic maintenance, and patient satisfaction score (via questionnaire) were evaluated at the last follow-up encounter. One participant in the stud group and 1 in the bar group were lost to follow-up. Thirty-one participants and 124 implants were statistically analyzed ($\alpha=.05$).

Five implants failed in 3 stud participants, and 2 implants failed in 2 bar participants. Estimated cumulative implant survival rates were 91.7% and 96.4% (implant as unit of analysis) or 81.4% and 86.2% (participant as unit of analysis) for the stud-retained and bar-retained groups, respectively. Neither difference was statistically significant. Except for the Modified Plaque Index ($P=.035$), no significant differences were indicated between groups in terms of implant survival rate, marginal bone loss, peri-implant clinical parameters, or prosthetic maintenance treatment. Peri-implant gingival hyperplasia occurred only in the bar group (incidence=14.3%, 3 participants, 8 implants). Participants in both groups reported a high degree of satisfaction.

The authors concluded that, within the limitations of this clinical trial, no significant clinical differences were identified between maxillary 4-implant overdentures with stud or bar attachments over the 3- to 9-year follow-up period, although a higher Modified Plaque Index was observed in the bar-retained group. The authors suggested that prostheses with stud attachments appeared advantageous with respect to cleaning or hygiene and repair. Further prospective clinical investigation with larger sample sizes and longer follow-up periods are needed to validate findings reported here.

Implant fixed prosthodontics

Although mechanical complications, particularly screw joint failure, are relatively rare compared with our initial experience several decades ago, mechanical problems continue to be reported. Clinical management of these complications is often very challenging and occasionally impossible. With this in mind, Katsavochristou and Koumoulis[182] reviewed the literature to investigate risk factors associated with abutment screw complications, to use recent data for identifying clinical screw failure, and to report on methods and outcomes of mechanical complication interventions.

A PubMed search (studies reported in English from 2004 to 2018) was conducted focusing on clinical studies related to abutment complications, screw loosening, and/or screw fracture. Animal studies, narrative reviews, expert opinions, and communications or letters were excluded. Additional exclusion criteria included reports on accessory prosthetic screws and abutment fractures, and all reports that did not provide adequate data. A total of 12 clinical prospective studies and case reports were finally included in the review encompassing single-implant crowns or 2-unit implant fixed partial dentures involving both internal and external abutment connection geometries. Clinical observations were initiated as early as 1996 with follow-ups for up to 13 years. Study sample sizes ranged from 93 to 328.

The incidence of abutment screw fracture (0.6%) was less than the incidence of abutment screw loosening (range: 7%-11.3%). Fracture of the screw body was the most frequent failure mode. Screw loosening or fracture

was often seen at first molars, while screw fracture was also prevalent at maxillary central incisors. No screw failure management method could be identified as the most optimal one, and the restorability of the implant after retrieval of fractured components may be compromised because of accompanied distortion or destruction at the connection interface. The authors indicated that standardized methods, parameters, and consistency in data collection are prerequisites for individual assessment of each implant system and identification of limitations and strategic improvements with respect to screw loosening and fracture.

Classic management of edentulous patients involved mandibular implant-supported metal-resin fixed complete dentures (MRFCDs) opposing conventional CDs. Follow-up duration of this treatment modality can be significant because of its historical application. McGlumphy et al[183] retrospectively evaluated implant and prosthetic complications related to this treatment approach over a 15- to 20-year postplacement follow-up period.

The dental records of 24 edentulous patients (8 men and 16 women, mean age 55.8 years at prosthesis placement) treated by using a mandibular MRFCD and a maxillary CD were reviewed. Mandibular restorations were supported by 5-6 interforaminal, external hexagon, dental implants. Mean posterior cantilever length was 20.58 mm (range 16.70-28.50 mm). Bilateral simultaneous posterior contacts and bilateral balanced occlusion were established in centric relation and excursive movements, respectively. All retention screws were torque fastened to manufacturer recommendations.

Complications for the implants, MRFCDs, and CDs were recorded over 4 different recall periods: 0-5 years, 5-10 years, 10-15 years, and more than 15 years. The survival and failure times based on Kaplan-Meier statistics were analyzed. Product-limit survival estimates were used to indicate cumulative survival rates.

Mean follow-up time was 18.5 years (range 15.4-20.6 years). The cumulative survival rates for the implants and MRFCDs were 91.8% at 16.9 years (CI: 85.2% and 95.5%) and 80% at 19.6 years (CI: 44.1% and 94.1%), respectively. Two mandibular MRFCDs failed; one because of framework fracture at the 19-year follow-up, and the other subsequent to tumor resection. Acrylic resin tooth fracture (45.8% of patients) and wear (75% of patients) were the most common complications with the MRFCDs. Retaining screw complications, including screw loosening (8.1% of retaining screws) and screw fracture (11.3% of retaining screws), were also common. In total, 50% of the patients experienced same type of screw complication, most occurring in the most distal implants bilaterally.

The authors felt that the outcomes seen in this retrospective investigation over the long term were generally favorable. Even though the sample size was small, the long-term data provided are both interesting and useful. Clinicians should be aware that potential maintenance complications, such as acrylic resin tooth fracture or wear and retaining screw loosening or fracture, with the prosthodontic approach may occur in the long term.

The clinical value of splinting adjacent implants by using an appropriate prosthesis design is a question that dates back at least to the 1980s. While this question is of interest in both fixed and removable implant prosthodontics, Ravidà et al[184] confined their research question to fixed prosthodontics. Their objective was to retrospectively study the performance of posterior bone-level dental implants restored with either 3 nonsplinted metal-ceramic crowns, 3 splinted metal-ceramic crowns, or a 3-unit metal-ceramic fixed partial denture supported by 2 implants.

Patients with 3-tooth edentulous spaces in the posterior mandible or maxilla, treated with 2 or 3 implants, and opposed by natural dentitions were identified. Selected patients were separated into 3 study groups based on the definitive prosthesis received: nonsplinted crowns (NSC) group, splinted crowns (SC) group, and FPD group. Implant survival and success rate data, as well as all biological and technical complications, were collected. The costs associated with each treatment options were compared.

An experimental population of 145 patients (64 men and 81 women; mean age 60.7 ±10.1 years; 40 NSC, 52 SC, and 53 FPD) receiving 382 bone-level implants (120 NSC, 156 SC, and 106 FPD) were included. Mean follow-up period was 76.2 months. Total success rate in the patient sample was 66.2% (NSC: 52.5%, SC: 61.5%, FPD: 81.1%). Implant survival rates were 92.5% (NSC), 88.5% (SC), and 100% (FPD), with significant difference identified between SC and FPD groups (P=.01). Overall, peri-implantitis was associated with 9.9% of implants (NSC: 7.5%, SC: 16.7%, FPD: 2.8%). Prosthodontic complications were seen significantly more often in the NSC group (32.5%) than in SC (15.4%) and FPD (13.2%) groups. Total cost (initial cost and cost for complications) incurred by the FPD group was significantly less than that in the NSC and SC groups (P<.001).

Within the limitations of the present investigation, a 3-unit implant-supported FPD restoring 2 implants seems to present the most ideal long-term therapeutic solution, among the investigated approaches, for rehabilitating a 3-tooth posterior edentulous area. The FPD was seen to demonstrate (a) a comparable peri-implantitis rate to NSC while lower than that of SC; (b) comparable survival rate to NSC while higher than that of SC; (c) similar complication rate to SC while lower than that of NSC; (d) higher success rate than both NSC and SC; and (e) lower total cost than NSC and SC.

Prosthodontic materials

Chemical and mechanical degradation affects the durability of dental restorative material. Clinical degradation of composite resins may occur from a chemical breakdown (hydrolysis or stress-induced effects), leaching and chemical composition changes, precipitation/swelling with subsequent voids and cracks, interfacial leaching, and corrosion with strength loss. Evaluation of chemical stability in simulating oral conditions (immersion testing) is common. Most reports address paste-type composite resins. However, the chemical stability of CAD-CAM composite resins remains unclear. Iwata et al[185] used an immersion testing protocol to evaluate the long-term chemical degradation of fillers in CAD-CAM composite resins for their reliability and to evaluate the impact on surface properties.

Four commercially available CAD-CAM resin composite resin blocks were tested (BLO: Block HC 2 Layer [Shofu], CER: Cerasmart [GC Corp], KA: Katana Avencia [Kuraray Noritaki Dental], KZR: KZR-CAD HR Block 2 [Yamakin Co]). Blocks were cut into 10.0×12.0×2.0-mm specimens, then polished and cleaned. Specimens were immersed in purified water held at constant temperatures of 37, 60, 70, or 80 °C and stored for 30 days. After storage, concentrations of leached elements in the solution were measured by using an inductively coupled plasma atomic emission spectrometer. Secondary electron images were obtained by using a field emission-electron probe microanalyzer (FE-EPMA) to characterize the specimen surfaces.

In general, immersion testing resulted in the leaching of silicon (Si), a major component, from all materials tested. Additionally, some materials leached high amount of barium (Ba) and/or strontium (Sr) in addition to lesser amounts of aluminum (Al) and zinc (Zn). The amount of leached elements increased with increasing immersion temperatures for all materials. Marked surface degradation was observed, particularly on the CER and KZR specimens at high immersion temperatures.

The authors concluded that filler elements in CAD-CAM composite resin blocks tested in this study leached into purified water over the 30-day course of the investigation. The leached elements and their quantities differed greatly among materials observed and depended on the oxide types composing the filler. The amounts of leached elements varied in a temperature-dependent manner. Additionally, marked surface degradation of some materials was demonstrated. The authors suggest that maintenance of physical and mechanical properties over the long term may not be possible, thus requiring further studies. The authors are also quick to point out that one material showed little surface degradation (KA). Such a material may be preferable for long-term use.

The application of CAD-CAM techniques has touched nearly all aspects of modern dentistry. One practical application is in the manufacturing of esthetic, durable, and well-fitting interim restorations in fixed prosthodontics. This application is particularly attractive when accomplishing complete-arch rehabilitation with an extended interim phase of the treatment. In consideration of the durability of available CAD-CAM materials, Kessler et al[186] investigated the 3-body wear of different additively manufactured interim materials, a PMMA for CAD-CAM milling, and a resin-based direct composite resin (control).

Eight specimens of each printable material (3Delta temp [Deltamed], C&B [Nextdent], Freeprint temp [Detax]) were additively manufactured on a DLP 3D printer. Postprocessing was carried out according to the manufacturer's specifications. Eight specimens from a block material (negative control: Telio CAD; Ivoclar Vivadent AG) were milled, and 8 specimens of a direct composite resin (positive control: Tetric Evo-Ceram; Ivoclar Vivadent AG) were directly developed and light polymerized. Three-body wear was simulated in an Academisch Centrum for Tandheelkunde Amsterdam (ACTA) wear machine. A specimen wheel and an opposing metal wheel were rotated against each other in a bowl containing a third-body medium. To simulate masticatory movements at physiological forces, the antagonist wheel rotated 15% slower than the specimen wheel imparting a contact force of 15 N. The materials were abraded through 200 000 cycles in a standardized, regularly renewed, aqueous suspension of ground millet seeds. The wear tracks were scanned at 50 000, 100 000, 150 000, and 200 000 cycles and analyzed. Worn specimen surfaces were examined with SEM.

After 200 000 cycles, mean wear was 50 ±15 μm for Tetric EvoCeram, 62 ±4 μm for 3Deltatemp, 236 ±31 μm for Telio CAD, 255 ±13 μm for C&B, and 257 ±24 μm for Freeprint temp. Wear rate was calculated to be 0.24 μm/cycle for Tetric EvoCeram, 0.30 μm/cycle for 3D Delta temp, 1.2 μm/cycle for Telio CAD, and 1.3 μm/cycle for both C&B and Freeprint temp. After 200 000 cycles, wear and wear rate for Tetric EvoCeram and 3Deltatemp were significantly less than those for other materials ($P<.05$). SEM revealed 3Deltatemp to have higher filler proportion than the other 3D print materials but less than Tetric EvoCeram.

The authors discussed that filler content influences the wear behavior of additively manufactured materials as well as dental restorative composite resin materials. Most of the 3D print materials investigated wore significantly different from each other and from the direct composite resin control. While most 3D print materials have a low inorganic filler load, which qualifies the materials for interim use only, one 3D printing material (3Deltatemp) has an optimized composition (high filler content) with superior wear resistance qualifying it for longer clinical service time, if wear is the qualifying factor.

While dental implant therapy is an established prosthodontic tool in modern dentistry, concern about the rising number of clinical reports detailing peri-implant inflammatory problems and crestal bone loss must be seriously considered. Estimated prevalence of peri-implantitis, considered by most to be an infectious disease, has been reported to range from 6.2% to 28% (implant level). It is possible that titanium (Ti) particulate debris, released from the implant surface via wear or chemical degradation, may stimulate adverse biologic responses when embedded in the peri-implant tissues aggravating coexisting inflammation. Pettersson et al[187] argue that a peri-implant microorganism-based inflammatory process in combination with released Ti particles may have profound effects. Therefore, by using a cross-sectional clinical study approach, the authors investigated the Ti content of biopsies from patients with severe peri-implantitis and compared it with that of nonimplant periodontitis patients (controls) to quantify the Ti particles in peri-implantitis specimens.

Thirteen patients referred for peri-implantitis and 11 for periodontitis treatment were enrolled. Disease severity was estimated. Biopsies obtained from both groups were chemically analyzed (inductively coupled plasma mass spectrometry) for Ti content. The biopsies from 2 participants from each group were analyzed microscopically (light microscopy, transmission electron microscopy, and SEM with element analysis) to discern the presence of particulate Ti.

All participants with peri-implantitis lost one or more implants despite undergoing contemporary therapy. Peri-implantitis tissue specimens contained significantly greater concentrations of Ti (98.7 ±85.6 μg/g, 95% CI: 56.2-141.3 μg/g) than control specimens (1.2 ±0.9 μg/g, 95% CI: 0.6-1.7 μg/g). Particulate metal was identified in peri-implantitis and control biopsies, but element analyses could confirm only the presence of Ti in peri-implantitis tissue. Mean Ti particle size in the peri-implant samples was 10.9 ±35.7 μm^2 (95% CI: 6.5-15.3).

The authors showed that human peri-implantitis tissue contains high concentrations of Ti compared with controls from human periodontitis tissue. Although non-Ti metal fragments were identified in both peri-implantitis and periodontitis tissues, the presence of Ti was seen only in peri-implantitis tissue. The authors concluded that Ti was the main foreign body material identified in peri-implantitis biopsies, and its high content has the potential to aggravate inflammation and adversely affect the prognosis of peri-implantitis therapeutic interventions.

This report did not identify the origin of the tissue-borne Ti particulate. The authors' previous work suggested that Ti particles may derive from scaling of the implant or corrosion. Ti is abraded from the implant surface during surgical insertion, and implants with a rougher surface show greater Ti release. A better understanding of the origin of Ti particles and how to reduce release into the peri-implant tissues may be crucial to a better understanding of peri-implantitis and the development of more effective treatment.

PERIODONTICS, ALVEOLAR BONE, AND PERI-IMPLANT TISSUES

This year's review covered topics relating to the assessment, prevalence, and treatment regimens of periodontal disease; the systemic health conditions affecting the periodontium; periodontal regeneration; 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.

Periodontal disease prevalence, etiology, and treatment

Historically, bacteria have been cited as the etiology of gingivitis and periodontitis inflammatory diseases. It is widely accepted that bacteria are necessary for disease development. Gingivitis and periodontitis are inflammatory conditions associated with bacterial overgrowth. However, the presence of specific bacteria does not guarantee progression to periodontitis. Bartold and Van Dyke[188] analyzed the evidence for the established thought that specific bacteria directly participate in the pathogenesis of periodontitis and questioned the long-held tenet that penetration of the periodontal connective tissues by bacteria and their products is a significant phase in the initial development of periodontitis. They conducted a literature search for studies on initiation of gingivitis and periodontitis by specific pathogens. The search results were insufficient for a systematic review and have been summarized in a commentary instead. They concluded that there is little evidence in the literature to support the commonly held concept that specific bacteria initiate periodontitis. Rather, they presented evidence for a paradigm supporting the central role of inflammation, rather than specific microbiota, in the early pathogenesis of periodontitis and discuss whether controlling the inflammation can influence the character and composition of the periodontal infection. This approach emphasizes the reduction of the inflammatory response as opposed to elimination of the bacterial insult.

If control of periodontal disease destruction can be centered upon the inflammatory state, the supportive role of an anti-inflammatory diet should be examined. Woelber et al[189] investigated the influence of an anti-inflammatory diet on different clinical parameters in patients with gingivitis. Thirty patients were randomly allocated to an experimental group and a control group stratified by their plaque values. The experimental group

had to change to a diet low in processed carbohydrates and animal proteins and rich in omega-3 fatty acids, vitamin C, vitamin D, antioxidants, plant nitrates, and fibers for 4 weeks. The control group did not change their diet. Both groups suspended interdental cleaning, periodontal parameters were assessed by a blinded dentist, and serological and subgingival plaque samples were taken. The authors demonstrated that although there were no differences regarding the plaque values, the experimental group showed a significant reduction in gingival bleeding, a significant increase in vitamin D values, and a significant weight loss. There were no intergroup differences regarding the inflammatory serological parameters, the serological omega fatty acids, or the subgingival microbiome composition. The diet of the test group significantly reduced gingivitis in a clinically relevant range, while serological inflammatory parameters and the subgingival microbiome seem to be unaffected.

A comorbidity for most oral diseases is a tobacco smoking habit. Resveratrol is a stilbenoid, a type of natural phenol, and a phytoalexin produced by several plants in response to injury such as a bacterial or fungal infection. These compounds are thought to act in a way similar to antioxidants. Sources of resveratrol in food include the skin of grapes. Correa et al[190] investigated the effect of the systemic administration of resveratrol (RESV) on oxidative stress during experimental periodontitis in rats subjected to cigarette smoke inhalation. Experimental periodontitis (EP) was induced in 26 male Wistar rats by the insertion of a ligature around one of the first mandibular and maxillary molars. The animals were assigned randomly to the following groups: cigarette smoke inhalation+resveratrol (SMK+RESV) (n=13) and cigarette smoke inhalation+placebo (SMK+PLAC) (n=13). The substances were administered daily for 30 days, and then the animals were euthanized. The maxillary specimens were processed for morphometric analysis of bone loss, and the tissue surrounding the first maxillary molars was collected for mRNA quantification of sirtuin 1 (SIRT1) by real-time PCR. The gingival tissues surrounding the mandibular first molars were collected for quantification of superoxide dismutase 1 (SOD1) and nicotinamide adenine dinucleotide phosphatase oxidase (NADPH) by using an ELISA assay. Reduced bone loss was demonstrated in animals in the SMK+RESV group compared with those in the SMK+PLAC group based on morphometric analysis. Resveratrol promoted higher levels of SIRT and SOD as well as reduced levels of NADPH oxidase in tissues derived from animals in the SMK+RESV group compared with those in the SMK+PLAC group. This study demonstrated that resveratrol is an efficient therapeutic agent that reduces exacerbation of bone loss found in animals with EP that were also exposed to smoke. The results suggest that its effects could be mediated, at least in part, by its antioxidant and anti-inflammatory properties which attenuate the effects of oxidative stress on EP in the presence of cigarette smoke.

The detrimental effects of smoking are not limited to the consumption of tobacco products. Chisini et al[191] conducted a systematic review examining the use of cannabis associated with periodontitis. Electronic searches were performed. Longitudinal and cross-sectional studies that investigated the association between the use of cannabis and periodontal disease were included. Meta-analyses and sensitivity analyses were conducted. A total of 143 records were found in the initial searches, and 5 articles were included in the systematic review and 4 in the meta-analysis. Overall, 13 491 individuals were included, of which 49.5% were men. Three of included studies investigated the relationship between cannabis and periodontal disease in adults, and the other 2 studies were performed in adolescents. A positive association was observed between the use of cannabis and periodontitis. Regarding the quality assessment, all studies presented high quality. The results of systematic review and meta-analyses demonstrate that the use of cannabis is associated with a higher prevalence of periodontitis.

Alveolar bone destruction associated with traumatic occlusion and periodontitis is well documented. However, the exact pathogenesis is unclear. As an important integrator of mechanical stimulation, the Hippo signaling pathway participates in mechanical transduction processes and regulation of cell morphology and various stress perceptions. Mechanical forces such as stress, strain, or distortion physiologically impacting cell density, stiffness of the extracellular environment, and cell geometry are known to regulate the localization and activity of Yes-associated protein/transcriptional coactivator with postsynaptic density protein (PSD95), drosophila disc large tumor suppressor (Dlg1), and zonula occludens-1 protein (zo-1) (PDZ)-binding motif (YAP/TAZ) pathway. Pan et al[192] examined the role of these signaling pathways in the development of experimental traumatic occlusion. This study aimed at exploring changes in YAP expression and their effect on periodontitis combined with traumatic occlusion. Mice were used to establish a periodontitis model by local administration of Porphyromonas *gingivalis* and a traumatic occlusion model by occlusal elevation (OE) by using composite resin bonding on the bilateral maxillary molar. The mouse fibroblast cell line and preosteoblast cell line were subjected to cyclic tensile/compressive stress and inflammatory stimuli to verify in vivo results. Severe bone resorption was observed by microCT scanning in the OE with *P. gingivalis* group, when compared with OE-only and *P. gingivalis*–only groups. Mechanical stress caused by OE activated the Hippo-YAP pathway in periodontal

tissues. These results suggest that abnormal stresses generated by OE activate the Hippo-YAP pathway. This study, although limited by its animal model, is interesting as it demonstrates a possible molecular mechanism for the alveolar bone destruction associated with traumatic occlusion. The Hippo-YAP pathway may be a potential target of topical drug therapy for traumatic occlusion.

From a public health perspective, the development of a vaccine for the prevention of periodontal disease would be of great benefit. Although prior immunization approaches targeting *P. gingivalis* have reported variable success, the vaccine remains experimental. Huang et al[193] examined the use of a cell-free protein synthesis (CFPS) as a platform to produce vaccinable targets suitable for efficacy testing in a *P. gingivalis*–induced mouse oral bone loss model. Recombinantly generated *P. gingivalis* minor fimbriae protein (Mfa1), RgpA gingipain hemagglutinin domain 1 (HA1), and RgpA gingipain hemagglutinin domain 2 (HA2) were combined in equivalent doses in adjuvants and injected intramuscularly to immunize mice. Serum levels of protein-specific antibody were measured by ELISA, and oral bone levels were defined by morphometrics. They found that recombinantly generated *P. gingivalis* proteins possessed high fidelity to predicted size and elicited protein-specific IgG after immunization. Importantly, immunization with the vaccine cocktail protected from *P. gingivalis* elicited oral bone loss. These data verify the utility of the CFPS technology to synthesize proteins that have the capacity to serve as novel vaccines.

Relationships between periodontal and systemic health

A relationship between periodontitis and rheumatoid arthritis (RA) has long been established. Because of genetic and environmental factors, anticitrullinated protein antibodies (ACPAs) are present in the serum of participants who are at risk of RA several years before the clinical manifestations present themselves. The role of these autoantibodies in the link between periodontitis and RA development is still unclear. Loutan et al[194] examined the periodontal status in first-degree relatives of patients with RA (FDR-RA). They examined this "at-risk" population for RA, examining the effect of ACPA positivity on periodontal disease susceptibility, without the complication of existing RA. Rheumatologic status and periodontal status were evaluated in a nested case-control study of FDR-RA with no diagnosis of RA at enrollment. The following parameters were assessed in 34 ACPA-positive (ACPA+) and 65 ACPA-negative (ACPA-) participants: gingival index (GI), plaque index (PI), probing depth (PD), bleeding on probing (BOP), and clinical attachment level (CAL). The researchers compared the 2 groups by using conditional logistic regression. They found that with ACPA+ individuals, the mean, PD, BOP, CAL, and number of sites per person with PD>4 mm and BOP were significantly higher than those with the ACPA– group. A significant finding was that all ACPA+ participants had periodontitis: 44.1% presenting moderate and 47.1% severe periodontitis. ACPA– participants had mainly mild (30.8%) and moderate (27%) periodontitis, differences being significantly different for both moderate periodontitis and severe periodontitis. In multivariable analyses, ACPA status and age were significantly and independently associated with periodontal conditions. The high prevalence and severity of periodontitis in FDR-RA was associated with seropositivity to ACPAs. This study further strengthens the hypothesis that periodontitis may be a risk factor in the development of RA.

Periodontal disease has also been linked to the pathologic findings in brain tissue similar to that found upon autopsy in patients who had suffered from Alzheimer's disease. *P. gingivalis*, a keystone pathogen in chronic periodontitis, was identified in the brain of patients with Alzheimer's disease in the form of proteases from the bacterium called "gingipains." Dominy et al[195] infected mice with *P. gingivalis*, resulting in brain colonization and increased production of αβ1-42, a component of amyloid plaques. The presence of this plaques has been associated with Alzheimer's disease. Furthermore, gingipains were neurotoxic in vivo and in vitro, exerting detrimental effects on tau, a protein needed for normal neuronal function. To block this neurotoxicity, Dominy et al[195] designed and synthesized small-molecule inhibitors targeting gingipains. Gingipain inhibition reduced the bacterial load of an established *P. gingivalis* brain infection, blocked αβ1-42production, reduced neuroinflammation, and rescued neurons in the hippocampus. These data suggest that gingipain inhibitors could be valuable for treating *P. gingivalis* brain colonization and possible neurodegeneration in Alzheimer's disease. However, these finding must be viewed with the understanding that no known treatment which has targeted the development of amyloid plaques and Tau protein production in the brain have been shown to prevent or reduce the clinical symptoms of Alzheimer's disease in humans.

Metabolic syndrome (MetS) consists of a group of metabolic conditions including central obesity, insulin resistance and associated glucose imbalance, dyslipidemia, and hypertension. MetS has been reported to affect 10%-84% of the population worldwide and around 25% of the population in developed countries. Tegelberg et al[196] investigated whether MetS is associated with deepening periodontal probe depths and alveolar bone loss. Their study was based on a subpopulation of the Northern Finland Birth Cohort 1966 survey (n=1964). The analyses were based on the metabolic data at ages 31

and 46 and probing pocket depth and alveolar bone level data at age 46. They found relative risks for PD≥4 mm and BL≥5 mm, which were higher in individuals with an exposure to MetS≥15 years (RR: 1.8, 95% CI: 1.6-2.1 and RR: 1.5, 95% CI: 1.3-1.9, respectively) than in those whose exposure was <15 years (RR: 1.2, 95% CI: 1.1-1.3 and RR: 1.1, 95% CI: 1.0-1.3, respectively). Consistently, stronger associations were found in never smokers. Women showed stronger associations of MetS with PD≥4 mm than men. The association with BL≥5 mm was observed only in men. They concluded that a long-term exposure by MetS was associated independently and in an exposure-dependent manner with periodontal pockets and alveolar bone level.

Periodontal regeneration

During initial preparation therapies, the acute phase response can be induced after scaling and root-planing (SRP). During this first 24-48 hours, a significant local and systemic inflammatory response is present, indicating the triggering of an acute phase reaction characterized by an increase of high-sensitivity C-reactive protein (CRP), IL-6, TNF-α, D-dimer, and serum amyloid A. Furthermore, in the first 2 days, endothelial dysfunction and an increase of blood coagulability are also detectable. Collectively these responses suggest a possible increase in the short-term cardiovascular risk for the patient shortly after periodontal therapy. Graziani et al[197] investigated the systemic effects of adjunctive use of enamel matrix derivative (EMD) in flapless periodontal treatment and compared acute phase (24 hours) and medium-term (3 months) inflammation and clinical outcomes after SRP with or without the application of EMDs in sites with a probing pocket depth (PPD)≥6 mm. They enrolled 38 periodontitis-affected participants who were randomized to SRP or SRP+EMD. Periodontal parameters were recorded at baseline and 3 months. Serum samples were collected at baseline, 1 day, and 90 days after treatment. They found that both treatments triggered an intense acute inflammation on day 1, which regressed to baseline values at 3 months. D-dimer and cystatin C levels did not show sharp increases in the SRP+EMD group 24 hours after treatment, compared with SRP. A significant difference between groups was observed for D-dimer. EMD application was also associated with better periodontal healing as shown by greater PPD reduction and clinical attachment level gain in sites with PPD≥6 mm and higher number of individuals with no residual PPD≥6 mm at 3 months. This study supports the use of EMD application after non-SRP as it resulted in lower fibrinolysis and better periodontal healing of deep pockets. For patients at high risk for vascular events, the adjunctive use of EMD may be considered during initial preparation therapies.

Minimally invasive periodontal flap management protocols have been recently developed which results in enhanced surgical outcomes from both a regenerative and esthetic perspective. Moreno Rodriguez et al[198] have developed an approach that uses a horizontal vestibular access incision facilitating the retention of the papillae. They conducted a study comparing the minimally invasive surgical technique (MIST) with this nonincised papilla surgical approach (NIPSA) in periodontal reconstructive surgery of deep intraosseous defects. Data on 30 patients with a deep intraosseous defect treated with either MIST (n=15) or NIPSA (n=15) were analyzed retrospectively. All patients met the same inclusion criteria and were treated following the same protocol, except for the surgical management of soft tissue (MIST versus NIPSA). Clinical parameters at baseline and 1 year after surgery, early healing at 1 week, and postoperative pain were assessed. Both the NIPSA and MIST techniques resulted in significant clinical attachment gain (CAG) and PD reduction (PDr) at 1 year after surgery. However, NIPSA resulted in significantly lower recession of the tip of the interdental papilla than MIST. Smoking negatively influenced early healing in both techniques. NIPSA and MIST techniques both resulted in significant improvements in clinical parameters. NIPSA showed significant soft-tissue preservation.

Successful periodontal regeneration within the furcation remains elusive. Promising results have been achieved with both autologous blood products, such as platelet-rich fibrin (PRF) and bisphosphonate gels. Wanikar et al[199] conducted a study evaluating the clinical and radiographic efficacy of 1% alendronate (ALN) gel in combination with PRF (PRF+ALN) and PRF alone in the treatment of grade II furcation defects. A split mouth study with 40 bilateral furcation defects was randomly divided into the PRF group and PRF+ALN group. Bone defect volume was the primary outcome evaluated at the end of 6 months with CBCT while the secondary outcomes being changes in clinical parameters including probing pocket depth (PPD), clinical attachment level (CAL), and horizontal PD (HPD) recorded at baseline, 3 months, and 6 months. They demonstrated the mean reduction in PPD, CAL, and HPD was 1.85 ±0.59 mm, 1.9 ±0.64 mm, and 1.7 ±0.73 mm, respectively, for the PRF group and 2.85 ±0.88 mm, 3.05 ±0.98 mm, and 2.3 ±0.73 mm, respectively, for the PRF+ALN group. At the end of 6 months, mean reduction in bone defect volume for the PRF and PRF+ALN groups was 8.65 ±3.84 mm^3 and 11.98 ±4.13 mm^3, respectively. This study is significant as it demonstrated both clinical and radiologic gains in the treatment of furcation defects by using a combination of PRF+ALN.

Bovine bone (BB) xenografts are commonly used in intraoral regenerative procedures, with high success rates. In a rabbit animal model, it has been demonstrated

that slowly resorbed deproteinized BB particles contribute to stable augmentation of the maxillary sinus by inhibiting bone resorption. Case reports have also shown histomorphometric data from a 10-year post follow-up with bovine bone and found the BB particles were in close proximity to the lamellar bone, without signs of graft resorption. In areas where this slowly resorbing bone graft is placed adjacent to an orthodontically moving tooth, the fate of the bone graft is unknown. Klien et al[200] investigated the biological mechanisms underlying alveolar bone regeneration (ABR) and orthodontic tooth movement into BB-regenerated sites. Two mouse models were established. The ABR model was based on osseous defects filled with BB. The orthodontic tooth movement-ABR model was used to move a molar into the regenerated site. Osseous morphometric analysis and tooth movement distance were evaluated with micro-CT. Histologic characteristics and osteoclast (OCS) accumulation were evaluated by hematoxylin and eosin and tartrate-resistant acid phosphatase staining (TRAP). Expression and location of the receptor activator of nuclear factor-kappa B (RANKL) and osteoprotegerin (OPG) were evaluated by immunofluorescent staining. They demonstrated bone healing peaking at 4 weeks. The distance of the orthodontic tooth movement into the bovine bone was significantly reduced versus that of the non–bovine bone controls. BB particles accumulated along the root's pressure side during orthodontic treatment. Despite the osteoclasts' presence adjacent to the BB particles, no BB resorption was observed. Increased RANKL expression was seen at the orthodontic tooth movement pressure zone, without any change in OPG expression. These 2 novel mouse models show that the lack of resorption of BB xenografts renders them inadequate for proper orthodontic tooth movement at a later stage. Clinicians should be aware of the use of BB in areas which may later undergo orthodontic tooth movement.

In some countries, the use of human allogenic grafting materials is not approved by regulatory agencies, primarily because of fear of disease transmission and the transmission of cell-free DNA (cfDNA) from the donor to the host. This regulatory environment has led to the widespread use of xenografts such as anorganic bovine bone mineral. In other countries, such as the United States, processed human bone allografts are commonly used in periodontal regeneration. Solakoglu et al[201] evaluated whether bone allograft material contains cfDNA and whether this foreign cfDNA can be released into the patient's blood circulation. Plasma samples were collected preoperatively and postoperatively on the same day, at 5 weeks, and 4 months from 25 women who received bone allograft material (test group) from male donors and from 10 women who were treated with autologous graft (control group, only preoperative and postoperative samples were collected). DNA was quantified and characterized in bone material and plasma samples by quantitative PCR with primers specific for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and Y chromosome and gel electrophoresis. DNA in bone material was digested by different concentrations of Dnase I. cfDNA Fragments with a size between 1 and 1.8 mug, at a length around 601 base pairs (bp), and smaller in each 100-mg allograft were detected. Treatment of the allograft with Dnase I completely degraded the longer but not the shorter DNA 90-bp fragments. Y-DNA was not detected in the patients' bloodstream at any time during the treatment and follow-up, but elevated levels of circulating cfDNA could be measured immediately postoperatively. The authors conclude that a transmission of DNA from allografts used for alveolar ridge reconstruction in humans is unlikely as the observed increase in circulating cfDNA in allograft and autograft patients immediately after operation may be elicited by the surgical procedure alone. The results of this study support the safety of allograft materials.

Soft tissues adjacent to teeth and implants

Treatment of noncarious cervical lesions (NCCLs) consists of either maintenance, placement of a cervical restoration, gingival augmentation, or a combination of these. Agudio et al[202] used a long long-term case series to assess the development/prevalence of NCCLs at sites that have and have not been treated with gingival augmentation after free gingival graft (FGG). Fifty-two patients had at least one test and one control site. Test sites showed absence of attached gingiva (AG) associated with gingival recession (GR) treated with FGG. Contralateral sites with or without AG served as controls. Patient/tooth/site-associated variables were recorded for each tooth/site at baseline (T0), 12 months after surgery (T1), during the follow-up period (T2) (15-20 years), and at the end of the follow-up period (T3) over 25-30 years. Mixed-effects logistic regression was used throughout the study. Forty-nine patients/130 sites were available for analysis at T2, whereas 44 patients/120 sites at T3. Twenty-two NCCLs >0.5 mm were restored in the test sites and in 35 in the untreated sites. The development of NCCL over time appeared associated with sites with attached KT<2 mm, as well as to teeth presenting a thin/nonmodified periodontal phenotype. This study supports the conventional wisdom that periodontal phenotype modification achieved by FGG placement may prevent the development/progression of NCCL. Evidence suggests that the thickness and width of the AG had a direct influence on the need of restoring these lesions during the 25- to 30-year observation period.

Relatively few studies have looked at the professional assessment or patient perception of esthetics after root coverage procedures. While the placement of connective

tissue grafts (CTG) seems to improve esthetic outcomes, the comparative advantage of the use of a collagen matrix (CMX) placed under a coronally advanced flap (CAF) has not be thoroughly studied. Pelekos et al[203] conducted a study by using 2 independent, trained, and calibrated assessors analyzing baseline and 6-month postoperative images from 183 participants with 475 recessions from a previously reported multicenter multinational randomized clinical trial. The root coverage esthetic score (RES) was assessed in its 5 constituent components after assessing the suitability of images blindly regarding treatment assignment and center. Data were analyzed at the tooth and participant level. One hundred fifty-five participants (81 CTG) and 393 teeth (207 CTG) were included in the analysis. CTG control participants had higher total RES scores. Analyses of RES subcomponents showed that the CTG group had higher scores in terms of gingival margin position but that better marginal tissue contour and soft-tissue texture were observed for the CMX group. No significant differences were observed for mucogingival alignment and gingival color. The CTG group had better overall RES scores while the better marginal tissue texture and marginal contour were observed in the CMX group.

Harvesting a CTG has obvious disadvantages as compared with the use of a nonautograft. Closure of the donor site is time-consuming and associated with some degree of patient discomfort. Typically, donor site closure is achieved by either suturing or with a cyanoacrylate tissue adhesive. Stavropoulou et al[204] compared the patient-centered outcomes, early wound healing, and postoperative complications at palatal donor area of CTG between cyanoacrylates tissue adhesives and polytetrafluoroethylene (PTFE) sutures. They enrolled 36 patients who required harvesting of CTG into a randomized clinical trial and assigned to one of 2 groups. In the "suture" group, wound closure was achieved with standardized continuous interlocking 6-0 PTFE sutures, while in the "cyanoacrylate" group, a high-viscosity blend of n-butyl and 2-octyl cyanoacrylate was applied until hemostasis was achieved. The primary outcome was the discomfort (eating, speaking) from the donor site during the first postoperative week; this was self-reported on a visual analog scale questionnaire. Secondary outcomes were the time required for suture placement or cyanoacrylate application, patient self-reported pain on the first day and the first week after surgery, the analgesic intake, and the modified early-wound healing index (MEHI). They found a nonsignificant difference in the median value of discomfort, which was 1.49 in the "suture" group and 1.86 in the "cyanoacrylate". However, the mean time required for suture placement was 7.31 minutes and for cyanoacrylate application 2.16 minutes ($P<.001$). No statistically significant differences were found between the 2 methods in reported pain level, analgesic intake, and MEHI. They concluded that cyanoacrylate performs similarly to sutures and can be used for wound closure of the donor site of CTG.

Successful immediate implant placement in the maxillary anterior zone remains to be a challenge when performed on patients with thin gingival phenotype or incomplete buccal plate. Zufia et al[205] presented a description of a unique clinical technique incorporating an immediate implant placement with simultaneous hard- and soft-tissue augmentation. This technique uses a combined epithelialized-subepithelialized connective tissue graft and cortical-cancellous autogenous bone graft for the treatment of incomplete buccal plate at an extraction site. The donor consists of a 4-layer graft taken from the maxillary tuberosity. Significant horizontal bone regeneration appears to have been achieved as well as soft-tissue augmentation for a central incisor in a single surgical step. After 3.5 years, the gingival contours and bone augmentation were stable with a pleasant esthetic result. The use of this 4-layer graft technique has shown to be successful regarding function and esthetic outcomes in anterior immediate implant placement. It reduces surgical interventions and treatment time and minimizes soft-tissue recession and bone resorption.

Long-term stability of the bone adjacent to a dental implant has been shown to be related to the amount of supracrestal soft tissue around the implant. Diaz-Sánchez et al[206] conducted a systematic review and meta-analysis to determine the extent to which supracrestal tissue attachment (STA) thickness affects marginal bone loss around dental implants. An electronic search was conducted and complementary sources covering the period up to June 2018. The studies were meta-analyzed based on implant position with respect to the alveolar bone crest (crestal/supracrestal). The marginal bone loss values were categorized according to STA width (thick/thin). Of the 1062 eligible titles, 9 articles were included in the review. The implants were positioned crestal or supracrestal with respect to the alveolar ridge. The difference between (thin/thick) STA was statistically significant among analytical subsets in terms of lesser marginal bone loss (crestal-positioned: weighted mean difference [WMD]=0.52, 95% CI: 0.03-1.01; $P=.036$; supracrestal-positioned). Implant positioning and patient age showed statistical significance in the meta-regression analysis. This review demonstrates that implants with thin STA result in greater marginal bone loss.

A secondary advantage of thick soft tissue adjacent a dental implant, especially in the esthetic zone, is the ability of the tissue to mask the visual appearance of the underlying neck of the implant and abutment. Titanium implants and abutments often present with a graying effect upon the peri-implant mucosa. Manufacturer-controlled electrolytic modification of the titanium surface will change the hue of the normally gray titanium.

Pink-shouldered implants and abutments have been fabricated to address the graying effect. Gil et al[207] assessed the visual effects of pink-neck implants and pink abutments with respect to the color of natural gingiva. The distribution pattern and magnitude of CIE-Lab color difference coordinates were also studied. Forty participants with a tooth in the maxillary esthetic zone deemed hopeless were recruited. Patients were randomized to either a conventional gray implant or a pink-neck implant. The hopeless tooth was removed, and patients received an immediate implant along with an immediate custom interim prosthesis. The interim prosthesis was maintained for 3 months to allow for complete healing of the implants. Two identical CAD-CAM titanium abutments only differing in color (gray and pink) were fabricated along with a ceramic zirconia crown. The gray abutment was delivered first with a zirconia crown, and it was replaced with the pink abutment 3 weeks later. Three weeks after insertion of each abutment with the zirconia crown, a spectrophotometer was used to collect the color of the peri-implant mucosa and natural gingiva, so the difference between the 2 sites could be calculated (ΔL* [difference in lightness], Δa* [difference in green-red axis], Δb* [difference in blue-yellow axis]). The natural gingiva measured was the gingiva of a contralateral or adjacent unrestored tooth. The effect of implant color and abutment on the color difference between peri-implant mucosa and natural gingiva was investigated with a linear regression model by using a generalized estimating equation (GEE) approach. Raw data demonstrated statistically insignificant smaller ΔL*, Δa*, and Δb* between peri-implant soft tissue and natural gingiva when the implant was pink versus gray. Furthermore, there were statistically insignificant smaller ΔL* and Δb* between peri-implant soft tissue and natural gingiva when the abutment was pink versus gray. Δa* Between peri-implant soft tissue and natural gingiva was significantly smaller when using a pink abutment regardless of the implant type. The authors demonstrated that by using an anodized pink abutment and/or a pink-neck implant, the color difference observed between the peri-implant mucosa and the natural gingiva in the redness spectrum was minimized.

The fabrication and modification of an interim implant restoration may facilitate the ideal shaping of the soft-tissue complex. A commonly used technique is to add subgingival restorative material to the provisional restoration. This additive procedure is designed to influence or "push" the tissues. However, this process can cause a temporary ischemia or blanching of the tissue. An adequate interim restoration should allow the tissue to recover from ischemia over a certain time. The dynamics of this tissue blanching is not well described. Yao and Wang[208] wanted to assess the time needed for peri-implant soft-tissue recovery. They examined interim restorations which were delivered on 25 single-implant sites 2 weeks after stage-2 surgery, and the gingiva appearance changes after delivery were recorded for 15 minutes by using a video camera. Gingiva color changes along the time were measured and analyzed. The color differences between peri-implant mucosa at 10 minutes and 0 minute, as well as between adjacent tooth gingiva, were all within a clinically acceptable range. The adaptive pressure technique by 2-stage contouring exhibited an optimal peri-implant soft-tissue profile within 10 minutes of the adaptive time.

Intraoral optical scanning technology is becoming more common place in the restoration of dental implants. The use of this technology can be problematic when attempting to register the shape of the peri-implant tissues. During a digital intraoral scan for an implant restoration in the esthetic zone, the peri-implant soft tissue will collapse rapidly after the interim restoration (IR) is removed, making it difficult to replicate the established emergence profile. Li et al[209] studied whether significant dimension differences could be found between peri-implant soft tissue supported by an IR and that immediately after removal of the restoration and to assess the changes over time. Optical scans were made of 12 single-implant sites in the esthetic zone of 10 participants. The scans in the first group replicated the peri-implant soft-tissue contour with the support of the IR; in the second group, scans were made at different times from 0 seconds to 20 minutes after removal of the restoration. The changes in the soft-tissue contour, including the height of the mesial papilla, distal papilla, and gingival margin, the facial and palatal soft-tissue thickness, and emergence profile discrepancies (EPDs), were assessed. A linear mixed model was built to estimate the EPD. After the removal of IR, the palatal soft-tissue thickness increased over time, and only minimal changes were found in the height of the mesial papilla, distal papilla, and gingival margin (up to -0.27 mm at 20 minutes). A significant EPD was immediately present at all the measurement sites after the removal of the IR. The linear mixed model showed a significant positive correlation between the natural logarithm of time and EPD. Significant positive correlations between gingiva thickness/implant depth and EPD were only seen at some of the sites. The authors concluded that only a small reduction in the papilla level occurred, but with no clinical influence on the proximal contact design of the restoration being detected. For the emergence profile, a significant but small discrepancy occurred immediately and continued to increase over time.

Bone biology and medication-related osteonecrosis of the jaw

The association between the risk of implant failure and medication is a developing area in dental implant

epidemiology. SSRIs have been shown to interfere with normal bone metabolism. Several groups have demonstrated conflicting results regarding the influence of selective serotonin reuptake inhibitors (SSRIs) on implant failure. Carr et al[210] recently published a study identifying the associations between implant failure and SSRI medication use in a cohort of consecutive patients receiving dental implants during a 20-year period. A retrospective review was conducted of all patients who received at least 1 dental implant from January 1, 1995, through December 31, 2014, assessing their history of SSRI use, active SSRI use, and SSRI use during follow-up with implant failure. Cox proportional hazards regression models assessed associations between demographic characteristics and SSRI use with implant failure, and outcomes were summarized with hazard ratios (HRs) and 95% confidence intervals (CIs). Follow-up SSRI use was analyzed with time-dependent covariates. During the study period, 5456 patients received their first implant (median age 53 years). The median duration of follow-up was 5.3 years for the 4927 patients who did not have implant failure. For the 529 patients who had implant failure, it occurred at a median of 0.5 years. After adjusting for age, sex, and era of implant, history of use of the SSRI, sertraline, was associated with an increased risk of implant failure among all patients and among the subset of patients with a history of SSRI use. They concluded that a history of sertraline use was associated with a 60% greater risk of implant failure; however, active SSRI use at the time of implant placement or during follow-up was not significantly associated with an increased risk of implant failure.

As the use of immediate implant therapies increases, the question of the appropriateness of placing a dental implant in an infected site arises. By using a canine animal model, Lee et al[211] investigated the histologic differences between immediate implants placed in chronically infected sites and noninfected sites. The histologic results of immediate implant placement also were evaluated on the basis of healing time and implant surface modification. Chronic endodontic-periodontic combined lesions were induced on the second, third, and fourth premolars of the hemimandible in 6 dogs, with the contralateral teeth as controls. Implants were immediately placed after the infected and noninfected tooth extractions by using implants with a machined surface, sandblasted with alumina and acid-etched surface, and chemically modified sandblasted with alumina and acid-etched with calcium solution surface. After 1 and 3 months, 3 dogs were euthanized, and the bone-to-implant contact, bone area fraction occupied, buccal and lingual first bone-to-implant contact from the implant platform, and buccal and lingual marginal bone loss were calculated. On histologic evaluation, no inflammation was observed around implants placed in the infected or noninfected sockets. At 1 month, no statistically significant differences were observed between the infected and noninfected sockets in buccal marginal bone loss and most aspects of the 3 different implant surfaces. At 3 months, no statistically significant differences were observed in parameters between the infected and noninfected sockets for 3 implant surfaces. This study supports the use of dental implants in previously infected sites associated with endodontic failure.

Zoledronate (zoledronic acid; ZA), a third-generation intravenously administered, nitrogen-containing cyclic bisphosphonate (BP), exhibits particularly high affinity for bone mineral, especially at sites of high bone turnover. BP's negative effect upon osteoclastic activity and survival is through the osteoclasts' inability to form a ruffled border essential for bone resorption. This effect of BPs results in a reduced bone resorption rate and subsequent turnover. In addition, BPs also have a negative effect on wound healing by the inhibition of angiogenesis. It has been advocated that caution should be exercised in placing dental implants in patients taking BPs because of possible alterations in the bone wound healing processes. Hou et al[212] proposed that the negative effects of systemic ZA administration could be offset by the role of different implant surface topographies. Twenty Sprague-Dawley rats were divided into 2 groups—test (bisphosphonate) and control (healthy). Bisphosphonate administration began 3 weeks before implant placement, and the animals received zoledronate (66 μg/kg) 3 times per week. Forty endosseous implants with a moderately rough (20 implants) or a turned surface (20 implants) were immediately placed bilaterally into extraction sockets of maxillary first molars. Animals were sacrificed after 14 and 28 days of healing, and en bloc specimens were harvested for histological and histomorphometric analyses. Statistically significant, higher bone-to-implant contact values were measured on moderately rough implants than on turned implants at 28 days and in the control group than in the test group for both implant surfaces. Histological observations for the control and the test groups demonstrated initial bone formation around moderately rough implants not only on the surface of the parent bone, as was the case with the turned surfaced implants, but also along the implant surface itself. The authors concluded that systemic ZA administration negatively influences osseointegration, but osseointegration was enhanced adjacent to moderately rough surfaces. Therefore, topographical surface modification may partially offset the negative impact of zoledronate administration.

ZA is also the most frequent agent associated with medication-related osteonecrosis of the jaw (MRONJ). Identification of novel approaches aiming to counteract its cytotoxic effects will be desirable to develop preventive therapies for MRONJ. The salivary peptide histatin-1 was

recently shown to promote oral wound healing, by acting in epithelial and endothelial cells. Castro et al[213] studied the effects of histatin-1 on cells exposed to ZA. Their study aimed to unveil the role of histatin-1 in osteoblastic and vascular cell lineages challenged with zoledronic acid. The effects of ZA, histatin-1, or their combination was evaluated in cytotoxicity (Trypan Blue exclusion) and cell migration (Boyden Chamber) assays. Caspase-3 cleavage was evaluated by Western blot. The angiogenic capacity of endothelial cells was assessed in a tubule formation assay in vitro. Castro et al[213] found that ZA decreased cell viability and migration of osteosarcoma cells (SAOS-2) and preosteoblasts (MC3T3-E1), in a dose-response manner. Importantly, histatin-1 restored both cell viability and migration in both cell lines upon challenge with ZA. These effects were recapitulated in endothelial cells (EA.hy926), as histatin-1 counteracted cytotoxic and antimigratory effects of zoledronic acid and restored the angiogenic capacity in vitro. The authors concluded that histatin-1 counteracts the cytotoxic and antimigratory effects of ZA in osteoblast-like and endothelial cells. Histatin-1 may play a role in the design of novel therapies aiming to prevent and treat BRONJ.

Alveolar ridge preservation, ridge and sinus augmentation procedures

Some extraction socket management strategies do not include bone grafting but rather clot stabilization alone. Guo et al[214] explored the effect of 2 commercially available hemostatic agents, a collagen sponge and oxide cellulose, on early healing of the extraction socket. By using a murine model, bilateral maxillary first molars were extracted, and the sockets were filled with or without hemostatic agents. Histology, histomorphometry, and immunostaining assays were performed on specimens harvested on postextraction day 1, 3, 7, and 14. In vitro studies were also designed to investigate the effect of agents on the dynamics of pH and viability of cells. They found that early socket healing was delayed by both agents but with different patterns. The migration of cells was impeded by oxide cellulose on postextraction day 1 compared with the collagen and the control group. The proliferation and osteogenic differentiation of cells were delayed by both materials. Moreover, apoptosis of periodontal ligament cells was present in the hemostatic agent groups. These effects are attributed to the compression to periodontal ligament by both agents, the acidic niche caused by oxide cellulose, and the intense foreign body reaction and inflammatory response caused by the agents. While the placement of hemostatic agents aids in the clinical management of the bleeding socket, their use delays the early extraction socket healing via different biological mechanisms.

Ridge preservation techniques aim to limit the dimensional changes after tooth extraction. Popular techniques include the use of either a collagen wound dressing or a use of a dense polytetrafluoroethylene (dPTFE) membrane. The dPTFE membrane has been advocated as an option that enhances the residual keratinized mucosal. Yet it is still unclear if the use of such membrane will be advantageous over a collagen wound dressing. Al Harthi et al[215] evaluated the outcomes of ridge preservation by using freeze-dried bone allograft with a collagen wound dressing. This study included 21 patients who had 1 molar extracted, and the site received ridge preservation by using freeze-dried bone allograft and a collagen wound dressing (test 2 group). Patients had 2 standardized CBCT scans, made within 72 hours and 3 months after extraction, to measure changes in ridge height and width, and buccal and lingual plate thicknesses. Changes in keratinized tissue width were recorded. Three-arm analyses were performed by using historic data from a previous randomized controlled trial by the same study group, in which 20 molar sites received a collagen wound dressing alone (control) and 20 received ridge preservation with freeze-dried bone allograft and a dense polytetrafluoroethylene membrane (test 1) by using the same methodology. They found a statistically significant difference in mean buccal ridge height changes between the control group (2.6 ±2.06 mm) and test 2 group (1.55 ±0.93 mm) but no difference in ridge and keratinized tissue width changes between groups. No correlation was found between buccal plate thickness and ridge width change. The authors completed freeze-dried bone allograft with collagen wound dressing as a barrier was used successfully for ridge preservation in intact molar extraction sites (<50% bone loss) and can be considered as a treatment alternative to freeze-dried bone allograft with a dense polytetrafluoroethylene membrane.

Studies examining the efficacy of socket preservation techniques frequently focus on the maintenance of the horizontal dimension of the alveolar ridge. While this dimension is undoubtably important, in the maxillary posterior areas, the residual vertical height will dictate the necessity for a secondary procedure such as a sinus lift. Cha et al[216] conducted a study examining whether alveolar ridge preservation reduces vertical changes in the posterior maxilla compared with spontaneous healing after tooth extraction. Forty participants requiring extraction of maxillary posterior teeth with root apices protruding into the maxillary sinus floor were consecutively enrolled. Patients were randomly assigned to either one of 2 surgical interventions: an alveolar ridge preservation procedure using collagenated bovine bone mineral and a resorbable collagen membrane (test) or no grafting (control). CBCT scans were made immediately and at 6 months after surgery, before dental implant placement. Based on radiographic data, the level of the sinus floor remained stable over time (baseline to 6 months) in the

test group. In the control group, the sinus floor level shifted more coronally than the test group. The test group demonstrated a significantly larger residual bone height than the control group at 6 months (7.30 mm [6.36, 8.20] versus 4.83 mm [3.94, 5.76], respectively). Implant placement without any additional sinus augmentation procedure was performed in 42.9% of test group participants, whereas in all the participants in the control group, an additional augmentation procedure was needed (100% of the participants). This finding is clinically relevant as it demonstrates alveolar ridge preservation in the posterior maxilla maintained the vertical bone height more efficiently and resulted in less need for sinus augmentation procedures at 6 months compared with spontaneous healing.

It is commonly understood that thicker buccal wall dimensions are important for the maintenance of bone levels adjacent to dental implants. However, there is a lack of knowledge concerning the critical buccal bone thickness required for securing favorable functional and esthetic outcomes, conditioned to the dimensional changes after implant placement. Monje et al[217] conducted a preclinical study to identify the critical buccal bone wall thickness for minimizing bone resorption during physiologic and pathologic bone remodeling. A randomized, 2-arm in vivo study in healthy beagle dogs was carried out. The first group of dogs was sacrificed 8 weeks after implant placement for histomorphometric examination of postsurgical resorption of the buccal bone wall. The second group of dogs was monitored during 3 ligature-induced peri-implantitis episodes and a spontaneous progression episode. Morphometric and clinical variables were defined for the study of physiologic and pathologic buccal and lingual bone loss. Seventy-two implants were placed in healed mandibular ridges of 12 beagle dogs. Two groups were defined: 36 Implants were placed in sites with a thin buccal bone wall (<1.5 mm), and 36 were placed in sites with a thick buccal bone wall (≥1.5 mm). No implants failed during the study period. For the great majority of the histomorphometric parameters, a critical buccal bone wall thickness of at least 1.5 mm seemed to be essential for maintaining the buccal bone wall during physiologic and pathologic bone resorption. Suppuration (+) and mucosal recession (-) were more often associated with implants placed in sites with a thin buccal bone wall. Therefore, a critical buccal bone wall thickness of 1.5 mm at implant placement is advised as a thicker peri-implant buccal bone wall (>1.5 mm) is exposed to significantly less physiologic and pathologic bone loss than a thinner buccal bone wall (<1.5 mm).

Sinus augmentation procedures have traditionally been classified as either using a lateral (window) or transcrestal (vertical) approach. Numerous transcrestal approaches have been developed. While these approaches are thought to be less invasive to the patient, they may be prone to more Schneiderian membrane perforation. Gargallo-Albiol et al[218] conducted a study which endoscopically examined the incidence of Schneiderian membrane perforation during transcrestal maxillary sinus floor elevation (SFE), in relation to the bone preparation technique, amount of bone graft, membrane elevation height, and different surgical steps. Seven cadaver heads corresponding to 12 maxillary sinuses were used to perform 3 SFEs via transcrestal approach per sinus (36 elevations). Each sinus was randomly assigned to either the Sinus Crestal Approach (SCA) drill kit technique (experimental group) or the conventional osteotome technique (control group). During all phases of the surgery, the integrity of the sinus membrane was monitored through endoscopic examination. A significant difference was found in the incidence of perforation and vertical elevation height between the study groups, favoring the experimental group. A safety elevation threshold of 5 mm without bone graft and implant placement was estimated. A significant correlation was observed between the residual ridge height and the incidence of perforation. The SCA drill kit demonstrated superior osteotomy preparation and membrane elevation capabilities than the osteotome technique, especially when a 6-mm SFE is indicated.

Collagen membranes are commonly used devices in socket preservation and ridge augmentation procedures. This type of membrane can vary substantially in composition, which may impact the healing response. The presence or absence of crosslinking of the collagen fibrils within the barrier is such a composition variable. Hong et al[219] studied the effect of 2 different ridge preservation techniques on soft- and hard-tissue dimensions by using 2 different collagen barriers as the variable. Thirty patients requiring tooth extraction were randomly allocated to either control group C (allograft covered with a noncrosslinked collagen membrane with primary closure) or experimental group E (allograft covered with crosslinked collagen membrane left exposed). Sites were surgically re-entered at 6 months. Soft- and hard-tissue measurements, CBCT, and cast measurements were made at baseline and 6 months. Twenty-eight patients were included in this analysis. When the 2 treatment groups were compared, the width of the buccal keratinized tissue in the E group showed an increase of 0.43 ±0.42 mm compared with net loss of 1.57 ±0.51 mm for the C group. Similarly, buccal tissue thickness has increased in the E group 0.46 ±0.22 mm compared with a loss of 0.15 ±0.23 mm in the C group. Volumetric assessment of the changes in the alveolar ridge for the E group showed a slight decrease (68.3 ±17 mm^3), whereas the C group has experienced almost double this loss (107.5 ±11 mm^3). Crestal width, measured on the CBCT scan, has shown significant

reduction in the C group (4.18 ±0.56 mm) compared with only 1.74 ±0.4 mm in the E group. Hong et al[219] concluded that the crosslinked collagen membrane with allograft placed intentionally nonsubmerged resulted in better preservation of the keratinized tissues (width and thickness) with similar and at times better osseous preservation after extraction.

Evidence supporting the use of these crosslinked collagen barriers was further provided by El-Jawhari et al.[220] They investigated the activities of human bone marrow-multipotent stromal cells (BM-MSCs) when loaded onto 2 differently structured pure collagen membranes. A crosslinked collagen membrane (CS) was tested versus a noncrosslinked bilayer collagen membrane, Bio-GideI (BG). After loading with BM aspirate containing native MSCs, cell attachment to the membranes was examined by using electron microscopy and flow cytometry. Furthermore, alkaline phosphatase (ALP) expression and calcium deposition levels were investigated for these BM-aspirate–loaded membranes. Culture-expanded BM-MSCs were also used to load membranes and confirm the MSC functional data. All membranes supported BM-MSC attachment. However, a larger number of attached BM-MSCs were detected for CS than for BG. In an osteogenic medium, ALP activity was higher for CS than for BG. Consistently, the normalized secreted vascular endothelial growth factor A (VEGF-A) levels were higher in BM-MSCs loaded on CS relative to BG. Collectively, both collagen membranes supported the osteogenic functions of BM-MSCs. However, CS was found to be overall superior probably because it provided more BM-MSC attachment. These collagen membranes could potentially be used to improve GBR outcomes in alveolar bone regeneration applications.

The choice of the ideal grafting material in sinus augmentation procedures has yet to be determined. Nishimoto et al[221] evaluated and compared the degree of new bone formation after maxillary sinus graft (MSG) by using 3 different bone graft materials. Patients with an edentulous posterior maxilla (unilateral or bilateral) were included in this study and underwent a 2-stage procedure. Each sinus was randomly assigned 1 of the 3 graft materials: anorganic bovine bone mineral (ABBM) (Bio-Oss), anorganic equine bone mineral (AEBM), or mineralized cancellous bone allograft (MCBA). Bone core samples were obtained from the lateral wall of the grafted sites at least 8 months after MSG. Bone quality was evaluated during bone core retrieval. A total of 28 sinuses (14 unilateral and 7 bilateral) from 21 participants, with a mean age of 61.5 (range 33-75) years, were included in the study. Twenty-eight bone cores (ABBM, n=9; AEBM, n=9; MCBA, n=10) were obtained at a mean healing time of 9.1 (range 8-12) months. Six maxillary sinus membrane perforations (≤5 mm) were noted and repaired during surgery (21.4%). Histomorphometric analysis of the harvested bone cores revealed statistically significant differences in the percentage of vital bone (VB%), residual bone materials (RBM%), and connective tissue/marrow (CT%) among the different graft materials. The VB% in the MCBA group (32.0 ±12.4%) was significantly greater than that in the ABBM (10.9 ±8.9%) and AEBM (9.1 ±5.9%) groups. The RBM% in the MCBA group (5.5 ±5.7%) was, however, significantly less than that in the ABBM (34.3 ±12.1%) and AEBM (38.9 ±5.3%) groups. There were no significant differences in VB% and RBM% between ABBM and AEBM groups (P=1.0). Newly formed bone and residual graft materials were integrated into the surrounding tissue with no sign of inflammation or foreign-body reaction. The authors concluded that MCBA had significantly greater new bone formation than ABBM and AEBM.

Peri-implant health and disease

There is no current consensus regarding the need for antibiotic therapy at the time of implant surgery. Romandini et al[222] conducted a systematic review asking the question, "In patients undergoing dental implant placement, which is the best antibiotic prophylaxis protocol to prevent early failures?" The MEDLINE, SCOPUS, CENTRAL, and Web of Knowledge electronic databases were searched in duplicate for RCTs up to July 2017. Additional relevant literature was identified through handsearching on both relevant journals and reference lists and searching in databases for gray literature. A network meta-analysis (NMA) was conducted, and the probability that each protocol is the "Best" was estimated. The authors found 9 RCTs, with a total of 1693 participants. Owing to the few events reported, it was not possible to conduct an NMA for adverse events; therefore, it was conducted only for implant failures (IF). The protocol with the highest probability (32.5%) of being the "Best" one to prevent IF was the single dose of 3 g of amoxicillin administered 1 hour preoperatively. Even if the single preoperative dose of 2 g of amoxicillin is the most used, it achieved only a probability of 0.2% to be the "Best" one. With the limited data available, it appears that the use of antibiotic prophylaxis is protective against early implant failures. Whenever an antibiotic prophylaxis is needed, there is still insufficient evidence to confidently recommend a specific dosage. Most importantly, the use of postoperative courses does not seem however to be justified by the available literature.

Our understanding of disease progression of peri-implantitis and influence of professional interventions is limited. For example, it not known whether nonsurgical or surgical therapies are better at halting the progression of the disease. Karlsson et al[223] examined the records of 70 patients diagnosed with moderate or severe peri-implantitis at ≥1 implant site 4 years earlier. Changes

of MBLs during the study period assessed on radiographs and predictors of disease progression were identified by Cox regression and mixed linear modeling. Patient files were analyzed for professional interventions related to the treatment of peri-implantitis. They found that the mean ±standard deviation bone loss at implants diagnosed with moderate or severe peri-implantitis was 1.1 ±2.0 mm over the observation period of 3.3 years. While nonsurgical measures including submucosal and/or supramucosal cleaning of implants were provided to almost all patients, surgical treatment of peri-implantitis was limited to a subgroup (17 participants). Surgically treated implant sites demonstrated a mean bone loss of 1.4 ±2.4 mm before surgical intervention, while only minor changes (0.2 ±1.0 mm) occurred after therapy. Clinical parameters (bleeding or suppuration on probing and PD) assessed at diagnosis were statistically significant predictors of disease progression. This study supports the notion that nonsurgical procedures were insufficient to prevent further bone loss at implant sites affected by moderate or severe peri-implantitis. Surgical treatment of peri-implantitis markedly diminished the progression of bone loss in this same group of patients.

The presence of retained excess cement has been linked to peri-implant disease. There is also emerging evidence that the type of cement used may have an impact on the development of peri-implant disease. De Martinis Terra et al[224] published a case report presenting 6 consecutive patients diagnosed with peri-implantitis associated with residual methacrylate cement. Clinical examination of the peri-implant sulcus demonstrated the adherence of the cement not only to the crowns but also to the soft tissues. These patients responded to cement removal and disinfection procedures. All crowns were recemented with a zinc oxide eugenol (ZOE)-type cement. Six patients, each presenting one methacrylate cement-retained implant restoration and showing peri-implant inflammation and bone loss were treated. All the patients were negative for bleeding on probing after 6 weeks, and this was maintained at 1 year of follow-up from nonsurgical therapy and crown refixation with alternative and resorbable cement. Of interest is that recementing with ZOE effectively resolved the inflammation and led to complete restoration ad integrum, as evaluated clinically and radiographically, after 1 year.

In a nonsurgical environment, the most ideal method for debridement of the implant surface is unknown. Removal of the submucosal accretions without alteration of the implant or abutment surface is a treatment goal. Keim et al[225] examined the in vitro efficacy of 3 different implant surface decontamination methods in a peri-implant bone defect model. A total of 180 implants were stained with indelible red color and distributed to standardized peri-implant bone defect resin models with a circumferential defect angulation of 30 degrees, 60 degrees, or 90 degrees (supraosseous defect). Sixty implants were assigned to each type of defect. All implants were cleaned by the same examiner. For each type of defect, 20 implants were cleaned for 2 minutes with one of 3 devices: curette (CUR), sonicscaler (SOSC), or airborne-particle abrasion with glycine powder (APA). Thereafter, photographs were made from both sides of each implant, and the cumulative uncleaned implant surface area was measured by color recognition technique. Scanning electron microscope images were examined to assess morphologic surface damages. The results showed that the cleaning efficacy as percent (%) of residual color was significantly different for each of the 3 defect angulations for each treatment device: 30 degrees CUR: 53.44%>SOSC: 19.69%>APA: 8.03%; 60 degrees CUR: 57.13%>SOSC: 11.4%>APA: 0.13%; and 90 degrees CUR: 48.1%>SOSC: 13.07%>APA: 0.58%. The differences among the 3 different cleaning modalities within each defect type were also significant. Scanning electron microscope images showed no surface damages after the use of APA. Airborne-particle abrasion is the most efficient (APA>SOSC>CUR) and less surface damaging treatment modality for each defect angulation in this in vitro model.

During the treatment of a peri-implant defect in the open or surgical environment, other implant surface debridement techniques are available. One of these techniques includes the use of a rotating titanium brush. de Tapia et al[226] evaluated the use of a titanium brush in the implant surface decontamination performed during the regenerative surgical therapy of peri-implantitis. A randomized double-blinded clinical trial, with a 1-year follow-up, was carried out. After a hygienic phase, peri-implantitis–affected implants were randomly assigned to a control or to a test group. In the control group, implant surface was decontaminated both mechanically and chemically with 3% H_2O_2 and plastic ultrasonic scalers, respectively, while in the test group, a titanium brush was also applied. Intrabony defects in both groups were filled with an alloplastic material (beta-tricalcium phosphate and hydroxyapatite) and covered with a collagen membrane. The primary outcome was the reduction in probing pocket depth (PPD) at the deepest site. Thirty patients were included, 15 in each group. At 12 months, reduction in PPD was 4.87 mm and 2.85 mm, respectively. The correspondent figures for residual PPD were 3.6 mm and 4.92 mm, respectively. The additional use of a titanium brush during regenerative treatment of peri-implantitis resulted in statistically significant benefits in terms of PPD reduction after 12 months.

The use of topic fluoride and hydrogen peroxide rinses is frequently prescribed as part of a home care regimen for the dentate patient. As we become more aware of the possible detrimental effects of implant surface alteration, the safe use of these topical agents

with regard to the implant surface should be considered. Peñarrieta-Juanito et al[227] evaluated surface changes on dental implant systems and ions release after immersion in fluoride and hydrogen peroxide. Ten implant-abutment assemblies were embedded in acrylic resin and cross-sectioned along the implant vertical axis. Samples were wet ground and polished. Delimited areas of groups of samples were immersed in 1.23% sodium fluoride gel (F) or in 35% hydrogen peroxide (HP) for 16 minutes. Gels were collected from the implant surfaces and analyzed by inductively coupled plasma mass spectrometry (ICP-MS), to detect the concentration of metallic ions released from the implant systems. Selected areas of the abutment and implant (n=15) were analyzed by atomic force microscopy (AFM) and SEM. Scanning electron microscope images revealed surface topographic changes on implant-abutment joints after immersion in fluoride. Implants showed excessive oxidation within loss of material, while abutment surfaces revealed intergranular corrosion after immersion in fluoride. ICP-MS results revealed a high concentration of Ti, Al, and V ions in fluoride after contact with the implant systems ICP-MS showed the release of metallic ions in hydrogen peroxide medium after contact with dental implants. This study suggests that therapeutic substances such as fluorides and hydrogen peroxide can promote the degradation of titanium-based dental implant and abutments leading to the release of possibly toxic ions.

There is increased interest in the role of titanium particles shed into the peri-implant tissues and a possible causation of peri-implant disease. Surveys have shown that ultrasonic scalers are routinely used in the debridement of peri-implant lesions. Harrel et al[228] conducted an in vitro study designed to evaluate if titanium particles are produced when an ultrasonic scaler is used on an implant. New airborne-particle abraded, large grit, acid etched (SLA) coated implants were subjected to ultrasonic scaling with stainless steel, titanium, and PEEK plastic tips. The implants were placed in a holding device, and the ultrasonic scaler was positioned on the SLA surface under 0.25 N force. The implants were subjected to 30 scaling motions. The ultrasonic coolant water was collected, and the number of metallic particles were counted under a light microscope. The particles were confirmed to be titanium via elemental analysis. The implants were visually evaluated for damage to the SLA coating. No metallic particles were detected in the water supplied to the ultrasonic scalers (passive control). Metallic particles were detected when implants were subjected to the ultrasonic coolant water only without the scaler tip touching the implant (active control). All implants that were scaled produced metallic particles and showed easily detectable damage to the SLA layer. All ultrasonic scaling, including the PEEK plastic tips, caused the production of titanium particles and caused damage to the SLA coating of the implant. Ultrasonic scalers should be used with great caution in the treatment of peri-implant conditions, and care should be taken to not touch the SLA surface of the implant.

If our regular professional cleaning of titanium implant surfaces results in the discharge of titanium particles and ions, what is the biological evidence that this therapy may be harmful? Metal particle release has been presumed as a potential initiator of crestal bone loss around oral implant through engendering an aseptic inflammation in the peri-implant tissue. Titanium particles may also function as stimulant factors, inducing marginal bone resorption around dental implants independent of bacterial infection. The titanium particles may also create an inflammation microenvironment leading to peri-implant bone resorption promoted by macrophage recruitment and macrophage polarization toward a proinflammatory M1 phenotype with production of inflammatory mediators. Wang et al[229] investigated the effects of titanium particles–induced foreign body reaction on peri-implant bone level and the related mechanism by using clodronate liposomes to deplete macrophages. To decipher the role of macrophages in vivo, it is necessary to establish a model of macrophage depletion in the whole animal. One method to obtain animal models efficiently depleted in macrophages in different tissues and blood is the use of a clodronate-liposome solution. Sprague Dawley rats with custom-made titanium screw implanted in the bilateral maxillary first molar area for 4 weeks to obtain osseointegration were randomly divided into 4 groups. Twenty microgram titanium particles were introduced into the peri-implant tissue to induce aseptic foreign body reaction, and macrophages were depleted by the local injection of 100 μL of clodronate liposome immediately and reinjection every 3 days until the sacrifice of the rats (Ti+LipClod group). Titanium-injected rats also treated with phosphate buffer solution (Ti+PBS) or empty liposome (Ti+Lip) as well as rats injected with PBS alone (control) were included as controls. Eight weeks later, animals were sacrificed, and specimens containing implants were collected. Half of the specimens were analyzed radiologically to measure bone-level change, and macrophage markers were also characterized by immunofluorescence to evaluate macrophage number, density, and phenotype distribution. The study demonstrated no obvious bacterial contamination in all titanium-injected areas, and the implant survival rate was 100%. Compared with Ti+PBS and Ti+Lip groups, macrophage density (1.64 ±0.86%) infiltrated into peri-implant tissue and bone loss (0.17 ±0.03 mm) around implant decreased significantly in the Ti+LipClod group. Immunofluorescence analysis showed that more macrophages infiltrated into peri-implant tissue in the Ti+PBS and Ti+Lip groups, predominantly with M1 phenotype.

In contrast, the macrophage density was lower and M2 phenotype was dominant in the control group. The authors concluded that titanium particles had a negative effect on peri-implant tissue by activating macrophages which induced an M1 macrophage phenotype promoting local secretion of inflammatory cytokines. This study revealed the marked impact of macrophage polarization with respect to peri-implant bone loss caused by titanium particles.

Knowing that titanium particles can induce an immune response, the effect of these particles on bone and soft-tissue cells types should be explored. Happe et al[230] studied the direct effects of different titanium particle concentrations on viability of human calvarial osteoblasts and human gingival fibroblasts. They took primary human calvaria osteoblasts (HCOs) and human gingival fibroblasts (HGF-1), cultivated the cells, and allowed them to adhere for 24 hours. Titanium powder concentrations (0.01-1.0 mg/mL) were added, and specimens were analyzed at 3 time points (24 hours, 7 days, and 21 days). Cell viability was analyzed by using living cell count, proliferation (MTT) assay, and a live/dead staining. Cytotoxic effects were evaluated by using the lactated dehydrogenase assay. Qualitative analysis of cell viability was performed. Release of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) was estimated with human IL-6/human TNF ±ELISA. Titanium concentrations of 0.1 mg/mL and 1.0 mg/mL showed medium- and long-term effects on cell growth and proliferation rates. Cytotoxic effects by release of lactate dehydrogenase were observable during the first 24 hours. Titanium powder seemed to be more cytotoxic to human gingival fibroblast cells than to human calvaria osteoblast cells. For human calvaria osteoblasts, only the highest concentration showed cytotoxic effects. Human calvaria osteoblasts secreted IL-6 only during the first 24 hours and only in the highest titanium concentration, whereas human gingival fibroblasts secreted IL-6 during the entire period. Incorporation of smaller and single titanium particles by cells was identified under scanning electron microscope analysis. This study demonstrated that cell viability is negatively correlated with titanium concentration.

Bacterial biofilms are a major problem in the treatment of infected dental and orthopedic implants. Removal of these biofilms without dissemination of titanium particles is a treatment goal. Ratka et al[231] investigated the cleaning effect of an electrolytic approach (EC) compared with a powder-spray system (PSS) on titanium surfaces. The tested implants (different surfaces and alloys) were collated into 6 groups and treated ether with EC or PSS. After a mature biofilm was established, the implants were treated, immersed in a nutritional solution, and streaked on Columbia agar. Colony-forming units (CFUs) were counted after breeding and testing (EC), and control (PSS) groups were compared by using a paired sample *t* test. No bacterial growth was observed in the EC groups. After thinning to 1:1 000 000, 258.1 ±19.9 (group 2), 264.4 ±36.5 (group 4), and 245.3 ±40.7 (group 6) CFUs could be counted in the PSS groups. The difference between the electrolytic approach (test groups 1, 3, and 5) and PSS was statistically significant. Only EC inactivated the bacterial biofilm, and PSS left reproducible bacteria behind.

The positive in vitro results of the electrolytic decontamination method were clinically demonstrated by Schlee et al.[232] They conducted a clinical trial assessing the 6-month outcomes after surgical regenerative therapy of peri-implantitis lesions by using either an electrolytic method (EC) to remove biofilms or a combination of powder spray and electrolytic method (PEC). Twenty-four patients with 24 implants suffering from peri-implantitis with any type of bone defect were randomly treated by EC or PEC. Bone defects were augmented with a mixture of natural bone mineral and autogenous bone and left for submerged healing. The distance from implant shoulder to bone was assessed at 6 defined points at baseline (T0) and after 6 months at uncovering surgery (T1) by periodontal probe and standardized radiographs. One implant had to be removed at T1 because of reinfection. None of the other implants showed signs of inflammation. Bone gain was 2.71 ±1.70 mm for EC and 2.81 ±2.15 mm for PEC. No statistically significant difference between EC and PEC was detected. Significant clinical bone fill was observed for all 24 implants. Complete regeneration of bone was achieved in 12 implants. Defect morphology impacted the amount of regeneration. They concluded that the EC protocol needs no further mechanical cleaning by a powder spray. Complete reosseointegration in humans with peri-implantitis is possible by using the EC protocol.

IMPLANT DENTISTRY

This review of the scientific literature in implant dentistry targets the practicing restorative dentist. It qualitatively screens published and indexed articles throughout the PubMed database for the year 2019. The foci of the review are clinical relevance and long-term reporting. Included in the review are detailed descriptions of the searches performed and exclusion and inclusion criteria. To be systematic, the following PubMed search was performed: "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, including date 01/01/2019-12/31/2019, English language, human studies, clinical trial, reviews, and meta-analysis. To be included, articles had to be published in journals referenced in the Journal

Citation Report, be related to dental implants, be relevant to treatment planning decisions, and be available in full text to the reviewer.

This year's literature review includes 23 clinical articles and 5 meta-analyses of clinical questions. Topics studied include implants in women with osteoporosis (1 article), soft-tissue health around implants (1 article), outcomes relative to various implant-abutment variables (8 articles), guided-surgery and digital workflow (4 articles), short versus long implants (2 articles), immediate versus conventional loading (6 articles), interim restorations (2 articles), and overdentures (4 articles).

Clinical trials and systematic reviews

The first clinical trial for review, by Temmerman et al,[233] is significant in scope and quality. This 5-year 4-center controlled prospective trial measures outcomes for implants placed in women with osteoporosis or osteopenia. Postmenopausal women, older than 60 years, received 2-8 implants and were followed up for at least 3 months. Bone mineral density was evaluated with DXA scans to obtain a T-score. T-scores of 0 to -1.0 are considered normal, -2.5 or less are diagnosed as osteoporosis, and between -1.0 and -2.5 are diagnosed as osteopenia. In this study, test patients had T-scores $\leq$-2, while healthy controls group patients had T-scores $\leq$-1. The same brand of implants was placed in patients by using a 2-stage protocol with abutment connection at 12 weeks. Restorative options included bar-attached overdentures or screw-retained fixed partial dentures.

Survival rate at 5 years was 96.5% for test patients and 100% for the healthy controls. This group difference is statistically significant (P=.004), but the patient-level survival values of 89.2% for test patients and 100% for the controls were not significant (P=.29). During the 5-year interval, 5 mechanical complications occurred (abutment screw fractures and connecting bar fractures), and 3 patients were treated for peri-implantitis. The differences in MBL alterations, plaque scores, bleeding on probing, probing pocket depth, and clinical attachment level, between the test and control groups, were not significant. It can be concluded from these results that oral implants can be safely used in osteopenic and osteoporotic postmenopausal women with similar outcomes as nonosteopenic and nonosteoporotic postmenopausal women.

With respect to peri-implant tissue health and prosthetic intervention, de Tapia et al[234] performed a well-designed controlled clinical trial to assess the impact of prosthetic contours on soft-tissue inflammation. Peri-implant mucositis is mainly influenced by the presence of plaque and the patients' abilities to provide daily hygiene at the implant or abutment tissue interface. The authors hypothesized that modifying prosthesis contours would permit better access and reduce peri-implant inflammation. Twenty-four participants received modified prosthetic contours, while 21 participants who did not receive modifications served as controls. All participants were subjected to identical hygiene protocols over the course of 6 months.

At 6 months, tissues surrounding prostheses with modified contours presented significantly lower bleeding and plaque indexes. Trial follow-up was short as specific aims did not require extended duration. However, the results contribute pertinent data to the clinical question, "Should we modify the prosthetic contours in situation of difficult access for oral hygiene to reduce soft-tissue inflammation?" The answer appears to be yes.

To address the relationship between implant-abutment interface and MBLs or other clinical outcomes, 8 articles were selected for review, of which 2 were meta-analyses. A well-designed multicenter investigation with 3 years of follow-up was conducted by Messias et al.[235] The study compares the outcome of 58 identical internal connection subcrestal implants placed in the same participants but at different depths, 0.5 mm and 1.5 mm.

According to patient response, there was no preference between the crowns fabricated on implants placed at different depths (0.5 mm and 1.5 mm). However, the implants placed at 1.5 mm demonstrated significantly greater marginal bone resorption This suggests that the establishment of biological width around implants can induce more bone remodeling when implants are more deeply placed.

Agustin-Panadero et al[236] placed 120 implants over 2 years and evaluated bone remodeling around 6 abutment-implant designs. The following bone-level implant connections were tested: Morse taper with internal hexagon connection (group 1); internal hexagon with dodecagonal connection (group 2); and internal hexagon connection (group 3). Tissue-level implants included convergent machined collar with internal hexagon connection (group 4); divergent machined collar with internal hexagon connection (group 5); and divergent polished collar with internal octagon connection (group 6).

The results indicated that tissue-level implants demonstrated significantly less marginal bone loss than bone-level implants, with bone loss of 0.46 mm versus 0.73 mm, respectively (P=.025). Implants demonstrating the least marginal bone loss (0.24 $\pm$0.22 mm) were tissue-level convergent machined collar with internal hexagon connections. Statistically significant outcomes were observed for only bone-level implants in group 2 and the tissue-level implants in group 6.

The authors suggested that marginal bone remodeling at 2 years in this study is primarily influenced by physiologic processes because participants were

medically and periodontally healthy, nonsmokers, with good oral hygiene, requiring single restorations in the absence of parafunctional habits. In combination with the previous 2 articles reviewed, these criteria, along with the short span of the study, demonstrate that the implant-abutment connection likely influences marginal bone remodeling, despite low clinical values.

Koutouzis et al[237] focused their well-designed clinical trial on marginal mucosal alterations and bone-level changes around identical, single-unit, bone-level implants restored with concave or convex titanium abutments. Two groups of 13 healthy patients received identical conical connection 3.5-mm-wide implants. All procedures were planned digitally, and implants were positioned 1 mm below the osseous crest as recommended by the manufacturer. Identical definitive abutments, one with concave and the other with convex profile, were delivered along with interim PMMA restorations at the time of surgery. Definitive restorations were initiated after 2 months without removing the abutments. Restorations were placed at 3 months after the surgery.

No statistically significant differences were found regarding bleeding on probing, pocket depth, or mucosal position between the 2 groups. Given experimental conditions, the abutment profile had no significant influence on the soft tissues at 1 year. However, MBLs were significantly influenced at 1 year. Concave and convex abutments were associated with 0.24-mm and 0.66-mm bone gain, respectively (P=.007). As the authors indicated in the discussion, "abutment macro-design can have an effect on establishment of the biologic width and consequently on the amount of bone remodeling," which is in accordance with previous studies in this review.

Cooper et al[238] reported on a clinical trial that compared at 3 years the peri-implant tissue response around 3 different implant-abutment interfaces with immediate placement of interim restorations in healed alveolar ridges. Implant sites had been previously augmented with rhBMP-2 with or without mineralized bone allografts. Implant-abutment interfaces included conical, flat-to-flat, and platform-switched restorations. Manufacturer's instructions were followed when incorporating matching abutments (Direct, Snappy, or GingiHue abutments). Immediate interim crowns were placed without occlusal contacts. Definitive restorations, delivered 12 weeks after implant placement, were pressed and lithium disilicate cemented on machined zirconia by using RelyX resin cement. Implant survival, MBLs, and peri-implant mucosal measurements were evaluated. At 3 years, 45 conical interface, 34 flat-to-flat, and 32 platform-switched restorations were evaluated. Fourteen implant failures were recorded, including 8 for the flat-to-flat and 6 for platform-switched interfaces. No specific correlation could be made for these failures. MBL changes occurred mainly during the first 6 months with significantly less change recorded for the conical interface (0.2 mm versus 1.1 mm and 1.2 mm, P<.001).

It is of interest, when considering the 3-year follow-up period, MBLs were "stable" for 72% of the conical, 3% of flat-to-flat, and 16.6% of platform-switched interfaces. Furthermore, probing pocket depths were significantly less for conical interface than for flat-to-flat interfaces at all time measurement points (P<.001, P=.011, P=.038, and P=.023). Bleeding on probing values were similar for all implants at 36 months. Mucosal dimension did not differ significantly between interfaces, while all pink esthetic scores increased during the 36 months of observation. This study is valuable because it compared 3 systems with different implant-abutment interfaces over a 3-year period.

An interesting 3-year study reported by Lago et al[239] involved a patient-controlled protocol that compared outcomes for tissue-level and bone-level implants within the same implant brand. Inclusion criteria included good general health, smoke less than 10 cigarettes per day, no active periodontitis, good oral hygiene, and no signs of bruxism. Implant restorations were splinted 2- or 3-unit fixed partial dentures. MBLs were recorded at baseline (day of loading) and at 1- and 3-year follow-up visits.

The MBL changes from baseline to 3 years were 0.18 mm and 0.14 mm for the tissue- and bone-level implants, respectively. Results demonstrated good early bone stability in healthy conditions and no significant differences between the implants investigated. This similarity in marginal bone stability for bone-level and tissue-level implants might be related to the quality of the implant-abutment seal provided in the system investigated.

Rosa et al[240] published a meta-analysis to evaluate marginal bone loss at conical internal connection and external connection implant-abutment interfaces. Fourteen controlled trials were selected for the meta-analysis.

For implant survival rate and MBL stability, no significant differences could be identified at any time point (1, 3, and 5 years) between internal connections and external connections implants. The only significant difference was more favorable PDs for internal connections at 1 year. Unfortunately, the number of studies comparing internal and external connections was very limited.

Another restorative variable that could influence the establishment of healthy peri-implant tissues is the height of the abutment. Chen et al[241] searched relevant published reports and completed a meta-analysis. Their stated goal was to evaluate the influence of abutment height on early and late marginal bone loss around implants. Four randomized controlled trials and 4 controlled clinical trials were brought into the analyses, which indicates the scarcity of studies. By definition, short

abutments were ≤2 mm and long abutments were >2 mm in height. Analyses was accomplished at 6-, 12-, and 12- to 36-month time points.

The results demonstrated a significant difference at only the 6-month time point, based on 7 of the included publications. At 6 months, shorter abutments lose 0.52-mm less marginal bone than longer abutments. This 6-month outcome is consistent with the biological width concept of bone remodeling. Differences were not statistically significant at 12- to 36-month time point because of other host-related factors (Plaque index and host-mediated gingival inflammation may affect bone levels after initial remodeling.), and bone remodeling may be clinically insignificant at dimensions below which operators are capable of detecting.

After flapless extractions, Bittner et al[242] followed up 40 patients treated with immediate implant placement and immediately placed interim restorations or custom healing abutments. Patients were healthy, nonsmokers, and free of periodontal disease. Definitive restorations were provided at 3 months and then observed for 6 months. Outcomes were correlated to implant position and tissue phenotypes. Radiographic measurements were made on CBCT scans at all time points.

Soft-tissue recession occurred in all patients, with a mean of 1.96 mm for thin versus 1.18 mm for thick phenotypes. As indicated by others previously, this study demonstrates the impact of clinical phenotype on the amount of short-term tissue recession.

Guided implant surgery and digital workflow

Bernard et al[243] compared implant loss and MBLs with various guided and nonguided surgical protocols for treating edentulous patients. The treatment groups investigated were group 1 (Mat Mu), materialize dental mucosa-supported stereolithographic guide; group 2 (Fac Mu), facilitate mucosa-supported stereolithographic guide; group 3 (Mat Bo), materialize bone-supported stereolithographic guide; group 4 (Fac Bo), facilitate bone-supported stereolithographic guide; group 5 (Free), freehand surgical implant placement; and group 6 (Template): surgical stent with pilot drilling. Three hundred fourteen implants were surgically placed by using 4-6 implants per patients. Forty-two overdentures and 30 fixed complete dentures were fabricated and placed.

At 3 years, 302 implants were followed up with no implant loss. At 1, 2, or 3 years, the protocol implemented did not influence bleeding on probing, pocket depths, plaque index, or marginal bone loss. The only significant correlation observed was that smokers encountered more marginal bone loss than nonsmokers (P=.012). These authors, and those who studies this previously, demonstrated that implementing guided surgical protocols do not negatively impact implant success or MBLs in edentulous patients.

Its simplicity makes the randomized controlled trial reported by Smitkarn et al[244] quite interesting. The authors compared the accuracy of static computer-assisted implant guided surgery to freehand implant surgery. Based on a power calculation, 27 participants were recruited for each experimental group and randomly allocated by an independent operator. A sleeve-embedded surgical guide was produced by using a CBCT examination, a surface scan, and a digital planning software program. In the freehand group, the CBCT and the digital planning were used to produce a conventional sleeveless guide. All implants were measured for implant stability quotient (ISQ) and insertion torque values at the time of surgical placement.

Postoperative CBCT images were obtained with the same machine, and the protocol was used preoperatively, then superimposed with the preoperative images. Angular and linear deviations were calculated. All deviation differences were statistically significant in favor of the sleeve-embedded surgical guide group including mean angle deviation (3.1 versus 6.9 degrees, P=.001), mean 3D implant shoulder deviation (1 mm versus 1.5 mm, P=.001), and mean 3D apex deviations (1.3 mm versus 2.2 mm, P=.001).

However, the median insertion torque was significantly lower for the sleeve-embedded guides than that for conventional guides at 22.5 Ncm versus 35 Ncm (P=.013), and ISQ values were also significantly lower for the sleeve-embedded guides.

Accuracy findings in this clinic trial are consistent with previous studies and demonstrate that sleeve-embedded guides provide better implant placement accuracy than conventional guides. Furthermore, this study might be the first to demonstrate that sleeve-embedded guides may provide less tactile feedback during osteotomy development and implant placement.

Younes et al[245] reported on a controlled clinical trial comparing the effectiveness of free-hand, partially guided and fully guided protocols for placement of at least 2 implants per participant. Three-dimensional measurements were recorded: angular deviation (AD), coronal global deviation (CGD), and apical global deviation (AGD). AGD was used to compare effectiveness.

The results indicated that the fully guided protocol produced significantly better accuracy. The free-hand procedure was the least costly. The cost increases for partially guided and fully guided protocols were 8.29% and 10.45%, respectively. While these cost increases were statistically significant, the authors believed that increased accuracy, shorter treatment times, and more controlled prosthetic outcomes avoiding cementation should make these procedures cost-effective in the long run.

Joda et al[246] performed a long-term prospective trial observing 20 healthy patients who received single-unit, soft-tissue level, implant-supported, CAD-CAM–processed, titanium abutments with porcelain veneered zirconia crowns. Interim cement was used to retain the crowns.

Implant survival rate was 95%. One implant failed at 54 months. At 5-year follow-up, plaque index was 21.4%, bleeding index 20.8%, and mean pocket depth 3.7, and 16% of patients presented with peri-implant mucositis without detectable progressive bone loss. Mean radiographic bone loss was 0.23 mm and 0.17 mm for mesial and distal sites, respectively. The authors confirm that these findings are favorable and confirm previous studies that used similar implants. CAD-CAM procedures did not hinder favorable outcomes for single-unit implant-supported restorations at 5 years.

With regard to short versus longer implants, Guljé et al[247] compared 6-mm implants in the posterior maxilla without grafting at 5 years to 11-mm implants with maxillary sinus floor augmentation. Twenty healthy patients comprised each treatment group. Implants were restored with custom titanium abutments and zirconia crowns at 2 centers, a university and a private practice.

One implant was lost in the 6-mm group, and none were lost in the 11-mm group. Two restorations were lost in the 6-mm group, one because of implant loss and the other because of porcelain chipping. No restorations were lost in the 11-mm group. Mean marginal bone loss at 5 years was 0.12 mm and 0.14 mm in the 6-mm and 11-mm groups, respectively. Patient satisfaction improved for all participants regardless of implant length.

No significant differences could be found between groups demonstrating similar treatment performance for short implants without grafting and longer implants with grafting in the posterior maxilla. This finding corroborates other similar studies permitting authors to propose the use of short implants without grafting in the posterior as an alternative to longer implant that necessitate sinus elevation.

Ravidà et al[248] performed a meta-analysis on clinical outcomes for extra-short (6 mm or less) versus longer (10 mm or more) implants. Overall survival rates were 96.69% and 97.5% for the extra-short and longer implants, respectively, which was not statistically significant. The 1-year and 3-year survival outcomes did not differ between groups. However, the 5-year outcome, based on 3 studies, demonstrated a lower survival rate for extra-short implants.

Most studies, 9 of 10 in the maxilla and 4 of 5 in the mandible, included implants in augmented bone. A mixed-effect analysis did not show significant survival differences for implants placed in augmented bone. However, marginal bone loss at 1 year was significantly greater for nonaugmented sites in both the maxilla and mandible.

Based on 16 studies, marginal bone loss at 1 and 3 years was significantly greater for the longer implants. At 1 year, early loading and screw-retained prostheses on longer implants demonstrated significantly more marginal bone loss than extra-short implants. This difference was not statistically significant at 3 years. Prosthetic complications were significantly greater only at 3 years in the extra-short implant group. Biological complication rates were higher only at 1 and 3 extra years for the short implants. Location and bone augmentation had no effect on biological complications. Significant increases in both cost and surgical time were associated with longer implants when sinus floor elevation was implemented.

The authors concluded that extra-short implants (6 mm or less) are a viable option to treat patients with atrophic posterior jaws when compared with longer implants that require augmentation procedures. However, prosthetic complication rates and 5-year survival were more favorable for longer implants, which precluded authors from providing strong recommendations.

A number of reports addressed immediate versus conventional implant-loading protocols. Weerapong et al[249] performed a controlled study to compare immediate loading of 6-mm versus 10-mm implants restored with mandibular molar single-unit restorations in healthy patients without parafunctional habits or periodontitis. The implants were placed by using a guided flapless surgical approach. A surgical placement torqued of 35 Ncm was achieved for inclusion in the study. Both short (n=23) and long (n=23) were restored by using stock titanium abutments and CAD-CAM interim restorations adjusted to centric occlusal contacts without eccentric contacts. A soft diet was recommended for 2-3 weeks. Data were collected at 6 months and 1 year. A single 10-mm implant and 2 6-mm implants failed over this time period. Implant stability and MBL data were similar. Despite the short-term follow-up period, results suggest that when high insertion torque is achieved, single-unit short implants can be immediately loaded when restoring mandibular molars.

The aim of a pragmatic prospective clinical trial by Ayna et al[250] was to compare immediate and delayed loading of 6-mm implants in the posterior maxilla. Periodontally healthy patients with available bone height of 6.5-8 mm and bone width of at least 8 mm were enrolled. A total of 48 implants that achieved the minimum peak insertion torque of 35 Ncm (mean 60.9 Ncm) comprised the immediate loading group, while 15 implants (mean insertion torque 24.5 Ncm) were assigned to the delayed loading group. Three implants failed, all in the immediate loading group. Survival differences between groups were not significant ($P>.05$). Plaque index was significantly higher in the immediate loading group during 1- and 2-year recalls. Significantly less bleeding

on probing, PD, and bone loss were observed in the delayed loading group. However, because of the small number of implants in the control group, determining correlations was not possible. The results indicate that although feasible and with favorable outcomes, studies with greater implants numbers and longer follow-up period are needed to recommend immediate loading of short implants in the posterior maxilla.

Chen et al[251] compared the impact of immediate, early, and conventional implant loading on clinical outcomes of fixed restoration. The authors' search of PubMed, Embase, and Cochrane databases for randomized controlled trials resulted in 49 published reports involving 39 clinical trials. Overall, 1785 participants who received 3486 implants followed up from 10 days to 180 months were analyzed. Implant-level survival rates of 96.8% and 98 0.6% in test and control groups, respectively, were significantly different. However, patient-level implant survival rates of 95% and 97.3% in test and controls groups, respectively, demonstrated no significant difference. Comparing immediate loading with early loading yielded no significant differences in implant survival. Implant-level survival rates were 96.3% and 96.3% for immediate and early loading, respectively, with patient-level survival rates of 94.6% and 95.5%. MBLs reported in 5 trials demonstrated no significant differences between test and control groups. Implant stability quotient (ISQ) values from 7 clinical trials revealed no significant differences between test and control implants. With regard to peri-implant tissue health as described by plaque index, PD, bleeding index, papilla height, free-gingival margin position, and width of keratinized tissue, the meta-analysis could not identify any significant differences.

Overall, this extensive meta-analysis indicated immediate loading to be associated with a higher incidence of implant failure when compared with conventional loading. However, considering survival rates greater than 95% identified in this analysis, a careful approach to early loading can be confidently implemented.

Alfadda et al[252] reported on a 10-year randomized controlled trial comparing 20 patients with edentulous mandibles, each receiving all-on-4 screw-retained, implant-supported restorations by using immediate and conventional loading protocols. Differences in implants success rate at 10 years were not statistically significant, with 6 of 80 implants lost in the conventional loading group compared with 3 of 48 implants lost in the immediate loading group. Mean MBLs were similar for the conventional (1.09 mm) and immediate (1.02 mm) loading groups, respectively. Mechanical complications were also statistically similar. For edentulous mandibles, this long-term trial supports immediate loading of implants placed 3 months after extraction (no grafting) without hindering implant success or other important clinical outcomes.

Salman et al[253] investigated immediate versus delayed loading in edentulous jaws by using 2 implants for LOCATOR-retained overdentures. Authors recalled 23 patients for 60-month follow-up examinations. No implants were lost in either immediate or delayed loading groups, and all mechanical complications, biologic complications, plaque scores, PDs, and bleeding on probing were statistically similar. Marginal bone-level changes were significantly lower in the immediate loading group (0.18 mm) than those in the delayed loading group (0.89 mm). The authors suggested that immediate loading may be more favorable because of early bone-level stress distribution to the implant interface which leads to a more favorable apposition-resorption ratio. The authors also mentioned that not preforming a second surgery or removing the abutment may contribute to crestal bone preservation. Overall, the study demonstrated similar clinical outcomes for the delayed and immediate loading groups.

A controlled clinical trial reported by Montero et al[254] measured Oral Health Related Quality of Life (OHRQoL) and Oral Impacts on Daily Performances (OIDP) outcomes in relation to the surgical and loading protocols. Three groups were defined: (a) nonguided surgery with conventional loading, (b) guided surgery with conventional loading, and (c) guided surgery with immediate loading. When comparing before and after performances, no significant differences in outcomes among the groups were observed. OHRQoL and OIDP outcomes appear to be valid patient assessments. While implant-supported restorations improve quality of life, discrimination between the tested surgical and loading protocols was not possible.

Focusing on the use of interim restorations and associated outcomes, Donos et al[255] recalled 16 patients at 5 years for examination. One group of patients was treated with nonoccluding interim crowns. The second group did not receive interim crowns. All outcomes were statistically similar, including esthetic outcomes as measured with papilla fill index and pink esthetic scores. Despite the limited patient population, 5-year observations confirm the favorable outcome of using single-implant nonfunctional immediate interim crowns.

In a randomized controlled clinical trial, Furze et al[256] compared modified pink esthetic scores (PES) and white esthetic scores (WES) at 3 years for patients with or without interim restorations. Pink esthetic scores were significantly higher when interim restorations were used (8.1 versus 5.5, P=.018). The same was true for white esthetic scores (7.5 versus 6.6, P=.19). The report did not evaluate patient-centered outcomes.

This study demonstrates limitations of operator-based analysis. During outcomes assessments, the 2

"experienced prosthodontists" who performed evaluations tend to be more critical than the patients. Therefore, while results indicate an association between PES and the use of interim restorations, the authors point out that extrapolation to global recommendations for use of interim restorations may not be warranted from these data.

Implant-assisted overdentures are represented by 3 articles here. Weigl et al[257] followed up 22 patients who received implant attachment elements under maxillary or mandibular implant-supported overdentures. Two to 6 implants per edentulous arch were available with a maximum of 4 implants in each mandible. Delayed loading was implemented, and denture frameworks were cast in metal to envelop secondary copings. Laboratory time and costs were estimated by surveying 12 laboratories to compare cast telescopic retainers, electroplated matrices, and prefabricated attachments.

Results indicated 90.5% of participants reported good or very good retention at 6 months, and 94.7% at 36 months. When patients qualified retention to be inadequate, an increase in abutment height helped. Twenty-one prostheses did not need relining after 3 years, and no base or framework fractures occurred. Overall, minimal complications were noted, including 3 pressure points adjustments on denture bases at 1 week and the need to pick up the retentive element on 1 patient twice due to a procedural error. Based on the survey, laboratories estimated a 200% increase in time of and a 179% increase in cost when comparing framework-associated prostheses with the prefabricated group. This study shows that prefabricated attachment retentive systems for implant-supported overdentures can provide satisfactory outcomes over at least 36 months in function.

By using a portion of the same patient population, Emami et al[258] evaluated the effectiveness of incorporating a third midline implant to improve outcomes of mandibular LOCATOR-retained overdentures. Phase one of the trial compared immediate and conventional loading protocols by using 2 implants while the third midline implant was restored with a nonfunctional healing abutment. After 2 years of function, each patient could elect to have their third midline implants connected by using a LOCATOR abutment and attachment. Seventeen of the initial 21 patients met the criteria of willingness to participate, successful implant, and physical and psychological capacity to complete the questionnaires. Most of the patients (88.2%) had high expectations for the conversion to 3 implants, which were met for 70.7% of these patients. Mastication improved for 88%, comfort for 82.4%, retention for 100%, and stability for 94% of the patients. Improvements in stability and ability to speak were statistically significant (P=.002 and P=.008, respectively), yet the additional implant did not adversely affect ease of insertion and removal. Interestingly, an anteroposterior movement was present for 35% of patients but perceived by only 6%. The fee range patients were willing to spend for the conversion to 3 implants was $1250, which increased to $1500 after the actual intervention, and 80% of patients would recommend this procedure to others. This study clearly demonstrated that, given reasonable treatment costs, the incorporation of a third implant beneath mandibular overdentures may be beneficial to patients requiring more comfort, retention, and stability.

The objective of a 5-year randomized controlled trial reported by Slot et al[259] was to compare 4- and 6-implant bar-retained maxillary overdentures. All patients received maxillary sinus augmentation with iliac crest bone 3 months before placement of 4 or 6 tissue-level implants in canine, premolar (for 6-implant treatments), and first molar positions. A total of 29 (4-implant group) and 31 (6-implant group) patients were evaluated, demonstrating 100% and 99.5% implant survival, respectively, with no influence on the prosthetic outcome. At 5 years, peri-implant bone loss was 0.58 mm and 0.60 mm, patient-level peri-implant mucositis was 27.3% and 39.4%, and peri-implantitis was 17.2% and 9.7% of patients, respectively. The number of implants restored did not influence patient satisfaction, which was very high. The authors concluded that 4 implants placed in augmented sinus sites and connected by a bar can be used successfully in implant-supported overdentures.

Finally, a reasonable question to pose when treatment planning an implant rehabilitation is, "Should implants be splinted or restored individually?" The objective of an analysis reported by de Souza Batista et al[260] was to systematically evaluate outcomes for splinted and nonsplinted implant-supported restorations. Nineteen randomized controlled trials, prospective and retrospective human studies, were selected for inclusion.

Implant survival rates were found to be significantly in favor of the splinted implants over nonsplinted implants (99.1% and 96.5%, respectively). The risk ratio for implant survival was 3.18 in favor of the splinted implants. External connection implants (P<.001) and implants placed in posterior areas of the mouth (P=.009) demonstrated significantly higher survival rates when splinted, with respective risk ratios of 3.70 and 2.20. However, for the internal connection implants, implant survival rates for location and splinting demonstrated no differences (P=.11) with a risk ratio of 1.95. No statistically significant differences were found when analyzing prosthetic complications between splinted and nonsplinted implants with a risk ration of 1.81 in favor of splinted implants. These risk ratios indicate that the risk for implant failure is greater for nonsplinted implants. Marginal bone loss for splinted and nonsplinted implants (11 studies), external (6 studies) and internal (7 studies) connection geometries, and at posterior sites (6 studies)

did not reveal any significant differences in the meta-analyses.

As splinting appears to have no negative impact on MBLs, the ease of hygiene previously associated with nonsplinted restorations may not be an important factor in maintaining marginal bone around splinted implants, particularly when patients are monitored with an aggressive maintenance protocol. However, this study did demonstrate that splinted implants were associated with more favorable survival rates.

DENTAL MATERIALS AND THERAPEUTICS

Opioids

The dental profession has been rapid to respond to the opioid epidemic by adopting prescribing guidelines, policy statements, and encouraging participation in state prescription drug monitoring programs (PDMP). In 2019, there were 3 articles emanating from the National Dental Practice-Based Research Network Collaborative Group that described the state of pain management training, participation in PDMPs, and patterns of prescribing among dentists from different localities. One article described dentists' training experiences and reported that the majority of 882 dentists (67%) experienced some prior training in pain management; however, prior training on the identification and assessment of drug addiction or abuse was reported by 48% and the identification of drug diversion only by 25%.[261] Most training was identified as occurring via continuing education. The conclusion was that more training is needed to focus on addiction assessment and identifying drug diversion. The second article looked at dentists' experiences in using their state PDMP and the impact participation had on prescribing patterns.[262] Of the 805 dentists responding to the survey, nearly half (47%) reported never accessing a PDMP. The most common reasons for not accessing were lack of awareness (57%) and lack of knowledge regarding registration and use (25%). Most PDMP users found the information helpful, leading to 33% not prescribing an opioid and an additional 25% prescribing fewer doses. States with a mandated use policy had a much higher dentist use of the PDMP than states without such a mandate. The third practice-based article compared the prescribing patterns of rural versus nonrural dentists.[263] This survey of 822 dentists found that rural dentists were significantly more likely to recommend nonsteroidal anti-inflammatory agents and acetaminophen combinations over opioids than their nonrural counterparts. An interesting associated finding was that these same rural dentists were more likely to report that opioid abuse or diversion was a problem in their practice and that they were more likely to refrain from prescribing opioids because of suspicions of abuse or diversion. These findings run counter to what many consider to be largely an urban problem.

Three articles in 2019 assessed dentists' prescribing patterns in countries other than the United States. An article described opioid prescribing by dentists in Manitoba, Canada, from 2014 through 2017.[264] Overall, dentists' prescriptions accounted for 3.8% of all opioid prescriptions, with codeine and acetaminophen combinations being the primary opioid prescribed in 97.4% of prescriptions followed by tramadol and acetaminophen in 1.7% and oxycodone with acetaminophen in only 0.7% of prescriptions. Prescriptions were generally for fewer doses, with 89% being for 5 or fewer days and nearly 88% of patients only receiving 1 prescription. One important finding, however, was that 20.6% of the opioid prescriptions were first time, with 5.6% dosing above the 50-mg morphine equivalent daily dose level. Once again, this emphasizes that who we prescribe to may be more important than how often we prescribe. This also serves as an important reminder that diligence is needed in limiting prescriptions to first-time users because of the age-related susceptibility of these patients toward future abuse. The second article from Canada was a retrospective study of health data comparing the prescribing practices of dentists to children and adolescents (age < 18) in Nova Scotia.[265] Dentists accounted for 18.3% of all opioid prescribers annually for this young age group, but this proportion grew to 59.9% of the total opioid prescription counts over the 7-year study period. Oral and maxillofacial surgeons were responsible for 80.7% of all dental-related prescriptions dispensed, and similar to the previous study, codeine was the most frequently prescribed drug at 78.6% followed by oxycodone at 11.1%. Few prescriptions were dispensed to children younger than 12 years, reinforcing the fact that opioid prescribing for dental issues is concentrated into the age demographic with the highest susceptibility for future abuse. A third article compared the opioid prescribing behavior of dentists in the United States to that in England.[266] Both pharmacy and clinic data from 2016 were compared between the 2 countries. The overall findings were that 37 times more US dentists prescribed opioids than dentists in England. US dentists also had a higher number of prescriptions per 1000 population at 35.4 (95% CI: 25.2-48.7) than English dentists at 0.5 per 1000 (95% CI: 0.03-3.7). The codeine derivative dihydrocodeine was the only opioid prescribed in England while US dentists prescribed a range of opioids containing hydrocodone (62.3%), codeine (23.2%), oxycodone (9.1%), and tramadol (4.8%). These results suggest that there are suitable alternatives for US dentists with lower potential for abuse and adequate patient acceptance.

Two articles focused on the use of opioids after third molar extractions. The first compared the prescribing patterns before and after implementing an institutionally mandated opioid prescribing protocol at the University of

Minnesota Division of Oral and Maxillofacial Surgery.[267] Protocol adoption resulted in the expected decrease in opioid prescriptions and increase in nonopioid analgesics, while the mean number of tablets prescribed dropped from a mean of 15.9-11.5. This appears to be rather moderated decline when taken in the context of the following study. This study was a novel prospective cohort investigation of patient analgesic use after third molar surgery at Boston Children's Hospital.[268] Patients were given a choice of using pain medication from 3 different prescriptions with corresponding instructions, including oxycodone 1 tablet every 6 hours as needed, ibuprofen 600-mg tablets with 1 taken every 6 hours as needed, and acetaminophen 325-mg tablets with 2 taken every 6 hours as needed. The 81 participants recorded their choice of medication and usage each day for 7 days. Surprisingly, the overall average number of oxycodone tablets used was 0.04 ±0.24 per patient, with the highest daily use being on day 2 postoperatively. Oxycodone was taken by only 6 of 81 patients, 3 opting to use on day 1, 4 on day 2, and 2 on days 3 and 4. No patients opted to use oxycodone after day 4, and 75 of the 81 patients used no postoperative oxycodone at all. In all, 466 of the originally prescribed 486 oxycodone tablets remained unused, as patients chose to manage pain primarily with ibuprofen and acetaminophen. This study demonstrates the low level of elective use of opioids by patients when given a choice and draws into question the levels recommended in the protocol described in the previous study.

A large-scale study of 2013-2015 Medicaid prescription data looked at the underlying diagnostic groupings of more than 5 million opioid-prescribed patients.[269] The most frequent grouping was orthopedic pain at 34.8% followed by dental conditions at 17.3%, back pain at 14.0%, and headache at 12.9%. Emergency departments were the most frequent origins of prescriptions, emphasizing the importance of access to dental primary care in managing nontraumatic dental conditions. A second study of 2014 and 2015 Medicaid data from the state of Washington looked at dental claims associated with opioid prescriptions.[270] This study found that 10.3% of the more than 126 000 dental visits resulted in an opioid prescription. Nearly 70% of these visits were associated with a dental code considered to be an invasive procedure. One discouraging finding was that visits for patients with a history of high-risk prescription use were associated with a significantly higher mean quantity of opioids supplied per prescription. A regression analysis showed that the probability of receiving an opioid prescription increased by 35.6% when the dental procedure was invasive and 11.1% when the beneficiary had prior high-risk prescription use. These results emphasize the importance of monitoring prior prescription history via the PDMP and the need for better training in recognizing high-risk behaviors in patients.

While the dental profession has responded positively in adopting changes in policy and prescribing patterns, the data indicate we can still do much more. Studies using delayed prescriptions and elective choice of analgesics indicate that the need for opioids is still far below what we are prescribing. Our continuing education needs to focus on evaluating, identifying, and counseling those at highest risk, and we need to be continually reminded that teens and young adults are most susceptible to future abuse. Using PDMPs has proven to improve our prescribing patterns, but we still have nearly half of dentists that have never accessed or used one. While the epidemic of opioid abuse appears to have peaked, we also need to be vigilant of addictions to substitute drugs, such as fentanyl and methamphetamine. These and other drug addictions can have disastrous implications to oral health, and as health-care providers, we are on the front line of fighting this addiction.

Silver diamine fluoride

A flurry of articles was published in 2019 looking at acceptance of silver diamine fluoride (SDF) treatment and the associated dark discoloration of lesions by providers, patients, and caregivers. A cross-sectional study of 104 parents of healthy children aged 12 years and younger were shown photographs of primary and permanent teeth before and after SDF staining.[271] Of these parents, 43.4% found staining to be unacceptable, with acceptance levels being higher in primary than in permanent teeth and higher in posterior versus anterior teeth. Parents of children with a history of being uncooperative during treatment also demonstrated a higher acceptance of SDF staining. A similar study collected thematic comments from 43 parents and identified 6 major themes of parental concern: esthetic concerns, psychosocial concerns, SDF treatment process, risks and side effects, situational benefits, and the dental treatment process.[272] This demonstrates that parents have more concerns regarding SDF than simply discoloration that need to be addressed for them to make well-informed decisions. An interesting scoping review of articles related to treatment acceptance included 9 studies of esthetic perception and acceptance of SDF treatment.[273] Factors influencing acceptance were tooth location, family income, parental schooling, ethnicity, and need for child behavioral control during treatment. The interesting finding was that tooth discoloration had a stronger negative influence on provider acceptance than upon parental acceptance, and this serves as a reminder that as providers, we need to be cautious about translating our own values to patients and caregivers. One study looked at patient age as one of the factors influencing caregiver acceptance of SDF treatment.[274] Nearly 80% of 546 caregivers accepted SDF treatments for their children, with the highest acceptance rates for children either

under 6 years or 9-14 years of age and the lowest acceptance in children at 6-9 years of age. No rationale was provided for this U-shaped relationship. One article assessed caregiver satisfaction with SDF treatment provided before their child's scheduled operating room or sedation appointment.[275] The caregivers for this high-risk group of children were overwhelmingly supportive of the interim SDF treatment, but this begs the question of whether restorative treatment via the operating room or sedation could have been avoided entirely for many of these patients. Finally, an article provided a 6-month prospective assessment of quality-of-life measures for preschool children receiving SDF treatment in a school-based setting.[276] Of the 113 preschool children treated and assessed via the Chinese Early Childhood Oral Health Impact Scale, there was no statistical difference between pretreatment and posttreatment scores. The study noted that there was a negative influence on impact from the parent section of the assessment, but not from the child section. This was the only study that assessed a child's perception of SDF treatment, an often-overlooked point of view.

Two articles reported on the teaching and professional knowledge of SDF. A survey of US predoctoral dental education programs (n=62) indicated that two-thirds of them taught SDF as part of their curricula.[277] Only 1 school reported not using SDF for arresting caries on primary teeth, but of the 62 reporting schools, only 18 indicated that there was an existing protocol for use. Hopefully the 2018 publication of guidelines for nonrestorative treatment of caries will help establish more protocols in the future. Of the 20 schools not currently teaching SDF, all indicated they would be adopting it in their curricula in the future. A survey of 6230 pediatric dentists resulted in 582 responses regarding their knowledge and attitudes related to SDF.[278] Only 3% of respondents were able to state that they were well or very well educated on SDF in dental school, and 9.6% reported being trained via their residency. The majority received training via publications (53%), online resources (41%), and continuing education courses (38%). This training resulted in the majority reporting that they felt they knew much or very much about the appropriate use of SDF and had positive attitudes about its use. Frequently cited indications included children with behavior problems (85%), medically fragile patients (85%), and patients with severe dental anxiety (81%). More than 30% of respondents reported using SDF often or very often, with 87% reporting that they expect to increase usage in the future. This is an excellent example of the rapid rate of adoption by pediatric dentists but points out the need for additional dental school education on SDF use.

Additional clinical trials continued to add to the body of evidence regarding the caries arresting effectiveness of SDF. One article described 32 children with 118 active caries lesions treated with one or 2 applications of SDF.[279] The teeth were re-evaluated at 3-week and 3-month intervals to assess lesion color and consistency as a measure of arrest. One hundred of 102 lesions evaluated at first recall were considered to be arrested, and all were arrested by the second recall. No incidences of pain or infection were reported. A randomized controlled trial of SDF treatment of dentin caries in primary molars of 68 preschoolers tracked multiple outcomes for 12 months[280] The teeth were randomly assigned to either SDF or atraumatic restorative treatment. The mean difference in arrested lesions between the 2 treatments was -0.07 (95% CI: -0.17 to 0.30). Time required for treatment was lower with SDF, there was no difference between treatments in the number of adverse responses reported, and a measure of oral health quality of life showed less impact from the atraumatic restorative technique, but this difference was only present when the parents' distress subscale was included. The overall conclusions supported that SDF required less chair time and had similar results to the atraumatic restorative treatment for arresting lesions, anxiety, adverse events, esthetic perception, and quality of life. Finally, the question of comparative effectiveness of 38% SDF to 25% silver nitrate followed by sodium fluoride varnish was addressed in a randomized clinical trial.[281] A total of 1070 healthy 3-year-old children with active dentin caries were randomly allocated to one of the 2 treatment regimens. After 18 months, there was no difference in the mean number of arrested surfaces (SDF=3.3 ±3.4, $AgNO_3$=3.2 ±3.5, *P*=.664). No significant side effects other than similar black staining were reported for either treatment. This trial provides much-needed evidence in demonstrating the equivalent effectiveness of the silver nitrate and fluoride varnish protocol used in earlier demonstrations and studies of caries arrest by silver compounds.

The adoption of SDF as a caries-arresting treatment has fortunately been led by mounting evidence for effectiveness and a much more rapid inclusion into dental education curricula and practice than most new technologies. The caries-arresting properties are well supported, and there is growing evidence around the preventive effectiveness against new caries development, but much still needs to be done to adequately support its use as a primary preventive agent. Many of the questions related to treatment protocols that were completely unknown just a few years ago have been addressed, and there appears to be growing consensus around when, where, and how to use SDF.

Antibiotics

Dentistry has been slow to develop clinical guidelines, but one hugely important guideline was published in 2019 relating to antibiotic use for the management of pulpal- and periapical-related dental pain.[282] This

guideline follows several medical guidelines on antibiotic use aimed at reducing the serious complications resulting from the growing problem of antibiotic resistance. The guideline was developed by an expert panel convened by the American Dental Association Council on Scientific Affairs and the Center for Evidence-Based Dentistry. Evidence was gathered relating to the use of antibiotics for the urgent management of symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulpal necrosis and symptomatic apical periodontitis, or pulpal necrosis and acute apical abscess, both with and without access to definitive, conservative dental treatment (DCDT) in immunocompetent adults. The panel weighed the evidence on benefits and potential harms associated with antibiotic use under each of these scenarios and formulated 5 clinical recommendations and 2 good practice statements. The recommendations can be summarized as follows:

- That dentists do not prescribe oral systemic antibiotics for immunocompetent adults with symptomatic irreversible pulpitis with or without symptomatic apical periodontitis. Clinicians should refer patients for DCDT while providing interim monitoring.
- That dentists do not prescribe oral systemic antibiotics for immunocompetent adults with pulpal necrosis and symptomatic apical periodontitis. Clinicians should refer patients for DCDT while providing interim monitoring. If DCDT is not feasible, a delayed prescription for oral amoxicillin (500 mg, 3×day for 3-7 days) or oral penicillin V potassium (500 mg, 4×day for 3-7 days) should be provided.
- That dentists prescribe oral amoxicillin (500 mg, 3×day for 3-7 days) or oral penicillin V potassium (500 mg, 4×day for 3-7 days) for immunocompetent adults with pulpal necrosis and localized acute apical abscess. Clinicians also should provide urgent referral, and DCDT should not be delayed.
- That dentists do not prescribe oral systemic antibiotics as an adjunct to DCDT for immunocompetent adults with pulpal necrosis and symptomatic apical periodontitis or localized acute apical abscess.
- That dentists do not prescribe oral systemic antibiotic as an adjunct to DCDT for immunocompetent adults with symptomatic irreversible pulpitis with or without symptomatic apical periodontitis.

The 2 good practice statements coming from the panel include

- That dentists prescribe oral amoxicillin (500 mg, 3×day for 3-7 days) or oral penicillin V potassium (500 mg, 4×day for 3-7 days) for immunocompetent adults with pulpal necrosis and acute apical abscess with systemic involvement. Clinicians should provide urgent referral as DCDT should not be delayed. If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer patient for urgent evaluation.
- That dentists perform urgent DCDT in conjunction with prescribing oral amoxicillin (500 mg, 3×day for 3-7 days) or oral penicillin V potassium (500 mg, 4×day for 3-7 days) for immunocompetent adults with pulp necrosis and acute apical abscess with systemic involvement. If the clinical condition worsens or if there is concern for deeper space infection or immediate threat to life, refer for urgent evaluation.

These recommendations and good practices were supported by the general lack of evidence showing potential benefits and the probability of substantial harms due to the development of infections by resistant organisms. The guidelines are a huge departure from the way many dentists were trained to practice and will require a great deal of faith and diligence to adopt as standards of care. The supporting documentation for these recommendations came in a subsequent publication of a systematic review and meta-analysis of the studies considered by the expert panel.[283] The report updated 2 existing systematic reviews that found no new randomized clinical trials and relied upon 3 trials and 8 additional reports for the analysis. The conclusions were that the evidence for antibiotic use either alone or as an adjunct to DCDT showed both benefit and harm for outcomes of pain and intraoral swelling but also had a large potential magnitude for additional harm due to antibiotic resistance development.

The magnitude of the challenge faced in changing practice patterns relative to antibiotic use is illustrated in several additional articles. The first reports an online survey of members of the Academy of Operative Dentistry and Academy of General Dentistry with 403 participating dentists.[284] Over a third of these dentists indicated they would prescribe antibiotics for symptomatic irreversible pulpitis in a permanent tooth without any sign of infection. A second study surveyed general dentists, pediatric dentists, endodontists, and oral surgeons in Massachusetts.[285] This study also reported low adherence to guidelines for prescribing antibiotics, with endodontists being the least likely to prescribe for irreversible pulpitis. The overall scope of antibiotic use by dentists can be illustrated through a study coming out of the Center for Disease Control and Prevention Epicenters of pharmacy benefit data.[286] This study found that from 2013 through 2015, dentists prescribed 2.4 million antibiotics to 38 million beneficiaries. Oral and maxillofacial surgeons accounted for the highest annual rate of 1018 prescriptions per 100 000 beneficiaries, followed by

periodontists at 458 prescriptions per 100 000 and endodontists at 388 prescriptions per 100 000. While the new guidelines focus on antibiotic use for endodontic conditions, it is apparent that the problems of overprescribing may be much broader. A study focusing on antibiotic use after third molar surgery reviewed the records of 992 patients and found that antibiotics were prescribed for 44% of extractions, while the overall infection rate was only 2.05% and there was no significant difference in infection rates between groups undergoing extractions with or without antibiotics.[287] Even the use of antibiotics for infection prophylaxis has been called to question in spite of the fact that clinical guidelines have been in place for decades. A retrospective analysis of dental visits from 2011 to 2015 was performed on the national integrated health claims database Truven for patients with dental insurance that had a presence or absence of cardiac diagnoses and dental procedures that manipulated the gingiva or tooth periapex.[288] The findings showed that more than 80% of antibiotics prescribed for infection prophylaxis before a dental visit were unnecessary. Dentists are not the only practitioners overprescribing for dental reasons. A study of emergency department data from the National Hospital Ambulatory Medical Care Survey found that 65% of emergency department visits with any dental diagnosis resulted in a prescription for an antibiotic.[289] The most frequent diagnosis associated with an antibiotic prescription was unspecified disorder of the teeth and supporting structures at 44%, followed by periapical abscess without sinus at 21% and dental caries at 18%.

Antibiotic resistance and proper stewardship of antibiotics have become a global issue that threatens us all. Dentistry needs to recognize that it is both part of the problem and part of the solution. Our rapid response to the opioid crisis, universal precautions around infection control, and the adoption of silver diamine fluoride have proven that we can respond quickly and appropriately when necessary. This is but one more call to action for that same rapid and appropriate response.

Vaping and e-cigarettes

One more new challenge to health was evident in 2019 with the Center for Disease Control and Prevention's report on the outbreak of lung injury associated with the use of e-cigarette or vaping products (EVALI).[290] This report is updated on a regular basis and tracks EVALI patient hospital admissions and deaths nationally. As of December 17, 2019, there were 2506 hospitalizations and 56 deaths related to the use of vaping products. Of those hospitalized patients, 16% were younger than 18 years, 38% of patients were 18-24 years old, and 24% of patients were 25-34 years old. Similar to HIV and the opioid crisis, this is a condition that is striking down young adults in their prime. The most likely causative ingredient identified thus far is vitamin E acetate, a thickening agent added to some vaping liquids, and the most frequent vaping products associated with EVALI are those containing tetrahydrocannabinol (THC). In addition, there have been more than 60 facial injuries and one death reported related to explosions and fires from vaping devices. The American Dental Association released an interim policy on vaping[291] that urgently advocates for regulatory, legislative, and/or legal action to ban the sale and distribution of all e-cigarette and vaping products, with the exception of those approved by the FDA for tobacco-cessation purposes and made available by prescription only. This policy also calls for research funding to study the safety and effectiveness of e-cigarettes and vaping products for tobacco-cessation purposes and their effects on the oral cavity. This policy mirrors one adopted by the American Medical Association. The American Dental Association also added "vaping" and alternative nicotine delivery systems to the existing policy focused on tobacco use and prevention, research, and regulation.

There is little research yet available on the oral effects of vaping and e-cigarettes. One article looked at the associations between electronic and conventional cigarette use with periodontal disease.[292] This study used data from the Korean National Health and Nutrition Examination Survey of 13 551 participants of which 187 men and 35 women were found to vape and 1957 men and 363 women smoked conventional cigarettes. The association of periodontal disease with these users was that 35.8% of men and 28.6% of women who vaped had periodontal disease while 44.0% of men and 35.3% of women who smoked conventional cigarettes had periodontal disease. The prevalence of disease was higher in both vapers and smokers than in nonusers, and both smoking and vaping were found to have significant associations with caries, toothache, and dental injuries. Another study analyzed the gingival crevicular fluid among cigarette smokers, electronic cigarette users (vapers), and never smokers.[293] More than 40 individuals in each group were given clinical examinations as well as collecting and analyzing crevicular fluid cytokine profiles. The mean scores for plaque index, PD, and clinical attachment levels were significantly higher for the cigarette smokers than for never smokers, but not different between cigarette smokers and vapers. One interesting finding was that bleeding on probing was most prevalent in the never smoker group. Marginal bone loss was higher in both cigarette smokers and vapors than among never smokers. For cytokine markers, the concentrations of IL-1β, IL-6, IFN-γ, TNF-α, and MMP-8 were significantly higher in cigarette smokers than in either vapors or never smokers. While some clinical markers of periodontal disease are higher in vapors than in never smokers, the levels of proinflammatory cytokines did not show the same trends. A similar study was carried out

looking at periodontal and cytokine markers around dental implants as they relate to smoking and vaping status.[294] Once again, bleeding on probing was highest in the nonsmoking cohort. Results were similar to those experienced around teeth for clinical markers, but this time, the levels of MMP-9 and IL-1β were higher in both the cigarette smoking and vaping cohorts than among the nonsmokers. Peri-implant levels of cotinine were compared between smokers, waterpipe users, e-cigarette users, and nonsmokers.[295] Plaque index and PD were both significantly higher for smokers, waterpipe users, and electronic cigarette users than for nonsmokers. Again, bleeding on probing was most prevalent in nonsmokers. Cotinine levels were significantly higher in cigarette, waterpipe, and e-cigarette users than among nonsmokers. While this is all early evidence of associations between e-cigarette use and periodontal health, there will likely be much more in the coming years as the call for additional research increases.

Where does that leave the average dental practitioner? One place to look is the Center for Disease Control and Prevention Interim Guidance for Health Care Providers for Managing Patients with Suspected e-cigarette, or Vaping, Product Use-Associated Lung Injury–United States, November 2019.[296] Dentists are on the front line of primary care and can play an important role in surveillance and patient guidance. This CDC document points out that EVALI currently has no specific test or marker for its diagnosis but is rather a diagnosis of exclusion. Recommendations, therefore, focus on asking patients with respiratory, gastrointestinal, or constitutional symptoms about the use of e-cigarettes or vaping products and referring those patients with such history for medical evaluation. Another recommendation is to emphasize to patients the importance of annual influenza vaccination for all persons 6 months or older, especially for patients who use e-cigarette or vaping products, as influenza is a major complication of EVALI. This guidance calls on all health-care providers to ask about vaping and e-cigarette use in a nonjudgmental manner and to offer or connect patients to services to stop e-cigarette or vaping use. The epidemic of EVALI seems to have peaked and is on the decline, but we will likely have many more unknown sequelae of vaping and e-cigarettes to deal with in our future.

Sealants

Two large studies were published in 2019 that evaluated the effectiveness of sealants placed on children's teeth under government-sponsored programs and first looked at the impact of a policy change covering sealants under the National Health Insurance program of the Republic of Korea.[297] This study compared prepolicy to postpolicy placement of sealants and the prevalence of untreated caries in 8161 children aged 6-14 years. The implementation of the sealant policy increased the likelihood of using dental sealants (OR=1.58, 95% CI: 1.33-1.87) and lowered the odds of having untreated caries (OR=0.65, 95% CI: 0.51-0.83). An interesting finding was that the increase in sealant utilization and decline in untreated caries were larger for middle- and low-income households than those observed in high-income households. A second large population cohort study investigated the caries prevalence over 3 years in a population of nearly 10 000 children in Guangzhou, China.[298] Caries status and sealant retention were assessed and compared in 2 cohorts, children receiving sealants 3 years before (n=4822) and children who had indications for sealants but had not received treatment (n=4396). After 3 years, the cohort with sealants had a 37% reduction (HR=0.63, 95% CI: 0.57-0.69) in the risk for caries as compared with the nonsealant cohort, and this reduction was observed to be larger for children living in rural areas (44%) than for those living in urban areas (35%). Sealant retention was found to be 72.2% over the 3 years. These studies further confirm the population impact of large sealant programs.

The effectiveness of sealants on primary molars was studied in a group of 297 children younger than 6 years that received sealants in either an outpatient clinic or an operating room setting.[299] Records were reviewed over 3 years tracking and comparing caries incidence in 1352 primary molars comparing sealed with nonsealed teeth. The odds of developing pit and fissure lesions in sealed molars as compared with nonsealed molars was 0.055 (95% CI: 0.011-0.285) for sealants placed in the outpatient clinic and 0.013 (95% CI: 0.001-0.159) for those placed in the operating room. In the primary molars that developed caries, the time for development of lesions was significantly longer for sealed teeth regardless of whether sealants were placed in either setting.

Children with special health-care needs are considered to be at higher risk for caries, and one study used the 2013-2014 National Health and Nutritional Examination Survey to compare the prevalence of sealants in children with and without special needs.[300] The findings showed that children with a physical disability had much lower odds of receiving a sealant (OR=0.5). Disparity was also noted among the lines of race and ethnicity with sealant prevalence for African-American children at 39% compared with Hispanic at 47% and white at 54%. Work still remains at reducing the disparity for access to sealants, and this study highlights the large gap that exists for children with special health-care needs.

Three articles addressed the use of sealants for the management of existing caries lesions. One compared the efficacy of resin or glass ionomer sealants in arresting microcavitated lesions (ICDAS 3) in first permanent molars.[301] A double-blind randomized controlled trial

followed up 41 six- to eleven-year-old children for a period of 2 years after having at least 1 qualified lesion sealed with resin or glass ionomer. The results showed that 98% of 102 lesions treated were arrested and only 2 showed radiographic progression with no differences between resin and glass ionomer sealants. A second systematic review and meta-analysis of nonrestorative treatments for caries summarized the evidence for arrest or reversal of cavitated and noncavitated lesions on primary and permanent teeth.[302] Forty-four trials with 7378 participants were assessed that included a total of 22 possible interventions, distilling the analysis down to 4 network meta-analyses. The results suggest that the order of highest effectiveness at arresting or reversing noncavitated occlusal, proximal, and noncavitated and cavitated root carious lesions on primary or permanent teeth was sealants+5% sodium fluoride varnish>resin infiltration+5% sodium fluoride varnish>5000-ppm fluoride toothpaste or gel. The data also indicated that 5% sodium fluoride varnish was the most effective treatment for arresting or reversing noncavitated facial or lingual lesions and that 38% silver diamine fluoride applied biannually was most effective at arresting advanced cavitated lesions on any coronal surface. The final study is an interesting multicenter 3-arm trial where patients with caries in primary teeth were randomized into 3 treatment strategies that included conventional caries restoration, biological management via sealing, and a third group with no treatment provided.[303] All 3 strategies included standard preventive measures such as diet counseling, plaque removal, topical fluorides, and fissure sealants. This study included 1144 children and tracked the primary outcomes of dental pain and/or infection for a period of 3 years. The interesting finding was that there was no evidence of a difference in the incidence or number of episodes of pain and/or infection among any of the 3 strategies. The proportions of children with at least 1 incident were 42% for those with restorations, 40% with the sealed lesions, and 45% in the no treatment group. This study demonstrates the influence of selecting the primary outcomes for a study. While there is a great deal of evidence showing a reduction in the clinical measures of caries arrest and progression by using caries management strategies, the more patient-centered outcomes of pain and/or infection do not appear to differ.

Composite resins

Two themes appeared in the 2019 literature related to dental composite resin materials, comparison of performance to glass ionomers and the performance of bulk-fill materials. While 2 of the articles related to glass ionomers only reported 1-year results, the fact that performance problems were apparent in that short period made them notable. A randomized clinical trial compared a high-viscosity glass ionomer (Equia Forte Fil; SDS), universal composite resin (Charisma Smart; Kulzer GmbH), and a bulk fill composite resin (Filtek Bulk Fill; 3M).[304] A total of 103 restorations were followed up over 1 year, and the high-viscosity glass ionomer was reported to show lower retention, color match, anatomic form, contact retention, marginal adaptation, and surface texture than the 2 resin-based materials. A second 1-year trial compared a nanofilled composite resin (CeramX; Dentsply Sirona) with a flowable modified glass ionomer with claimed bioactivity (ACTIVA Bioactive; SDS).[305] In this trial, the failure rates were 24.1% for the glass ionomer and 2.5% for the composite resin, with the main reasons for glass ionomer failure being lost restorations, postoperative symptoms, and secondary caries. The trial was discontinued because of the high glass ionomer failure rate. One longer term study evaluated the performance of high-viscosity glass ionomer and posterior composite resin in primary molars over 3 years[306] The restorations were class II proximal lesions on otherwise healthy preschool children. After approximately 3 years, the failure rate for glass ionomer was 17.1% compared with 4.9% in the composite resin group, with the primary reason for failure in the glass ionomers being significant loss of the restoration or marginal ridge. All 3 of these studies illustrate the physical limitations of glass ionomer restorations in stress bearing areas.

There were 3 systematic reviews and meta-analyses that compared bulk-fill composite resins with conventional composite resins looking at different aspects. The first was a systematic review and meta-analysis of bulk-fill composite resins and conventional composite resins in the restoration of posterior teeth. Ten articles comprising 941 restorations were analyzed with a mean follow-up of 33.6 months[307] The meta-analysis found no difference in the failure rates between conventional and base/flowable bulk-fill composite resins (P=.31; RR, 1.49; 95% CI: 0.69-3.25) or between conventional and full-body/sculptable bulk-fill composite resins (P=.12; RR, 1.89; 95% CI: 0.84-4.24). A second systematic review and meta-analysis compared the times necessary for placing bulk-fill and conventional composite resin restorations.[308] Three studies were included, and the results showed that treatment times were lower when full-body bulk-fill composite resins were used as compared with conventional composite resins, but there was no difference between the times needed to place flowable bulk-fill and conventional composite resins. The third systematic review and meta-analysis took a different track and did comparisons between the physical and chemical properties of bulk-fill composite resins and clinical performance.[309] Properties of volumetric shrinkage, polymerization stress, cusp deflection, microhardness, and conversion were compared between various bulk-fill materials and

conventional composite resins, and an attempt was made to correlate differences in properties with differences in clinical performance. As has been observed in other comparisons of in vitro properties to clinical performance, while differences were noted in physical or chemical properties, it was impossible to associate these differences with the clinical performance of the materials. Once again, the final answers appear to be in long-term clinical trials and not in laboratory evaluations.

A systematic review was published of studies tracking urinary concentrations of bisphenol A (BPA) before and after dental treatments by using resin-based materials.[310] Seven studies qualified, 4 in children and 3 in adults. In all studies, urinary BPA increased in the 24 hours after dental treatment, and 1 study showed it returned to baseline by 14 days after treatment and remained at baseline 6 months after treatment. This review reaffirms what many prior studies have shown regarding the low and transient exposure potential to BPA from composite resins and sealants.

A 5-year clinical trial compared the performance of composite resin restorations with margin defects that had been repaired or resealed versus simply observed without any repairs.[311] There were 271 restorations in 104 patients at 5-year recall that were evaluated by using United States Public Health Service criteria for color, margin discoloration, and margin adaptation. Penetrating discoloration was noted in 81% of the unrepaired restorations versus 46% in the repaired/resealed restorations, and margin crevice formation was observed in 21% of unrepaired versus 11% of repair/resealed restorations. In spite of these differences, there was no difference in recurrent caries at less than 6% overall or in restoration failures. This is another example of where margin failure or discoloration does not necessarily correlate with caries susceptibility or clinical success.

Amalgam

Amalgam continues to be a material in search of a disease, with a few articles appearing in 2019 that are not worth noting as they continue to claim causality without providing evidence beyond weak associations and without demonstrating any clinically manifested adverse outcomes. The most important publication related to amalgam in 2019 is without question the US Food and Drug Administration's update of the Epidemiological Evidence on the Adverse Health Effects Reported in Relation to Mercury from Dental Amalgam: Systematic Literature Review (2010-Present).[312] This review is an update of several prior historical reviews that addressed amalgam-attributed outcomes in the general population and certain vulnerable subpopulations, such as pregnant women, developing fetuses, breastfed infants, and children under the age of 6. Prior reviews failed to find conclusive evidence of a relationship between dental amalgams and clinically manifested adverse outcomes in these populations. What sets this review apart from prior versions is that the current review is not limited to specific adverse outcomes or subpopulations considered at higher risk. This more comprehensive review includes the biomedical evidence on the likelihood of mercury transformation from elemental to organic within the body and the possible consequences of that transformation. Current evidence shows the possible increase of mercury in body fluids due to either occupational or nonoccupational exposure to amalgam, but the evidence that this exposure results in clinical manifestations such as tremor or other neurological conditions is lacking, resulting in no increased risk of adverse systemic effects. The report goes on to state that it may be reasonable to assume that genetic factors can affect mercury kinetics and excretion, but the existing evidence using current biomarkers is inadequate to clinically identify individuals that may be subject to these factors. The summary statement of this review goes on to state, "considering the totality of the evidence, including the most recent comprehensive review of clinical studies published since 2010, there is not sufficient evidence of a relationship between clinically detectable adverse health outcomes and dental amalgam mercury exposure, which is consistent with previous analyses conducted by the Department of Health and Human Services (DHHS) and FDA."

The one adverse condition sited in this 2019 FDA review that demonstrated a true causal relationship with amalgam was lichenoid lesions. One article described the resolution of lichenoid lesions in patients after removal of amalgam and replacement with feldspathic ceramic inlay or onlay restorations.[313] Twenty-four patients with oral lichenoid lesions underwent patch testing resulting in 16 with positive responses that received restoration replacement. After 3 months, complete healing was noted in all patients where the oral lesions were in close contact with the amalgam restorations. A second case report was also published where a patient exhibited positive patch testing, and an oral lichenoid lesion resolved after replacing the adjacent amalgam restoration with composite resin.[314]

One study evaluated the performance of dental amalgam by comparing the influence of patient- and material-related factors on the prevalence of recurrent caries in a population of 450 patients with 4036 restorations.[315] The findings were that secondary caries prevalence was significantly higher with composite resin restorations, class II restorations, high-caries-risk patients, and smokers. Not surprising, the area most frequently involved was the gingival margin of class II restorations.

Amalgam came under fire on the international front in 2019 when a group of 6 northern African nations presented a resolution to ban rather than phase out

amalgam at the third meeting of the Conference of the Parties to the Minamata Convention on Mercury in Geneva, Switzerland.[316] The proposal was rejected after much debate as the conference called for the continued phase down of all mercury-containing products. This event serves as a reminder that the deadline for installation of amalgam separators in the United States is July 14, 2020. The electronic code of federal regulations title 40, chapter I, subchapter N, part 441 Dental Office Point Source Category codifies regulations related to the universal adoption of best management practices for amalgam waste, including the use of amalgam separators.[317] Some important aspects of this regulation are that it applies to dental facilities placing or removing amalgam restorations and discharging wastewater to a publicly owned treatment work (POTW). Specifically excluded are dischargers from the specialties of oral pathology, oral and maxillofacial radiology, oral and maxillofacial surgery, orthodontics, periodontics, or prosthodontics. The requirements call for the installation of separators compliant with American National Standard/American Dental Association Specification 108 for Amalgam Separators (2009) with Technical Addendum (2011) or the International Organization for Standardization 11143 Standard (2008). The reporting requirements are a one-time compliance report submitted to the local Controlling Authority no later than October 12, 2020, or no later than 90 days after operations of a new dental facility. Additional documentation requirements are described in the regulation.

Fortunately, amalgam separators have proven to be relatively simple technologies that are easy to install, low cost, and highly effective. While dental amalgam is a relatively small contributor to the overall global mercury burden, it has been shown to account for as much as 40% of the mercury burden for a local wastewater treatment works. Installing and maintaining a separator, along with practicing all the amalgam best-management practices is simply the right thing to do and demonstrates the profession's commitment to being proper stewards of the environment.

OCCLUSION AND TEMPOROMANDIBULAR DISORDERS

TM disorders: Etiology

There were 2 articles that outlined the role trauma plays in the development of structural changes in the temporomandibular (TM) joint. The first, by Born et al,[318] investigated the prevalence, sociodemographic correlates, and clinical predictors of traumatic dental injuries (TDIs) in the primary dentition among a community-based sample of preschool-age children. The sample comprised 1546 preschool-age children (mean age 49 months, range of 24-71month) in North Carolina public preschools. Information on sociodemographic, extraoral, and intraoral characteristics was collected and analyzed with bivariate and multivariate methods, including logistic regression modeling and marginal effects estimation. The prevalence of dental trauma was 47%, with 8% of TDIs qualified as "severe" (pulp exposure, tooth displacement, discolored or necrotic teeth, or tooth loss). In bivariate analyses, horizontal overlap and lip incompetence were significantly associated with TDI. Horizontal overlap remained positively associated with severe trauma in multivariate analysis, with an increase in the likelihood of severe trauma, per millimeter of horizontal overlap. Children with increased horizontal overlap (>3 mm) were more likely to have experienced severe TDI than those with $\leq$3 mm. Horizontal overlap is a strong risk factor for TDIs in the primary dentition. Incorporating and operationalizing this information may help TDI prevention and guide families of preschool-age children.

Sharmaa et al[319] authored a prospective cohort study of temporomandibular disorder (TMD) incidence in adult participants who reported experiencing jaw injury and who had 4 times the risk of developing TMD when compared with noninjured counterparts. There was a positive and strong association between first jaw injury and incidence of TMD onset. This association was observed regardless of whether the injury was extrinsic or intrinsic. Given the increased risk of developing painful TMD after jaw injury, it seems prudent to monitor individuals who experience either intrinsic or extrinsic injury, especially when early identification and treatment of TMD symptoms is associated with less painful and shorter episodes of complications.

TMJ imaging: MRI

Kamio et al[320] reported an incidental finding during head and neck magnetic resonance imaging (MRI) screening in patients with TMDs. The objective of this study was to determine the number and frequency of incidental findings (IFs) detected during head and neck screening, relative to sites and diseases.

The study evaluated 1717 patients (433 male, 1284 female) with suspected TMD who underwent TMJ MRI. Results indicated that at least one IF was detected for 461 patients. The most common IF site was the maxillary sinus. There were 21 different IFs (1.2%) associated with TMD symptoms or for which an association with TMD symptoms could not be ruled out. The authors suggested that the combination of conventional and craniofacial MRI may permit detection of lesions other than those associated with TMDs, thereby supporting the usefulness of MRI. Detection of IFs will likely require development of therapeutic strategies than those used exclusively for TMDs.

Orhan et al[321] also reported on IFs detected during MRI screening of the TMJ. Bilateral TMJ MRIs in sagittal

and coronal planes from 518 patients with TMJ symptoms were retrospectively evaluated. Patients diagnosed with IFs were referred for consultation and clarification of the findings. Patient age, sex, IFs, and locations were recorded. Seventy-eight (15%) patients were diagnosed with 117 IFs, 43 with a single IF, and 35 with more than one IF. Most frequent locations were paranasal sinuses and mastoid air cells. Most frequent definitive diagnoses were inflammatory and cystic lesions. While examining TMJ MRI images, it is important to identify IFs or other pathologies that may mimic signs and symptoms of TMJ disorders.

Sun et al[322] discussed the use of head and surface coils for TMJ MRIs. The surface coil can be used in the conventional TMJ imaging, and the phased array head coil can be used for routine postoperative examinations or dynamic imaging. Further meticulous research is needed for the application of this technology to specific diseases. In a clinical setting, coil selection should be made based on disease location, lesion size, and initial diagnosis to improve image quality and diagnostic accuracy of the MRI examination.

TMJ imaging: CBCT

Tadinada et al[323] explored the role of CBCT in orthodontic therapy. Radiographic analysis using 2D and 3D imaging plays an important role in orthodontics. Traditionally 2D imaging modalities, such as panoramic imaging and cephalometric radiography, have been used for basic orthodontic treatment planning and to monitor treatment progress. While most clinicians carry out traditional orthodontic management with 2D imaging, concerns related to missed diagnoses and guesswork have always existed.

Medical grade multislice computed tomography was the only option for 3D analysis of areas of interest, but radiation dose discouraged orthodontists from routine use, particularly with the young patient population. CBCT provides relatively lower radiation dose and good spatial resolution for evaluating areas of interest in 3D. Some key advantages of CBCT over conventional CT imaging include relatively low radiation dose, significantly smaller footprint, shorter acquisition and reconstruction time, and lower cost of scans and equipment. With these advantages, the role of CBCT in contemporary orthodontics has increased.

Applications of CBCT in orthodontics include evaluation of skeletal and dental malocclusions, localization of impacted canines and molars, evaluation of potential temporary anchorage sites, and orthognathic surgical planning. CBCT also plays a valuable role in airway analysis and in managing syndromic patients, including cleft lip and palate. Osseous components of TMJ are also well visualized with CBCT. Therefore, arthritic, osteopenic, and osteoporotic changes can be evaluated by using CBCT. Moreover, patient-specific surgical guides and other devices can be manufactured from the 3D information obtained from CBCT scans and produced via CAD-CAM processing. While clinical applications range from evaluation of anatomy to pathologic identification of maxillofacial structures, the key advantage of CBCT remains high-resolution images at relatively lower radiation doses.

For 2D imaging modalities typically used in orthodontics, radiation doses expressed as effective dose for panoramic imaging varies between 4 and 10 μSv. Cephalometric examination range between 3 and 5 μSv. These dosages depend on manufacturer and machine type. As reference, a complete mouth series ranges from 12 to 58 μSv based on collimation used.

Two-dimensional and 3D radiation doses cannot truly be compared as acquisition physics and associated risk are distinctly completely different. Radiation dose related to most imaging modalities is expressed as effective dose. It is difficult to express CBCT dose ranges in effective dose because of dependence on the anatomic area being imaged. Risk estimates for a small-volume CBCT scan of the anterior maxilla is completely different from posterior mandibular scans. While some amount of anatomic overlap may occur with the size of the field of view (FOV), the overall challenge of accurate calculation must relate to both anatomic area and FOV, but neither independently. For most currently available machines, effective dose ranges between 20 and 100 μSv. While this may seem significantly greater than the aforementioned 2D modalities, a true comparison for small-volume CBCT must be made with a 3D modality such as multislice CT, whose dose ranges are typically 1000-2000 μSv for a single jaw. Effective radiation dose varies for different CBCT units depending on FOV and scan obtained. By adjusting settings, patient radiation exposure can be reduced. The key to safe practices in radiographic examination is to follow the principle of ALARA (as low as reasonably achievable). CBCT scans should only be ordered when clear clinical justification exists, and there is a reasonable expectation that the resulting image(s) will yield clinical benefits. Settings should also be adjusted to minimize the effective radiation dose as much as possible, such as by obtaining the scan by using an FOV that optimizes diagnostic efficacy.

Arayasantiparb et al[324] investigated associations between radiographic and clinical findings in patients with TMJ osseous alteration. Degenerative joint disease (DJD) is a common, noninflammatory pathology affecting the TMJs. DJD is generally defined as a degenerative condition of the joint characterized by deterioration and abrasion of articular tissue and concomitant remodeling of underlying subchondral bone due to overload of the remodeling mechanism. The progressive destruction and loss of articular cartilage results from an imbalance

between predominantly chondrocyte-controlled reparative and degradative processes. DJD is an age- and sex-related disease thought to result from acute trauma and joint overloading relating to parafunctional habits, missing teeth, and occlusal interference. Common signs and symptoms of DJD are joint noise (crepitation), pain on normal functional movement, pain on palpation, and limited range of motion. Early changes in the synovial membrane are only detectable with biopsy and arthroscopy. Radiographic evidence typically lags behind articular tissue changes, thus frequently escaping early clinical detection.

DJD is generally diagnosed by patient history and clinical examination. A patient must report joint noises with jaw movement or function within the last 30 days or during the examination. The examination must be positive for crepitus during at least 1 excursive movement. DJD can be subclassified in the presence of joint pain. DJD without pain is defined as osteoarthrosis, while DJD with pain is defined as osteoarthritis. Clinical diagnosis must be confirmed by computed tomography (CT) imaging displaying one of the following radiographic characteristics: subchondral cyst, erosion, generalized subchondral sclerosis, or osteophytes. Furthermore, laboratory tests for rheumatoid factor (RF), antinuclear antibody (ANA), and erythrocyte sedimentation rate (ESR) are used to exclude other autoimmune-related joint diseases. As bone changes are important characteristics of DJD, CBCT is the imaging technique of choice as it provides high diagnostic quality, no superimposition, 3D multiplanar images at lower radiation dose than conventional and medical CT.

Arayasantiparb et al[324] followed up 73 patients (142 TMJs) who were 20 years of age or older and imaged with CBCT. The presence of condylar flattening, osteophytes, and erosion could be identified in sagittal sections. In the coronal sections, the examiners identified the presence of sclerosis and erosion. Subchondral cysts were detected when round or oval-shaped, osteolytic areas presented beneath the cortical bone of the condylar head in all 3 planes. Radiographic findings from CBCT images were evaluated for the presence or absence of the following 5 characteristics: generalized subchondral sclerosis of the condyle (an area of increased cortical density extending into marrow space); osteophyte formation (marginal bony outgrowths on the condyle); erosive condylar bony change (an area of decreased cortical and adjacent subcortical density); subchondral cyst (well-circumscribed osteolytic subcortical bone without cortical destruction); and flattening of the condylar articular surface (flat bony contour deviating from normal convex form).

Radiographic examination of CBCT images showed flattening in 127 joints (89.4%), sclerosis in 22 joints (15.5%), subchondral cyst formation in 13 joints (9.2%), erosion in 97 joints (68.3%), and osteophytes in 124 joints (87.3%). There was a statistically significant correlation between crepitation and the 4 radiographic characteristics of sclerosis, subchondral cyst formation, erosion, and osteophyte formation.

Lee et al[325] discussed anterior joint space (AJS) narrowing in patients with TMD. Data from 100 TMD patients (55 women; mean age 34.34 ±14.88 years) diagnosed by using the Diagnostic Criteria for Temporomandibular Disorders, including 50 patients with acute TMD (aTMD) and 50 patients with chronic TMD (cTMD), were analyzed. Bilateral osteoarthritis was significantly more frequent in patients with cTMD than in those with aTMD (50% versus 30%, respectively; $P<.05$). AJS values for both right and left TMJs were significantly smaller in the patients with cTMD than in those with aTMD (4.18 ±1.71 mm^2 versus 7.35 ±1.71 mm^2, and 6.20 ±2.88 mm^2 versus 7.34 ±2.47 mm^2, respectively; $P<.05$). In patients with cTMD, narrowed AJS was correlated with increased dysfunction index ($r=-0.373$, $P<.01$). Lee et al[325] concluded that over time, AJS of the TMJ can become narrowed in patients with TMDs.

The evaluation of condylar anatomical conditions by CBCT has been increasingly used in dental practices. Tomographic interpretation of TMJ and adjacent structure variations can assist in clinical decision-making as evaluation and diagnosis of TMDs, as well as different stages of ortho-surgical treatment, are key to accurate treatment planning. The anatomical complexity of the TMJs can make image interpretation challenging. Conventional CT is well established with up to 96% accuracy when compared with measured bony components. CBCT has gained popularity in dentistry for its availability, ease of use, low radiation requirement, and low cost. With this in mind, Scariot et al[326] examined the correlation between 3D tomography and dry skull measurements.

Known anatomic diversity of temporomandibular articulation, compounded by factors that influence radiographic images, lead to concerns related to radiographic data validity. For CBCT, studies have investigated image reliability against real measurements of maxillofacial anatomy. The clinical significance of image distortions is still widely debated. The objective of this study was to compare tomographic measurements of dry skull mandibular condyles with CBCT images and consider the clinical significance.

Evaluated were 66 dry skulls at 8 anatomical landmarks with 4 measurements made bilaterally by using a digital pachymeter. Measurements were then made from the landmarks on CBCT images and compared one by one with the real values.

While CBCT provides good images with fine detail, image distortions can hinder the accurate diagnosis of important pathologic conditions, such as the size of osteophytes, erosion, extent of fractures, possibility of

ankylosis, developmental abnormalities, and the condyle-fossa relationship in open- and closed-mouth conditions. The authors indicated that small dimensional differences identified in this study are unlikely to significantly impact the choice of treatment.

Han et al[327] reported on the 3D cephalometric analysis of the maxilla. Clinical evaluation of the midface, including paranasal and upper lip regions, is highly subjective and complex. Traditional and 3D cephalometrics were not developed with the clinical appearance of these midfacial areas in mind, thus may be unsuitable as aids in diagnosing dentofacial deformities. The aim of this study was to correlate traditional and newly defined landmarks and measurements with the clinical appearance of the midface.

Fifty-two participants who received full-field CBCT were recruited. A single blinded examiner assessed each participant's midfacial region (including paranasal and upper lip), and a second blinded examiner obtained traditional and newly defined cephalometric measurements. Statistics assessed correlations between traditional and novel cephalometric measurements and clinical midfacial findings. The influence of paranasal soft-tissue thickness was also analyzed. Performance of any classification derived from statistically significant variables was analyzed with micro-F scores and area under the receiver operating characteristic curve (AUC).

Both traditional (SNA) and newly defined measurements (SN-ANS, SN-PR, SN-NP, SN-h, SN-CEJ) had no significant correlation to clinical paranasal diagnosis. However, in the absence of upper lip procumbence or protrusion, SN-NP and SN-h had significant correlation to clinical paranasal diagnosis. For upper lip analysis, both traditional (SNA) and new (SN-CEJ) measurements had strong correlation with clinical upper lip diagnosis. All significant cephalometric variables were shown to have good intraobserver and interobserver reliability except SNA, which had a low interobserver reliability. Fitted models for paranasal and upper lip analyses showed low micro-F scores, indicating low precision and recall. However, AUC values of 0.7019 and 0.6362 for the paranasal and upper lip analysis, respectively, suggest improved performance of the model with a larger sample size.

Newly defined measurements SN-h and SN-NP correlated with clinical paranasal diagnosis only in the absence of upper lip procumbence and protrusion. SNA and SN-CEJ were strongly correlated with clinical upper lip diagnosis. However, fitted models based on this study sample yielded low micro-F scores, making the fitted models currently unsuitable for anything besides correlation with clinical findings. A larger sample size will be necessary to further clarify the potential roles of these measurements, especially given reasonable AUC values. Findings of this study demonstrate the highly subjective and relative nature of midfacial diagnosis and the importance of clinical judgment despite the potential utility of some traditional and new measurements.

Occlusion

Kajii et al[328] address how osseous changes in the mandibular condyle affect backward rotation of the mandibular ramus in Angle class II patients with idiopathic condylar resorption. Osteoarthritis or osteoarthrosis of the TMJ, also known as DJD of the TMJ, is characterized by resorbed deterioration and simultaneous remodeling of the articular cartilage and subchondral bone. Condyle resorption can be caused by TMJ pathologies, such as adolescent internal condylar resorption (AICR, formerly called idiopathic condylar resorption or ICR), reactive arthritis, and connective tissue/autoimmune diseases. Radiologically, osteoarthritis of the TMJ has been identified by osseous changes, such as mandibular condyle erosion, osteophytes, deformities, and flattening on the margins of the articular surface. Women are more commonly affected, and host factors, such as age, hormones, and systemic disease, may contribute to resorptive deterioration and dysfunctional remodeling of the TMJ, even when biomechanical stresses are physiologically normal. Alternatively, excessive mechanical stress may provoke resorptive deterioration and dysfunctional remodeling in the absence of predisposing host factors. In AICR, it is postulated that the articular disc becomes displaced anteriorly, and the condyle is then surrounded by the hyperplastic synovial tissue that continues to release chemical substrates that penetrate the condylar head causing condylar resorption.

This case-control study evaluated 20 Japanese women diagnosed with Angle class II malocclusion and bilateral ICR of the TMJ (ICR group). Another 24 Japanese women with Angle class II malocclusion without ICR (non-ICR group) served as controls. Inclusion criteria were horizontal overlap >4.5 mm, ANB angle >5.0 degrees, full class II or end-to-end molar relationships, and age $\geq$15 years at initial examination. Exclusion criteria were congenital anomalies, history of rheumatoid arthrosis, history of trauma, and previous orthodontic treatment. No patients in the non-ICR group had symptoms of TMD.

Standardized pretreatment lateral cephalograms made at initial examination were used to analyze skeletal and dental morphology. Panoramic pretreatment radiographs made at initial examination were used to measure condylar height and ramus height. MRI scans obtained immediately after panoramic radiographs were used to evaluate osseous TMJ changes for all participants in the ICR group. No MRIs were obtained in the non-ICR group.

Two experienced individuals, blinded to clinical information, independently assessed condylar osseous

changes in MRIs for ICR diagnosis, based on CT findings such as mandibular condyle erosion, osteophytes, subchondral cyst, generalized sclerosis, cortical sclerosis, and flattening. A diagnosis of osseous changes was evaluated carefully. Images that lacked clarity were rejected. Two condylar metrics were used: condylar height/ramus height (CH/RH) and CH/(CH+RH). A line from nasion perpendicular to the Frankfurt horizontal (FH) plane was determined. The functional occlusal plane was represented by a line drawn through the occlusal surfaces of the maxillary and mandibular first molars, second premolars, and first premolars. Conventional used linear and angular measurements were compared between ICR and non-ICR groups.

Mean values for facial angle and pogonion to nasion perpendicular, which represent the anterior-posterior position of the mandible, were significantly smaller in the ICR group. The mean value for point A to nasion perpendicular, representing the anterior-posterior position of the maxilla, was also significantly smaller in the ICR group. Mean values for U1 to SN plane and U1 to FH plane, which represent labial inclination of the maxillary incisors, were significantly smaller in the ICR group. Mean horizontal overlap, representing the distance between the labial surface of the mandibular incisors and the labial aspect of the incisal edge of the maxillary incisors, was also significantly smaller in the ICR group. The mean value of functional occlusal plane angle was significantly larger in the ICR group. The mean value of Wits appraisal (sagittal intermaxillary relationships projected onto the functional occlusal plane) was significantly smaller in the ICR group. However, there was no significant difference in mean ANB angle (also represents sagittal intermaxillary relationships) with regards to the cranial base.

In the present patient population, the authors demonstrated that Angle class II patients with ICR had significantly smaller condylar ratio, shorter mandibular ramus height, more clockwise rotation of the ramus, greater retrusion of the mandible, less labially inclined maxillary incisors, and a steeper functional occlusal plane than Angle class II patients without ICR. Angle class II patients with ICR demonstrated shorter condylar height (attributed to condylar osseous changes) that may affect subsequent backward rotation of the mandibular ramus.

In a related study, Porto et al[329] surveyed orthodontists about knowledge and beliefs regarding TMDs. Authors indicated 2 objectives: to identify whether there is a discrepancy between orthodontists and TMD experts related to diagnosis and treatment of TMD patients, and to influence the TMD curriculum in orthodontic residency programs and to better prepare orthodontists in diagnosis, treatment, and referral of TMD patients.

Among those that responded to the survey questionnaire, 148 were residents, 1132 were private practitioners, and 61 were full-time faculty members. Of the respondents, 62% did not feel they received enough instruction in TMD during residency training and 50.2% indicated a lack of comfort treating patients with TMD. The authors concluded that orthodontic residency programs in the United States need to improve methods of teaching TMD concepts. Although most orthodontists (in this study) are comfortable diagnosing TMDs, less than half feel comfortable treating these patients. Additionally, the difference in responses between orthodontist and TMD expert groups was significant for 71% of the questions.

Huang et al[330] reported on patient and practitioner characteristics and treatment recommendations emerging from the National Dental Practice-Based Research Network Adult Anterior Open Bite Study. Authors e-mailed a survey to 8870 members of the American Association of Orthodontists. Group consensus was determined when more than 50% of participants support a specific response. Previously published responses from TMD experts were used as a reference for evaluation.

The aim was to identify and describe US practitioner and patient characteristics associated with treatment recommendations for adult patients with an anterior open occlusal relationship. Practitioners and patients were recruited from the National Dental Practice-Based Research Network. Practitioners were asked about demographic characteristics and their treatment recommendations for these patients. Practitioners also reported on their patients' dentofacial characteristics and provided initial cephalometric scans and intraoral photographs. Patients were asked about their demographic characteristics, previous orthodontic treatment, and goals for current treatment.

Four treatment approaches were evaluated: aligners, fixed appliances, temporary anchorage devices (TADs), and orthognathic surgery. Extractions were also investigated. Predictive multivariable models were created comparing various treatment approaches, as well as extraction or nonextraction decisions. Ninety-one practitioners (mostly orthodontists) and 347 patients were enrolled between October 2015 and December 2016.

Increased aligner treatment recommendations were associated with white and Asian patients, the presence of tongue habits, and female practitioners. Therapy involving TADs was recommended more often in academic settings. Recommendations for orthognathic surgery were associated with specific demographic factors (availability of insurance coverage and practitioner race or ethnicity) and dentofacial characteristics (anteroposterior discrepancies, more severe anterior open occlusal relationships, and steeper mandibular plane angles).

Extraction recommendations were largely associated with severe crowding and incisor proclination. The authors concluded that both doctor and patient demographic factors and dentofacial characteristics were significantly associated with treatment recommendations for adults with anterior open occlusal relationships.

In a case report related to anterior open occlusal relationships, Park et al[331] presented a 12-year-old girl diagnosed with idiopathic condylar resorption (ICR) 10 months after completing orthodontic treatment for class II division I malocclusion. A common dilemma when treating anterior open occlusal relationship is defining the etiology. ICR can lead to an anterior open occlusal relationship. Although orthodontic treatment should be delayed until active ICR has ceased, treatment may unintentionally be initiated because anterior open occlusal relationship may not appear before or during orthodontic therapy. When a young patient with a high mandibular angle and previous skeletal or dental class II malocclusion returns with an open occlusal relationship during the retention phase, the patient's condyles must be carefully examined to determine the presence of resorptive TMDs such as ICR.

Currently, controversy over etiology and treatment of ICR is a continuing challenge. Orthodontists should closely monitor conditions and offer informed treatment options to patients with risk factors for ICR or clinical signs of condylar resorption that might develop at any stage of orthodontic therapy, including the retention phase.

Wolford and Galiano[332] reported on adolescent internal condylar resorption (AICR), a progressive disease that affects only the TMJ, resulting in condylar resorption in all 3 planes of space, malocclusion, facial deformity, and TMJ dysfunction, with or without pain. AICR is poorly understood and commonly unrecognized by dentists and physicians. Onset is almost always between 11 and 15 years of age, predominately in girls (8:1) during pubertal growth. These patients have characteristic clinical signs, such as high occlusal plane (HOP) angle facial morphology, slow but progressive mandibular retrusion, and class II malocclusion with or without an anterior open occlusal relationship. Imaging studies involving CBCT, lateral cephalograms, CT, and MRI can demonstrate condylar resorption, articular disc anterior displacement, and associated dentofacial deformity.

AICR is a distinct condylar resorptive pathology with respect to etiology, pathophysiology, clinical presentation, imaging characteristics, and treatment protocol. Incorrectly, AICR has been grouped with other TMJ resorptive conditions such as idiopathic condylar resorption, idiopathic juvenile condylar resorption, idiopathic condylysis, condylar atrophy, progressive condylar resorption, and cheerleader syndrome. There are several specific TMJ local and systemic pathologies different from AICR that can cause mandibular condylar resorption. Local factors include osteoarthritis, reactive arthritis, avascular necrosis, infection, traumatic injuries, and others. Connective tissue or autoimmune systemic factors include juvenile idiopathic arthritis, rheumatoid arthritis, psoriatic arthritis, scleroderma, systemic lupus erythematosus, Sjogren syndrome, ankylosing spondylitis, and others.

Condylar resorption is often associated with orthodontic or orthognathic surgical treatment. These therapeutic modalities are likely coincidental not causative, although they may exacerbate ongoing pathologic processes. As AICR occurs between 11 and 15 years of age, initial appearance typically coincides with orthodontic treatment. If AICR is unrecognized and untreated after orthodontics or orthognathic surgery, posttreatment instability is predictable.

Specific factors and facial morphologies significantly increase susceptibility to AICR, including female to male ratio of 8:1; onset age 11-15 years during pubertal growth, HOP facial morphology (dolichocephalic), and predominance of class II skeletal and occlusal relationships with or without an anterior open occlusal relationship. AICR rarely occurs with low occlusal and mandibular plane angle (brachycephalic) facial types or in class III skeletal relationships. Only the TMJs are affected. No other joints are involved. There are no known genetic correlations to AICR. All presentations appear to be isolated incidents. Occurrence rate in the general population is unknown.

AICR diagnosis is typically made based on patient history, clinical examination, and imaging. Before onset, patients may have normal facial balance or may have a class II skeletal and occlusal relationships. The disease usually progresses bilaterally with the following clinical characteristics: a slow progressive posterior mandibular shift starting during pubertal growth; development of a HOP angle facial morphology with retruded mandible and maxilla; development or worsening of the class II occlusal relationship with or without an anterior open occlusal relationship; and TMJ symptoms such as pain, headaches, noises, and ear symptoms.

In unilateral presentations, or in bilateral presentations with differential condylar resorption rates, the following can occur: shift of mandibular dental midline and chin toward affected side; development of ipsilateral class II occlusion and posterior reverse articulation with ipsilateral occlusal prematurity; and development of anterior and contralateral open occlusal relationship. Although TMJ symptoms (joint pain, headaches, myofascial pain, clicking, popping) can be present, they may be mild or nonexistent. Clicking and popping may be absent as the disc becomes nonreducing relatively early in the pathological process. Conversely, hyperplastic synovial tissue may thicken,

providing smooth condylar translation onto the displaced disc.

AICR patients without TMJ symptoms or joint sounds are diagnostically challenging but require treatment to stop disease progression, re-establish function and facial balance, correct obstructive airway problems if present, and eliminate pain. AICR patients commonly have partial nasal airway obstruction with hypertrophied turbinates and a decreased oropharyngeal airway dimension because of the retruded mandibular position. If other joints in addition to the TMJs are symptomatic, the disorder is not likely to be AICR. Diagnostic laboratory studies may be indicated, particularly if other joints are involved, to evaluate for connective tissue or autoimmune diseases or reactive arthritis. There are no laboratory tests specific for AICR.

Imaging modalities useful in diagnosis and treatment planning for AICR include CBCT, lateral cephalometric radiography, TMJ-CT scans or tomograms, panoramic radiography, and MRI. Characteristic AICR findings identifiable on lateral cephalometrics include skeletal or dental class II deformity with or without an anterior open occlusal relationship, high occlusal and mandibular plane angles, reduced height of posterior maxilla and mandibular rami, overangulated mandibular incisors, and significant decrease in oropharyngeal airway potentially leading to sleep apnea symptoms. TMJ imaging may reveal either normal to excessive joint space (because of synovial tissue hyperplasia within the joint) or decreased joint space. Involved condyles will appear smaller in size corresponding to the aggressiveness of the disease. Imaging of the condyles may reveal cortical thinning, loss of cortical integrity, or less commonly relatively normal cortical appearance. Superimposition of serial cephalogram TMJ-CTs at 6- to 12-month intervals will typically demonstrate the existence and rate of active condylar resorption.

MRI may be used to demonstrate decreased condylar head size and volume, anterior disc displacement with or without reduction on opening, thinness or loss of cortical continuity on the condylar head of the condyle (or occasionally normal appearance), and normal or increased joint space with amorphous appearing soft tissue between condyle and fossa or potentially decreased joint space. The degree of deformation or degenerative disc changes depends on duration of displacement extent of reduction on opening. Discs deform or degenerate more rapidly when they fail to reduce. Treatment depends on disc salvageability and the loading capacity of the reduced condyles. There is typically a 4-year window from onset of AICR to surgical intervention where the disc remains salvageable and an acceptable outcome can be achieved.

Entering the superior joint space, the articular disc will be anteriorly displaced with or without deformation and degenerative changes. Hyperplastic synovial tissue will cover the condylar head and may appear amorphous with little vascular component and no inflammation. The condylar head and glenoid fossa will reveal intact fibrocartilage covering both structures with no evidence of erosion or osteophytic formation. If the fibrocartilage is absent and bony erosion is visible, the disease process affecting the TMJ is not AICR. Histologically, bilaminar tissues will usually display synovial hyperplasia without inflammation.

Early clinical experience treating AICR patients with traditional orthognathic surgery and ignoring the TMJs resulted in poor outcomes with significant mandibular relapse. It quickly became evident that in the presence of unstable and unhealthy TMJs, orthognathic surgery would be prone to relapse. Ignoring TMJ pathology and treating AICR with orthognathic surgery alone is likely to result in continued condylar resorption, redevelopment of functional and esthetic deformities, class II malocclusion with anterior open bite, worsening TMJ symptoms and dysfunction, worsening pain, and the need for additional surgery. Because most of these patients have retruded jaws, HOP angle facial morphologies, and decreased oropharyngeal airway dimensions, the more severe patients are prone to significant sleep apnea symptoms. Optimal functional and esthetic results may be achieved by disc repositioning with Mitek anchors and counterclockwise rotation advancement of the maxilla and mandible.

TMJ arthroscopy and arthrocentesis techniques will not remove hyperplastic synovial tissues, nor will they reposition the articular disc into a normal functional position. Thus, arthroscopy and arthrocentesis are contraindicated in the management of AICR. TMJ surgery (disc repositioning, arthroplasties, high condylectomies) can alter mandibular position and occlusion. Therefore, performing TMJ and orthognathic surgery simultaneously or during separate operations is an important decision.

Careful management of occlusion and parafunctional habits during the postoperative period is critical to predictable and high-quality outcomes. Authors do not use occlusal devices to control postoperative parafunction but commonly prescribe clonazepam, or other muscle relaxers, to limit parafunctional habits and force applications over the course of a few weeks. With the removal of TMJ pathology, correction of the occlusion, and elimination sleep apnea symptoms by increasing the oropharyngeal and nasal airway, it is unusual for AICR patients to experience long-term issues with clenching and bruxism. When end-stage TMJ-AICR requires reconstruction by using total joint prostheses, the mandible can be advanced and rotated counterclockwise, if indicated. Asymmetries may be corrected with custom total joint prostheses without the need for additional mandibular osteotomies.

Engelmeier and Phoenix[333] provided an excellent historical review of lingualized occlusion for removable prosthodontic restorations. Lingualized occlusion has been defined as "a form of denture occlusion that articulates the maxillary lingual cusps with the mandibular occlusal surfaces in centric, working, and nonworking mandibular positions." While lingualized occlusion has been an option for nearly a century, the past 35 years has witnessed a resurgence of interest that rivals anatomic and neutrocentric denture occlusions. The development of dental implants and the use of implant-assisted overdentures for management of edentulism have stimulated reevaluation of removable prosthodontic occlusion. Because of reported esthetic, biomechanical, and technical advantages, lingualized occlusion has, for some, emerged as a logical choice. Of note, several authors have extolled the advantages of lingualized occlusion without listing any disadvantages or contraindications.

Advantages of lingualized or lingual contact occlusion include good esthetics; good bolus penetration; straight forward technique; additional stability in parafunction (balance); reduced lateral forces with dominant vectors directed toward alveolar ridges; ease of adjustment; an area of closure contact which accommodates foundation changes; more adequately adapts to class II, class III, and reverse articulation situations; and offers generally compatibility with the tenets of neutrocentric occlusion.

Swallowing

Fassicollo et al[334] investigated changes in swallowing as related to chronic TMD. Twenty-three patients diagnosed with chronic TMD (experimental group), including disc displacement with reduction (DDR) and pain, and 27 healthy volunteers (control group) were compared. Surface electromyography (EMG) of the temporalis, masseter, sternocleidomastoid, and suprahyoid muscles was performed during swallowing tasks (10-15 mL of a thin liquid and spontaneous saliva). Data were collected and normalized.

Compared with controls, TMD patients showed prolonged duration for swallowing of the thin liquid and saliva. Additionally, they required a longer time to reach peak muscle activity. While the mean relative value of peak muscle activity was similar among groups, the suprahyoid peak activity was significantly lower in the TMD group during swallowing of the thin liquid. Moreover, TMD patients recruited jaw elevator muscles proportionally more than controls. Orofacial myofunctional status was moderately correlated with EMG parameters. Patients with chronic TMD showed temporal prolongation and changes in the relative activity of the recorded muscles during the swallowing. This study contributes additional evidence regarding the reorganization or compensation of muscle activity in patients with chronic TMD.

Botox therapy

In an animal study, Dutra and Yadav[335] studied condylar changes associated with botulinum toxin (Botox) injections. The objective was to determine if Botox, injected into the masseter muscle, was associated with transient structural changes to mandibular condylar cartilage (MCC) and subchondral bone.

Botox (0.3 U) was injected into the right masseter of 6-week-old female mice. Control mice received no injections. These experimental and matched control mice were killed 4 or 8 weeks after a single Botox injection. Mandibles and mandibular condyles were analyzed by microscopic computed tomography (μCT) and histology.

Bone volume fraction was significantly decreased for subchondral bone on the Botox-injected side, when compared with the contralateral control side and control mice at 4 and 8 weeks after injection. Furthermore, histology revealed reduced mineralization and cartilage thickness in the MCC on the Botox-injected side 4 and 8 weeks after injection. Effects on MCC and subchondral bone associated with the Botox injection persisted 8 weeks after injection, thus were not considered to be transient.

Patel et al[336] systematically reviewed the literature to assess the usefulness of Botox for treating patients with TMD and/or bruxism, thereby to determine if there is a place for Botox in the therapeutic management of this patient population. Is the clinical use of Botox justifiable given the current spectrum of treatment available to manage TMD and/or bruxism?

A systematic review of relevant literature was conducted, including the data sources of MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, and OpenSIGLE. The resultant articles were subjected to inclusion and exclusion criteria and then assessed for bias by using the Cochrane framework. Eleven trials met inclusion criteria. The primary outcome measure was changes in pain experience in groups treated with Botox, relative to appropriate controls. Secondary outcomes included changes in the bruxism event frequency, changes in maximum mouth opening, changes in occlusal force, and changes in electromyography (EMG) of muscles of mastication.

Evidence to support the use of Botox in the management of TMD and/or bruxism is not unequivocal. Several studies have shown promising results, thereby justifying further investigation. Given current evidence, consideration of Botox should continue. However, owing to financial implications and possible side effects, the most conservative therapeutic approaches should certainly be considered first.

Anterior repositioning appliances

Lei et al[337] authored a study to determine the effect of anterior repositioning splints (ARS) on condylar osseous

changes in adolescents/young adults with early-stage DJD. Sixty-nine patients with early-stage TMJ-DJD were randomly allocated to 2 treatment groups: conservative therapy with ARS (experimental group) or conservative therapy without ARS (control). Participants with acute TMJ closed-lock had their displaced discs physically reduced by mandibular manipulation before ARS therapy. Clinical and CBCT data on 59 patients (86.4% female, mean age 17.95 ±4.53 years, 67 joints) were attained before treatment and at 6 and 12 months after treatment. Osseous changes after treatment were categorized as progressed, unchanged, repaired (remodeled without new bone formation), and regenerated (remodeled with new bone formation).

About 85.5% of patients completed the study, with 28 participants (32 joints) in the splint group and 31 (35 joints) controls. Occurrence of condylar repair and regeneration was significantly higher with ARS (78.1% of joints) than with controls (48.6% of joints). Moreover, condylar regeneration was exclusively observed in 50% of joints with ARS. Of the 14 joints in the splint group that received TMJ closed-lock physical reduction, 85.7% exhibited condylar regeneration. The splint group also had significantly lower incidence of progressive TMJ degeneration (3.1%) than the control (37.1%).

This randomized controlled study indicated an association between splint therapy and condylar osseous changes in adolescents/young adults with early-stage TMJ-DJD. The TMJs in these young people showed a remarkable capability for repair and regeneration with conservative ARS therapy. Prompt intervention for disc displacement with reduction is therefore advocated, and the proper disc-condyle relationship may be important for condylar repair and regeneration. Biomechanical repair and regeneration within the TMJs present an attractive area to pursue with basic science and clinical research.

SLEEP-DISORDERED BREATHING

An ever-growing body of evidence illustrates that sleep disorders (such as sleep-related breathing disorders or SRBDs) or the effects of several diseases may influence alterations in sleep architecture. Additionally, changes in sleep structures may impact the course of disease and, in turn, mortality.[338]

The body of literature dealing with obstructive sleep apnea (OSA) and the use of mandibular advancement therapy provides little true guidance for the committed practitioner. Specific details of the appliance design research (such as appliance thickness, amount of protrusion, vertical dimension, patient comfort, durability, complications) are generally lacking. This has led to the all too common conclusion, "All appliance designs are basically the same," along with the statement, "Let the patient choose the design of their liking and maybe they will wear it." Dentistry knows and understands that all appliances placed in the mouth for various reasons have differences. Detailed and scientifically supported information on materials and technique is what dentists depend on for patient care. The mandibular advancement appliance is no exception.

If dentistry is to have a true medical device that can be relied upon to provide a consistent outcome for OSA, specific information is needed to guide that care. Research needs to provide this important information, or it is of little value.

Along with not providing detailed information concerning the appliance, inadequate sample sizes, short study durations, and loss of participants to appropriate follow-up are problematic for some articles. Omission of the multifactorial nature of anatomic and lifestyle factors that contribute to or exacerbate SRBDs must be considered and included for research efforts to be relevant. Widely varying criteria for therapy efficacy and success make comparison difficult between articles. The lack of professional consensus within the sleep medicine community regarding problems faced by patients adds still more confusion. At the very least, standard definitions of disease severity that differentiates male from female patients are sorely needed. With these issues in mind, the present review illustrates a wide variation in topics and quality of current published reports on SRBDs.

Oral appliance therapy

More studies are attempting to discern predictors of treatment success with oral appliance therapy (OAT) for OSA patients or describe OSA patient phenotypes to guide treatment approaches. A prospective study explored potential predictors of successful mandibular advancement device (MAD) therapy for individuals with OSA, specifically in patients with anatomic narrowing and sleep-related collapse levels in the upper airway (UA).[339] Sixty-two patients with OSA, registering a median apnea-hypopnea index (AHI) of 34, were treated with a custom-fabricated, monobloc MAD. The upper airway was evaluated by inspection, nasopharyngoscopy, overnight acoustic reflectometry recording collapses, and cephalometric imaging of soft-tissue dimensions and skeletal parameters. Polysomnography (PSG) was assessed at baseline and after at least 5 weeks of therapy with the MAD. Independent predictors of an actual reduction in AHI and treatment success, defined as an AHI reduction of $\geq$50% with residual AHI<10, were determined, by using multivariable linear and logistic regression. Positional OSA (POSA) and nonsupine AHI (adjusted for UA narrowness and collapses, along with sex, age, body mass index [BMI], neck circumference or NC, and baseline AHI) were the only independent predictors.

The results revealed that POSA indicated success with this MAD, and nonsupine AHI was inversely related to success. Cephalometry was not predictive. Two predictive models were proffered—one based on POSA having a specificity of 70% and sensitivity of 69%, and the other based on nonsupine AHI, generating a receiver operating characteristic (ROC) curve (area under ROC=0.78). By using the ROC model, specificity could be increased to 80% without lowering sensitivity. The authors concluded that only variables related to sleep position proved to be independent predictors of success with MAD therapy. They explain these results by the MAD-limiting mandibular movement toward the airway when sleeping supine.

Another prospective trial hypothesized that upper airway collapse sites, patterns, and degrees assessed during baseline drug-induced sleep endoscopy (DISE) affect MAD outcomes.[340] One hundred OSA patients underwent baseline type 1 PSG. MADs were fitted intraorally at fixed 75% maximal protrusion. A total of 72 patients completed 3-month follow-up PSG and baseline DISE. Response was defined as AHI reduction $\geq$50% or deterioration as AHI increases during MAD treatment compared with baseline.

Adjusting for pretreatment AHI and BMI, individuals with tongue base collapse exhibited 3.69 greater odds (range 1.27-10.73; *P*=.013) of responding. Complete concentric collapse (CCC) at the level of the palate (mean 5.32; range 1.21-23.38; *P*=.023) and complete lateral to lateral oropharyngeal collapse (mean 6.62; range 1.14-38.34; *P*=.033) related to deterioration. Results for tongue base collapse and CCC at the palatal level were confirmed in the moderate to severe OSA subgroup. Applying these results to this selected subgroup increased response rate with 54% and decreased deterioration rate with 53%; these results were verified by using other response and deterioration definitions.

The authors concluded that 3 baseline DISE phenotypes were identified that significantly related to MAD treatment outcome, 1 beneficial (tongue base collapse), and 2 adverse (CCC at the level of the palate and complete lateral to lateral oropharyngeal collapse). They note that confirmation in future prospective studies could guide patient selection for MAD outcomes.

A review article examines phenotyping of OSA patients to bring OAT into the realm of precision medicine.[341] OSA is a highly prevalent disorder around the world characterized by repeated obstruction of the pharyngeal airway during sleep, leading to oxygen desaturation, intermittent hypoxia, and sleep fragmentation. As awareness of OSA has risen in the past 20 years, there is growing recognition that OSA is a highly heterogeneous disorder, and the application of a precision medicine therapeutic framework could significantly improve patient outcomes. This approach may permit the prediction of who is affected by OSA, who requires therapeutic intervention, who is susceptible to symptoms and comorbidities, which treatment should be used, and who will respond positively to therapy. To achieve this, it will be necessary to understand intermediate OSA phenotypes in terms of their contribution to disease pathogenesis, clinical and physiological expression, and treatment responses.

The authors discuss recent publication of a number of studies by using unsupervised (cluster) analytical approaches to generate new insights, demonstrating the viability of a precision medicine approach in sleep medicine. They posit that these advances will most surely influence the emerging field of dental sleep medicine and emphasize that dentists need to be aware of these developments.

Another report used a clinically applicable method to estimate OSA traits from routine PSG and identify an endotype-based subgroup of patients expected to show superior efficacy with OAT.[342] The authors noted that OAT is efficacious in many patients with OSA, but prediction of treatment outcome is difficult. Small, detailed, physiologic studies have identified key OSA endotypic traits (such as, pharyngeal collapsibility, and loop gain) as determinants of greater oral appliance (OA) efficacy. In 93 patients (baseline AHI$\geq$20 events/h), they assessed whether PSG-estimated OSA traits (pharyngeal collapsibility and muscle compensation, nonpharyngeal loop gain, arousal threshold, and ventilatory response to arousal) were associated with OA efficacy (percent reduction in AHI from baseline) and could predict treatment response. Multivariate regression (with interactions) defined endotype-based subgroups of "predicted" responders and nonresponders, based on 50% reduction in AHI. Treatment efficacy was compared between the predicted subgroups (with cross-validation).

The authors found that greater OA efficacy was associated with favorable nonpharyngeal traits (lower loop gain, higher arousal threshold, and lower response to arousal), moderate (nonmild, nonsevere) pharyngeal collapsibility, and weaker muscle compensation (overall R^2=0.30, adjusted R^2=0.19, *P*=.003). Predicted responders (n=54), as compared with predicted nonresponders (n=39), demonstrated greater decrease in AHI from baseline (mean 73 and range 66-79 versus mean 51 and range 38%-61%; 95% CI; *P*<.001) and a lower treatment AHI (mean 8 and range 6-11 versus mean 16 and range 12-20 events/h; *P*=.002). Differences persisted after adjustment for clinical covariates, including baseline AHI, BMI, and NC.

The study concluded that quantifying OSA traits by using clinical PSG can identify an endotype-based subgroup of patients that is highly responsive to OAT. The authors suggest that prospective validation of this conclusion is warranted.

A single-center, prospective cohort study sought to measure fatigue and hypersomnolence in patients with OSA treated with a MAD, by using Epworth Sleepiness Scale (ESS) for hypersomnolence and Checklist Individual Strength questionnaire (CIS20R) for fatigue.[343] Fifty-eight individuals with OSA filled out ESS and CIS20R questionnaires at baseline and after 3 months of MAD use. Thirty-nine full data sets were collected. Statistical analysis for questionnaire reliability, comparison between baseline and 3-month follow-up, correlation between changes in values of the 2 questionnaires, and changes in AHI were performed.

CIS20R exhibited excellent reliability in these individuals at baseline and 3-month follow-up (Cronbach α=.97), while ESS showed a marginally good reliability (Cronbach α=.82). The CIS20R showed high levels of fatigue at baseline, and ESS showed a normal level of daytime sleepiness. AHI, ESS, and CIS20R were significantly reduced with MAD treatment. A significant correlation between ESS and CIS20R was observed. No significant correlation between any of the questionnaires and change in AHI was evident.

The investigators concluded that the CIS20R questionnaire results demonstrated a high level of fatigue in OSA patients and that the questionnaire can be used to evaluate changes in fatigue because of 3 months of MAD therapy. The ESS failed to show similar characteristics. The authors propose the combined use of ESS (for hypersomnolence) and CIS20R (for fatigue) when following up OSA patients undergoing treatment with MAD.

Analysis of data emerging from ORCADES (a French prospective multicenter cohort study) was accomplished to compare efficacy of mandibular repositioning devices (MRD) in men and women with obstructive sleep apnea syndrome (OSAS).[344] The authors indicate that MRDs are effective treatment for OSAS, especially in patients who refuse or cannot tolerate continuous positive airway pressure (CPAP) therapy. However, sex differences in the response to therapy and predictors of response were not clearly defined. The ORCADES study included patients with newly diagnosed mild-to-moderate or severe OSAS who rejected or were noncompliant with CPAP. MRD therapy was titrated over 3-6 months. The primary endpoint was treatment success ($\geq$50% decrease in AHI), while complete response was defined by using a range of AHI cutoff values (<5/h, <10/h, <15/h).

Overall treatment success rates were 89% in women and 76% in men (*P*=.019). Corresponding rates in those with severe OSAS (AHI>30/h) were 10% and 68% (*P*=.001), respectively. In women versus men, overall complete response rates at AHI cutoff values of <5/h, <10/h, and <15/h were 49% versus 34% (*P*=.005), 78% versus 62% (*P*=.016), and 92% versus 76% (*P*=.003). Multivariate analysis revealed that significant predictors of MRD success were vertical overlap and baseline apnea index in men and NC and no previous CPAP therapy in women. Sex differences noted in the occurrence of side effects included TMJ pain as the most common reason for discontinuing MRD therapy. The authors concluded that MRD therapy was effective in women with OSA of any severity, with significantly higher response rates than for men, especially in severe OSAS.

Another study explored the influence of weight gain on treatment outcomes for OSA patients undergoing MAD therapy.[345] As a component of a follow-up study involving OSA patients treated with MAD in a primary oral health-care setting, a cohort of 28 patients reporting worsening of daytime or nighttime OSA symptoms received more detailed examination. Twenty-one participants had a complete set of recordings and were enrolled in the study.

Only 3 patients had lost weight during the study period. A mean weight gain of 3.6 ±7.1 kg was significant (*P*=.035). Linear regression showed that weight gain was independent and significantly associated with lower mean peripheral oxygen saturation 92.4 ±1.8%/h *P*=.019) and lowest oxygen saturation 80.1 ±7.2%/h; *P*=.024) scores.

The authors concluded that weight gain is detrimentally associated with MAD therapy in OSA patients. They suggest that regular follow-up by an experienced dentist is advisable to evaluate for possible worsening of OSA. Patient support to promote weight control may be an important adjunct to MAD therapy for OSA.

A prospective case series investigation set out to determine whether high-resolution pulse oximetry (HRPO) is a viable method for successfully titrating MADs for treatment of OSA patients.[346] One hundred thirty-six participants were eligible; 133 were fitted with a custom-made MAD, and 101 individuals completed all phases of treatment including final efficacy testing. The vertical and horizontal dimensions of the appliances were adjusted based on 3 nights of sleep study by using a Minolta 300i and SatScreen software program (Konica Minolta Sensing) after each adjustment. Additionally, cephalometric evaluation proved to be beneficial, by using the stated guidelines for exposure.

Significant improvements in OSA severity were apparent in patients with mild, moderate, and severe OSA. HRPO provides reliable guidance in the titration process of MAD therapy. In 67 participants (66.3%), a respiratory event index (REI) of <5 events/h was achieved (complete response). An REI of <5 is the normal criterion used for successful treatment with CPAP. Adherence rate at the 1-year anniversary of MAD initiation was >90%. It must also be noted that >80% of patients were CPAP failures. Women had a slightly higher success rate than men, and age did not appear to be a significant predictor of success. BMI did not appear to be an overly significant predictor of success.

The authors concluded that OSA can be effectively treated with a MAD at any severity level, and HRPO provides critical information to guide oral appliance titration allowing equivalence with CPAP. (Disclosure: The author of this section of the Annual Review of Selected Scientific Literature is also the lead investigator on the study being reported.)

A review in *Sleep Medicine Clinics* gave an overview of oral appliance therapy for the treatment of OSA patients.[347] Oral appliances protrude the mandible and/or tongue imposing structural changes on the upper airway (UA). The UA is a muscular tube, and its dimensions are enlarged with mandibular and tongue advancement. Protrusion of the mandible and tongue stretches the muscles, promoting a reduction in UA collapsibility with airway shape change and increased muscle tone. The authors note that oral appliances are effective and evidenced-based options for managing OSA.

A separate investigation aimed to test a specific oral appliance and evaluate long-term side effects with therapy, specifically to evaluate tooth movement and changes in occlusion over a minimum of 2 years[348] A Canadian sleep center recruited specific patients diagnosed with sleep apnea (n=18). Patients were fitted with an OA. Impressions were made at baseline and after approximately 1 and 2 years of device use. Casts were marked, scanned, and scored. Maxillary and mandibular anterior tooth crowding was assessed. Horizontal overlap and vertical overlap were measured independently at a separate institution. By using the Sleep Apnea Quality of Life Index (SAQLI-10), patients were surveyed on compliance, satisfaction with their OA, and quality of life.

The results revealed that a rigid appliance fabricated with proprietary CAD-CAM technology led to no significant changes in tooth position during the 2- to 3-year test period, nor were there occlusal changes at maximum intercuspation (MIP) measured by horizontal overlap and vertical overlap. At 2 years, the mean change in Little Irregularity Index for the mandibular anterior teeth was 0.007 mm (95% CI: -0.03, 0.05), which was not statistically different from zero ($P>.05$). Patients were highly satisfied with the device and considered it beneficial.

The authors concluded that a key component to any treatment is the patient's acceptance of the device and willingness to wear it for a long term. When patient compliance is observed, hard-acrylic resin sleep appliances have little effect on tooth movement and occlusion in MIP based on horizontal overlap and vertical overlap.

A different investigation sought to evaluate the magnitude and progression of dental and skeletal changes associated with long-term OA treatment, in addition to determining the predictors of these changes, based on the premise that OAT is a life-long therapy option.[349] Lateral cephalometric images of adults treated for primary snoring or mild to severe OSA with a custom-made titratable MAD for a minimum of 8 years were retrospectively studied. The magnitude and rate of progression of any changes over time was discerned, and initial patient and dental characteristics were investigated as possible predictors of the observed side effects. Records of 62 individuals with an average treatment duration of 12.6 years (range 8-21 years) were included.

Cephalometric analysis revealed significant ($P<.001$) maxillary incisor retroclination (mean approximately 6 degrees) and mandibular incisor proclination (mean approximately 8 degrees) over the study period. Maxillary incisors exhibited a constant rate of retroclination -0.5 degrees/year. The rate of mandibular incisor proclination was variable. The number of treatment years was significantly associated with these variables ($P<.001$). A greater BMI and subspinale-nasion-supramentale (ANB) angle were associated with more maxillary and mandibular incisor proclination retrospectively. Although statistically significant ($P<.001$) skeletal changes were noted over this extended observation period, the difference in the sella-nasion-supramentale (SNB) and mandibular plane angles were approximately 1 degree and deemed clinically insignificant.

The authors noted that the project represents the longest observation period to date examining MAD side effects with up to 21 years of follow-up for some patients. It confirms that there are significant and progressive dental changes with prolonged device use. Conversely, over the same period, skeletal or postural changes were negligible. Additionally, treatment duration was the predictor consistently associated with the magnitude of the observed side effects.

A different trial evaluated the efficacy of combination therapy by using MADs in addition to expiratory positive airway pressure (EPAP) valves on patients who demonstrated incomplete or no response to MADs alone.[350] The authors noted that >50% of OSA patients have incomplete or no therapeutic response with either therapy alone remaining at risk for adverse health outcomes. Twenty-two individuals with OSA (AHI=22, range 13-42 events/h) who were incomplete or nonresponders (residual AHI>5 events/h) on an initial split-night PSG with a novel MAD device and oral airway were enrolled. An additional split-night PSG study was performed with MAD+oral EPAP valve and MAD+oral/nasal EPAP valves, randomly ordered.

Compared with MAD alone, the MAD+oral EPAP significantly decreased the median AHI, with further reductions recorded for the MAD+oral/nasal EPAP combination (AHI=15, range 10-34 versus AHI=10, range 7-21 events/h; $P<.01$). Larger reductions occurred in supine nonrapid eye movement AHI for MAD+oral/nasal EPAP combination therapy (ΔAHI=23 events/h; $P<.01$). Complete response (AHI<5 events/h) was observed with MAD+oral/nasal EPAP in 9 patients, while

13 patients had ≥50% reduction in AHI with no MAD. However, sleep efficiency was lower with MAD+oral/nasal EPAP versus MAD alone or MAD+oral EPAP (78 ±19% versus 87 ±10% or 88 ±10%, respectively; $P<.05$). The authors concluded that combination therapy with a novel MAD and simple oral or oronasal EPAP valves reduces OSA severity to therapeutic levels for a substantial proportion of incomplete/nonresponders to MAD therapy alone.

Comparable health effects of MAD and CPAP therapy have been attributed to greater compliance with MAD therapy as compared with CPAP. This study sought to directly compare objective compliance with randomly assigned MAD and CPAP therapy in patients with moderate OSA.[351] Compliance was monitored in 59 participants with AHI=15-30 events/h as part of a 12-month randomized controlled trial. Objective MAD usage was recorded by using the Theramon microsensor (Theramon). Objective adherence with CPAP was monitored by using the built-in registration software program with SD card readout. Self-reported adherence with both therapies was recorded by using a questionnaire.

Forty participants (68%) completed the study with the therapy to which they were randomly assigned. Median (interquartile range) objective adherence (hours/night) in the third month was 7.4 (range 5.2-8.2) for MAD and 6.8 (range 5.7-7.6) for CPAP ($P=.41$). In the 12th month, median objective adherence (hours/night) was 6.9 (range 3.5-7.9) with MAD and 6.8 (range 5.2-7.6) with CPAP ($P=.85$). No significant changes in adherence were identified between the third and twelfth months for either MAD ($P=.21$) or CPAP ($P=.46$). Changes in adherence between MAD and CPAP were not significantly different ($P=.51$). Self-reported adherence was significantly higher with MAD than with CPAP at all follow-ups. Self-reported adherence with CPAP was less than objective CPAP adherence in the sixth and twelfth months ($P=.02$).

The authors concluded that objective adherence with MAD and CPAP is comparable and consistent over time. Self-reported adherence is greater with MAD than with CPAP, leading to an interesting discrepancy between objective recorded and self-reported CPAP compliance.

A multicenter randomized controlled trial compared the clinical and cost-effectiveness of MAD therapy with CPAP therapy in moderate OSA.[352] Participants with an AHI=15-30 events/h were randomized to either MAD or CPAP therapy. Incremental cost-effectiveness and cost-utility ratios (ICER/ICUR, in terms of AHI reduction and quality-adjusted life-years or QALYs, based on EuroQol Five-Dimension Quality of Life questionnaire) were calculated after 12 months, all from a societal perspective. For the 85 randomized patients (CPAP n=42; MAD n=43), AHI reduction was significantly greater with CPAP (median AHI reduction=18.3, range 14.8-22.6 events/h) than with MAD therapy (median AHI reduction=13.5, range 8.5-18.4 events/h) after 12 months. Societal costs after 1 year were higher for MAD than for CPAP (mean difference €2.156). MAD was less cost-effective than CPAP after 12 months (ICER €305, range €3.003 to €1.572 per AHI point improvement). However, in terms of QALY, MAD performed better than CPAP after 1 year (€33.701, range €191.106 to €562.271 per QALY gained).

The authors concluded that CPAP was more clinically effective (in terms of AHI decrease) and cost-effective than MAD. However, QALY was better with MAD than with CPAP. The authors also noted that CPAP is the first choice of therapy in moderate OSA, and MAD may be a good alternative.

Pathophysiology and medical implications

A systematic review was performed to explore the different aspects of primary snoring.[353] Also known as simple or nonapneic snoring, primary snoring is regarded as the first stage of sleep disordered breathing (SDB) without severe medical consequences for the snorer and bed partner. Despite it being a highly prevalent phenomenon in the general population, knowledge is limited because of a lack of consensus on terminology. A review of the definitions of simple or primary snoring was conducted to acquire an inventory of current practices and compare these definitions with the conceptual definition from the American Academy of Sleep Medicine (AASM).

PubMed and Web of Science were searched from July 2016 onwards without any language limitations, and 362 references were obtained. After selection based on titles, 39 remained, among which 29 contained a definition or reference to a definition. In 69% of the studies, a cutoff <5 apnea-hypopnea events/h of sleep on the AHI was used. Despite this tendency, the cutoffs ranged from 0 to <15 events/h Unfortunately, the cutoff and occasional requirements did not match the conceptual definition from the AASM. The authors stated that a consensus must be reached on an operational and clinically relevant definition based on the clear conceptual definition.

Others examined how the severity of apneas, hypopneas, and related desaturations is associated with OSA-related daytime sleepiness.[354] Multiple Sleep Latency Tests (MSLT) and PSG recordings from 362 patients with OSA were retrospectively analyzed, and novel diagnostic criteria (obstruction severity and desaturation severity), incorporating severity of apneas, hypopneas, and desaturations, were computed. Conventional statistical analysis and multivariate analyses were used to investigate the connection among AHI, oxygen desaturation index (ODI), conventional hypoxemia parameters, and novel diagnostic parameters with mean daytime sleep latency (MSL).

In the whole population, 10% increase in values of desaturation severity (RR=2.01; *P*<.001), obstruction severity (RR=2.18; *P*<.001), and time below 90% saturation or $t_{90\%}$ (RR=2.05; *P*<.001) induced significantly higher risk of having MSL ≤5 minutes than 10% increase in AHI (RR=1.63; *P*<.05). In severe OSA, desaturation severity had significantly (*P*<.02) stronger negative correlation (ρ=-0.489; *P*<.001) with MSL than AHI (ρ=-0.402; *P*<.001) and ODI (ρ=-0.393; *P*<.001).

Based on general regression modeling, desaturation severity and male sex were the most significant factors predicting daytime sleep latency. The authors concluded that severity of sleep-related breathing cessations and desaturations is a stronger contributor to daytime sleepiness than AHI or ODI and therefore should be included in the diagnosis and severity assessment for OSA.

A longitudinal analysis of a prospective community-based cohort was performed to evaluate the natural history of childhood OSA and factors associated with spontaneous remission and persistence and incident OSA from childhood to late adolescence/early adulthood.[355] Understanding the natural history of childhood OSA may help to determine disease prognosis and guide risk stratification and management strategies.

Participants from a cohort established for an OSA prevalence study were invited to participate in a 10-year follow-up study. Two hundred forty-three individuals (59% male) took part, and their mean age was 9.8 ±1.8 years at baseline and 20.2 ±1.9 years at follow-up. The mean follow-up duration was 10.4 ±1.1 years. Associations between baseline and follow-up log-transformed OSA index (OAHI) differed by age. A significant positive association was observed only among participants aged ≥10 years at baseline. Overall PSG remission rate (with OAHI <1 event/h at follow-up) of childhood OSA was 30%, and 69% had an OAHI <5 events/h at follow-up. Complete remission of OSA was associated with female sex. Incidence of adolescent/adult OSA with an OAHI ≥5 events/h at follow-up was 22%. Male sex and higher BMI z-score were associated with incident OSA.

The authors concluded that a proportion of children with OSA, particularly girls, had complete resolution during transition to late adolescence or early adulthood. Childhood and adolescent OSA are distinct entities, with the latter more likely to persist into adulthood. Obesity and male sex are consistent key risk factors for incident OSA.

A cross-sectional study examined the prevalence of sleep problems such as OSA, insomnia, and daytime sleepiness in commercial motor vehicle (CMV) drivers compared with the general population.[356] Sleep habits and problems were compared in 110 truck drivers with 1001 matched controls from the general population. The assessment was based on self-administered questionnaires including the Berlin questionnaire, the insomnia severity index, and the Epworth sleepiness scale (ESS). A multivariate regression analysis was performed with determine whether CMV operators were independently associated with these sleep problems compared with controls.

Prevalence of a high risk of OSA and insomnia was 35.5% and 15.2%, respectively, in CMV drivers, which was significantly higher than that in the controls (12.2% and 4.1%, respectively; *P*<.001 for both). Although CMV operators demonstrated higher ESS scores than controls, the prevalence of daytime sleepiness did not differ between the 2 groups (19.1% and 16.8%; *P*=.54). After adjusting for covariates, CMV drivers had 3.68 times greater odds (95% CI: 2.29-5.84) of OSA and 2.97 times greater odds (95% CI: 1.46-6.06) of insomnia than controls. However, the degree of daytime sleepiness was not significantly associated with the CMV operators.

The authors concluded that the prevalence of OSA and insomnia in CMV drivers was greater than that in the general population. Daytime sleepiness was associated with increased BMI, depression, OSA, and short sleep duration, regardless of CMV driving as an occupational factor.

Symptom subtypes have been described in clinical and population samples of OSA patients. However, it is unclear whether these subtypes have different cardiovascular (CV) consequences. This report set out to characterize OSA symptom subtypes and assess their association with prevalent and incident cardiovascular disease (CVD) in the Sleep Heart Health Study.[357]

Data from 1207 individuals with OSA (AHI ≥15 events/h) were used to examine the existence of symptom subtypes by using latent class analysis. Associations between subtypes and prevalence of overall CVD and its components (coronary heart disease, heart failure, and stroke) were assessed by using logistic regression. Kaplan-Meier survival analysis and Cox proportional hazards models were used to evaluate whether subtypes were associated with incident events, including CV mortality.

Similar to previous studies, 4 symptom subtypes were identified, including disturbed sleep (12.2%), minimally symptomatic (32.6%), excessively sleepy (16.7%), and moderately sleepy (38.5%). Although no significant associations with prevalent CVD were found, in adjusted models, the excessively sleepy subtype was associated with more than 3-fold increased risk of prevalent heart failure compared with each of the other subtypes. Symptom subtype was also associated with incident CVD (*P*<.001), coronary heart disease (*P*=.015), and heart failure (*P*=.018). The excessively sleepy subtype exhibited increased risk (hazard ratios 1.7-2.4) compared with other subtypes. When compared with participants without OSA (AHI<5), a significantly elevated risk for

prevalent and incident cardiovascular events was observed mostly for those in the excessively sleepy subtype.

A critical review of the pathophysiological mechanisms and epidemiological links between OSA and cutaneous melanoma or cancer, as well as future challenges that should be examined to better understand the relationship and its validity, was conducted.[358] Melanoma is the most aggressive of all skin cancers and carries a high mortality rate. Malignant transformation of melanocytes underlies the occurrence of this malignancy, which accounts for nearly 5% of all skin cancers, but it represents a large proportion of cutaneous cancer-associated deaths. Known risk factors for cutaneous melanoma include increased lifetime ultraviolet light exposure, family history of melanoma, degree of skin pigmentation, and hair color. The identification of new risk factors for development of melanoma or factors related to melanoma aggressiveness is crucial to the development of new treatment options.

Over the past several years, a potential association between cancer and OSA has been advanced and has gained substantial interest in the sleep community. Several biologically plausible pathways support this connection. However, a crucial limitation in the scientific literature is that the large majority of relevant studies were not originally designed to address this association, exploring all cancers as the outcome variable, rather than focusing on specific cancer types or sites. It is reasonable to assume that not all tumor cells originating from different organs and tissues will respond equally to the intermittent hypoxia, sleep fragmentation, and immune dysregulation that characterize OSA, which could account for the conflicting and contradictory results reported by the published studies to date. The authors note that among the scarce studies that have specifically examined links between specific cancer sites and OSA, melanoma has received a majority of the attention, therefore serves as the focus of their critical review.

A prospective cohort study sought to examine the associations of individual insomnia symptoms with risks of incident cardiocerebral vascular diseases (CCVD) and possible moderating factors among Chinese adults.[359] The China Kadoorie Biobank prospectively recruited participants from 10 areas across China. Data from 487 200 adults, 30-79 years of age, who were free of stroke, coronary heart disease, and cancer at baseline, were examined. Three insomnia symptoms were assessed at baseline, including self-reported difficulties in initiating or maintaining sleep (DIMS), early morning awakening (EMA), and daytime dysfunction (DDF) for ≥3 days/wk. Incidences of CCVD were followed up through disease registries and national health insurance databases until 2016.

During a median 9.6 years of follow-up, 130 032 individuals with CCVD were documented. Cox regression analysis demonstrated that the 3 insomnia symptoms (DIMS, EMA, and DDF) were associated with increased risk of total CCVD incidence, with respective adjusted hazard ratios (HRs) of 1.09 (95% CI: 1.07-1.11), 1.07 (95% CI: 1.05-1.09), and 1.13 (95% CI: 1.09-1.18). Individuals with individual symptoms also had increased risks of ischemic heart disease (IHD; HR, 1.13, 1.09, and 1.17) and ischemic stroke, but not hemorrhagic stroke. Individuals with all 3 symptoms were at an elevated risk of 18% for CCVD, 22% for IHD, and 10% for ischemic stroke, compared with nonsymptomatic adults. Associations among the 3 symptoms and CCVD incidence were consistently more robust in younger adults and those without baseline hypertension ($P<.05$ for interaction).

The authors concluded that individual and coexisting insomnia symptoms (DIMS, EMA, and DDF) are independent risk factors for the incidence of CCVD, especially in young adults or adults who have not developed hypertension. It is noteworthy that OSA is not mentioned as a factor or comorbidity in the study, especially in light of the recent research claiming that up to 80% of insomnia is comorbid with OSA.[360]

The next investigation aimed to retrospectively determine to what extent differences in hypopnea scoring influenced loop gain (LG) measurement.[361] Unstable ventilatory control (high loop gain) is a causal factor in the development of OSA. Methods for quantifying LG by using PSG have been developed and predict favorable outcomes to UA surgery. However, this method depends on respiratory event scoring and therefore may be affected by hypopnea scoring criteria.

Therefore, 46 PSGs performed before and after UA surgery were retrospectively examined. PSGs were rescored according to 3 different AASM hypopnea definitions: (a) the 2007_{alt} criteria that required ≥50% flow reduction with ≥3% oxygen desaturation or arousal; (b) the 2012_{rec} criteria that required ≥30% flow reduction with ≥3% oxygen desaturation or arousal; and (c) the 2012_{acc} criteria that required ≥30% flow reduction with ≥4% oxygen desaturation. Loop gain and AHIs were compared among definitions by using linear regression and Bland-Altman limits of agreement (LOA). Responders to surgery were classified by a ≥50% reduction in AHI and $AHI_{post\text{-}op}$ <10 events/h. Responders were determined separately for each AASM criteria. Receiver Operating Characteristic (ROC) curve analysis predicting surgical outcomes was performed for each LG measurement derived from each criterion.

The results revealed near-perfect agreement between LGs derived by using the 2007_{alt} and 2012_{rec} criteria (R^2=0.99, bias=-0.003, LOA=-0.016 to 0.010). Greater variability was found for 2012_{acc} than for 2007_{alt} (R^2=0.70, bias=-0.015, LOA=-0.099 to 0.070) and 2012_{rec} (R^2=0.69, bias= +0.018, LOA= -0.068 to 0.104) criteria. Both 2007_{alt}

and 2012_{rec} LGs significantly predicted surgical response with similar area-under-the-curve or AUC (2007_{alt} AUC=0.86, 95% CI: 0.75-0.97; 2012_{rec} AUC=0.84, 95% CI: 0.71-0.97). 2012_{acc} LGs were a poor predictor of surgical response (AUC=0.62, 95% CI: 0.43-0.80).

The authors concluded that LG measured non-invasively from PSG can be influenced by respiratory event scoring. The authors recommend caution when using the 2012_{acc} criteria with this method, as findings may not be generally applicable to other LG values derived from other scoring criteria.

Sleep bruxism

A cross-sectional study examined the prevalence of probable sleep bruxism (SB) in the primary and mixed dentitions, using noninstrumental approach, to evaluate whether sleep quality is associated with probable SB in different age ranges.[362] This school-based cross-sectional study involved children aged 2-5 years (primary dentition, n=372) and 8-10 years (mixed dentition, n=563) enrolled in public schools. The children's parents were involved as well. Sleep characteristics, socioeconomic status, and presence of probable SB were assessed with questionnaires. Seven trained examiners (Kappa>0.7) evaluated tooth wear. Children were selected following a stratified sample (for ages 2-5 years) and a system of proportionality, including schools and classrooms (for ages 8-10 years). Unadjusted and adjusted Poisson regression analyses were performed with probable SB as a dependent variable. Independent variables included family income, parent schooling, drooling, tooth wear, and sleep quality. Independent variables presenting $P \leq .20$ were included in the adjusted model.

The prevalence of probable SB was 22.3% in primary and 32.7% in mixed dentition. Probable SB was significantly associated with poor sleep quality ($P<.001$) in mixed dentition (prevalence ratio=1.80, 95% CI: 1.34-2.44) adjusting for age and drooling. In the primary dentition, the adjusted regression did not demonstrate association between analyzed characteristic and probable SB. Sex, socioeconomic status, head of household economic status, drooling, and tooth wear were not associated with probable SB in either dentition. The authors concluded that prevalence of probable SB is higher in mixed than in primary dentition and poor sleep quality is associated with probable SB in children aged 8-10 years.

ORAL MEDICINE AND ORAL AND MAXILLOFACIAL SURGERY

Dentoalveolar surgical procedures have become an integral part in the curriculum of all dental specialties.[363] While this favorable development increases each dentist's therapeutic options and improves patient care, it requires not only practical skill but also advanced scientific knowledge in preoperative risk assessment, perioperative and postoperative complications management, and postoperative care. Publications addressing the prevention and management of oral surgery–associated sequelae are accumulating.[364-366] The cause of surgical failure must not only be sought in the surgical procedure and associated challenges but also in wound healing processes impeded by systemic or pharmacotherapeutic conditions. The aim of the 2019 scientific literature review in oral medicine and oral and maxillofacial surgery is to report the latest scientific information addressing the physiology and pharmacology of drugs interfering with wound-healing processes and to provide relevant information that will facilitate preoperative risk assessment algorithms for surgically active dentists.

It is common knowledge that wound healing is a multistep procedure that begins with hemostasis and blood clot formation and ends with scar formation or resolution.[367] To ensure smooth transition from tissue damage to complete healing, intermediate granulation tissue must be established which is then penetrated by blood vessels and infiltrated with immunologically active cells.[367-369] Tissue debris and microbiologic remnants are then removed by immunologic activity; the proliferation and maturation of connective tissue is ignited leading to the final step of this process, remodeling.[367,369]

While successful stepwise completion healing can be achieved within days in soft tissues, hard-tissue wound healing involves the significantly more time-consuming restoration of bone defects.[368,370] This requires the invasion of osteoclasts and osteoblasts, arrangement of functionally active bone-forming units, and defect reconstruction via callus to woven bone to lamellar bone.[367,370] All of these hard-tissue healing stages are regulated by the timely excretion and targeted effects of growth factors. Each of these steps may be impeded by the mechanism of action of certain drugs, which may result in wound-healing disturbances and surgical failure.

A prerequisite for wound healing is hemostasis and the formation of the fibrin and blood clot.[5] Both antiplatelet drugs and anticoagulants affect hemostasis, reducing either thrombocyte aggregation (Common antiplatelet drugs include acetylsalicylic acid or aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, dipyridamole.)[371] or fibrin clot establishment (Common anticoagulants include warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban.)[371,372] and may lead to intraoperative and postoperative hemorrhage and hematoma. Extensive postoperative swelling and bacterial invasion may be promoted by these developments which can result in wound dehiscence, infection, and surgical failure. An overview of pharmacologic details of antithrombotic

Table 1. Tabulation of commonly prescribed antithrombotic drugs with information about pharmacokinetics, pharmacodynamics, and perioperative conduct (list not complete and subject to change)[377,378]

Drug	Mechanism of Action	Half Life	Peri-operative Conduct
Aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine	Irreversible inhibition of platelet aggregation	>1 wk	Do not discontinue treatment unless indicated by prescribing physician, never discontinue treatment with aspirin
Rivaroxaban, edoxaban, apixaban, betrixaban	Reversible inhibition of factor Xa	7-14 h (betrixaban 19-27 h)	Discontinue according to guidelines peri-operatively after bleeding risk assessment
Warfarin/phenprocoumon	Reduction of coagulation factors II, VII, IX, X	Warfarin 40 h, phenprocoumon 160 h	Discontinue according to guidelines peri-operatively after bleeding risk assessment

drugs and recommended perioperative conduct is found in Table 1.

A large group of drugs interferes with the immunologic response and the generation of granulation tissue required for uneventful wound healing. This group comprises antirheumatic drugs, immunosuppressants, and antineoplastic drugs. The most commonly used antirheumatic drugs are disease-modifying antirheumatic drugs (DMARDs).[373] The following drugs are regarded as DMARDs: methotrexate (MTX), sulfasalazine, hydroxychloroquine, doxycycline, and leflunomide.[373] The administration of these drugs can be continued when performing limited outpatient surgical procedures (such as dental surgery; MTX max. dose <30 mg/wk). Conflicting evidence is reported for leflunomide (Arava; Sanofi).[373,374] In general, it appears to be safer to stop leflunomide administration after consultation with the prescribing physician peri-operatively.[374,375]

Biological agents have become popular in the treatment of rheumatic disorders. These drugs target tumor necrosis factor, interleukins, or white blood cells directly and should be discontinued peri-operatively to prevent complications during wound healing (Table 2).[373,375] The same applies to the Janus-kinase inhibitors that have recently been approved for the therapy of rheumatoid arthritis and various chronic inflammatory illnesses. Common drugs from this group include tofacitinib (Xeljanz; Pfizer) and baricitinib (Olumiant; Eli Lilly and Co).[376]

Immunosuppressants are used in various medical fields, including rheumatology, oncology, nephrology, dermatology, pulmonology, endocrinology, ophthalmology, gastroenterology, allergy medicine, orthopedics, and surgery after organ transplantation. The most widely prescribed immunosuppressants are glucocorticoids. Glucocorticoids (GCs) are potent drugs with complex mechanisms of action, the common final path of which is inhibition of immunologic processes. GCs of variable potency exist. As long as the daily GC intake is below a determined threshold dose (which varies depending on the type of GC, patient age, and organ function), the occurrence of serious adverse events is unlikely.[377,378] In those patients, GC therapy can safely be continued peri-operatively.[378] However, long-term GC effects may negatively impact bone healing.[377] If the therapeutic GC doses exceed the physiologically safe levels, a peri-operative adaptation or reduction of the drug dose under the supervision of the prescribing physician should be accomplished.[378]

Table 2. Tabulation of biological DMARDs with information about pharmacokinetics, pharmacodynamics, and perioperative conduct (list subject to change due to future developments and further FDA approvals)[379,382]

Drug	Mechanism of Action	Peri-operative Conduct
Adalimumab (Humira) Etanercept (Enbrel) Golimumab (Simponi) Infliximab (Remicade) Certolizumab (Cinzia)	TNF-α-antagonism	Discontinue peri-operatively as advised by prescribing physician
Rituximab (Rituxican)	Lymphocyte surface antigen antibody	
Anakina (Kineret) Tocilizumab (Actemra) Ustekinumab (Stelara) Secukinumab (Cosentyx)	Interleukin antagonism	
Belimumab (Benlysta)	B-lymphocyte antagonism	
Abatacept (Orencia)	T-lymphocyte antagonism	

DMARDs, disease-modifying antirheumatic drugs; FDA, Federal Drug Administration.

All other immunosuppressant drugs (including ciclosporin A, mycophenolate-mofetil, tacrolimus, azathioprine) usually interfere with wound healing and organ function extensively.[373] It is generally recommended that patients under therapy with these drugs be treated surgically in specialized centers.[373]

Oncological patients under active treatment with antineoplastic drugs should not be subjected to elective dental surgical procedures.[379] However, if patients had undergone chemotherapeutic treatment in the past, no special adverse effects on soft-tissue wound healing should be expected. The "safe" time between the last application of an antineoplastic drug and elective dental surgery is 60 days[379]

While remarks to this point in the review mainly relate to drugs that have potential to negatively affect soft-tissue healing, the following discussion will address new insights into pharmacons, the short- or long-term use of which reduces bone turnover, inhibits bone healing, or induces osteoporosis. The associations

between reduced bone turnover, consecutive dental implant failures, and wide use of the antidepressant drug group selective serotonin reuptake inhibitors (SSRIs) has attracted much research attention in the past year.[210] The intended mechanism of action of SSRIs is to increase the serotonin (5HT) concentrations in synaptic clefts of the central nervous system. However, because of the systemic effects of the drugs, 5HT levels are enhanced in the entire body.[380] New research revealed that chronically elevated 5HT levels have catabolic effects on bone.[366,381] While immediate bone-healing processes do not seem to be influenced by SSRI intake, long-term dental implant survival might be reduced in patients who have been exposed to long-term SSRI therapy.[210,366,382]

In the last years, an increased incidence of certain fracture types, osteoporosis, and a reduction of bone mineral density, has been observed in patients who had been exposed to proton pump inhibitors or PPIs (such as, omeprazole, pantoprazole) over an extended period of time.[383] These findings have ignited research interest in the associations between PPI use and dental implant survival.[366,382,384-386] Critical assessment of the data led to the assumption that the risk of implant failure is increased in long-term PPI users.[366,382] Immediate soft- or hard-tissue wound healing do not seem to be influenced by the intake of this drug.[366]

NSAIDs are another group of commonly prescribed drugs, the permanent use of which has recently been implicated in bone metabolism.[387] Prostaglandins, the production of which are inhibited by NSAIDs, seem to exert pleiotropic effects on osteoblasts and osteoclasts, which may lead to reduced bone turnover rates as observed in in vitro and animal studies.[388,389] Current evidence regarding real effects of NSAIDs on bone healing and dental implant osseointegration in humans has yet to be fully elucidated.[389] It appears that immediate postoperative analgesic short-term NSAID therapy does not have detrimental effects on bone healing.[389] In the context of bone healing, it is interesting to note that despite the undeniable positive effects of vitamin D on bone healing and the prevention of osteoporosis, the influence of vitamin D supplementation on the success rates of dental implant osseointegration remains unknown.[370,385,390]

The research published in 2018 and 2019 confirmed previous observations that oral surgical procedures (including dental implant surgery) for patients who receive low-dose treatment with antiresorptive agents (bisphosphonates and denosumab) for osteoporosis can be performed safely and with a manageable risk for development of osteonecrosis of the jaw (ONJ).[391,392] However, the general risk of ONJ occurrence is elevated in patient cohorts exposed to antiresorptive agents, notwithstanding the application dose.[392]

The latest research addressing potential benefits of peri-operative antibiotics in oral surgery procedures well worth the discussion. Many clinicians are of the opinion that prophylactic antibiotics facilitate wound healing and contribute to superior surgery and implant success rates. The controversial results of 2 high-quality systematic reviews published on this topic in 2019 evaluating the identical literature pool highlights the ongoing uncertainty about accurate and useful clinical recommendations in this matter.[222,393] While Romandini et al[222] indicated that perioperative antibiotics can reduce dental implant failure rates, Khouly et al[393] concluded the opposite. Further research will be necessary to clarify this issue for the profession.

A myriad of pharmacons are implicated in wound-healing processes. The neglect of their administration might put surgical success in affected patients at risk. In any case, the patient's history must be meticulously explored for optimal presurgical risk assessment.

DENTAL CARIES AND CARIOLOGY

Following the tendency of the previous decade, the year 2019 has been characterized by increased publication of articles on the subject of dental caries compared with the previous year. Although most of the research, particularly on the topic of genetics, is still aimed at full comprehension of the mechanisms of caries formation and development, which are not yet fully understood, we can definitely see a trend in the modern research on dental caries, which follows a trend of modern medicine in general, aiming at the development of highly selective antibacterial treatment modalities. The microbiome of a healthy human is extremely diverse and of crucial relevance, contributing enormously to immune regulation, digestion, and colonization resistance against potential pathogens (Human Microbiome Project, 2012).[394]

This information has produced a major paradigm shift from the idea of one single pathogen producing one specific single disease, that has characterized the twentieth century, to that of dysbiosis and polymicrobial diseases. Current theories on bacterial diseases are based on the concept that the alteration of the equilibrium (bacterial homeostasis) among the bacterial community is the ultimate reason for the increased virulence of a bacterial specie. Therefore, treatment should not be aimed toward an indiscriminate removal of all the bacteria but to the shift of the whole community toward a healthy status. Despite this, most therapeutics, currently in use to treat microbial diseases, have a wide spectrum of activity. The adverse outcomes of broad-spectrum antimicrobial treatments against many diseases are now clear because the administration of broad-spectrum antibiotics eradicates not only the pathogen of interest but also a consistent number of overall microbiota.[395] This becomes the perfect environment for the growth of antibiotic-resistant pathogens or recolonization with a less-than-

optimal, potentially even harmful, microbial community.[396] The microbial agents that are considered to be the primary contributors to caries pathogenesis normally have 3 peculiarities: extraordinary production of acids as a by-product of carbohydrate intake, high tolerance to acidic conditions, and the capability to form a biofilm on the tooth surface. Therefore, more specific targeting of pathogenic species by treatment modalities that leave the rest of the microbial community intact is a goal that has inspired a significant amount of research in recent years, by focusing on a specific action against the bacteria that produce acid from dietary sugars (*Streptococcus mutans* and *Lactobacilli*), by modifying the pH (arginine) and finally by interfering with the ability of the microbial community of forming a biofilm (interaction with EPS formation).

A minireview published by Baker and Edlund[397] synthetically and effectively discusses the above-mentioned concepts and also the current available treatment tools against dental caries. In the following paragraphs, we will follow, in part, the authors' outline to discuss the dental literature on this subject but focused only the year 2019.

Control measures: Diet

Caries is not a classic infectious disease because the pathogenic species associated with it are necessary, but not sufficient, to cause the disease. A continuous source of carbohydrates is also necessary for the carious process to proceed. Western diet with its high content in highly processed carbohydrates has led to widespread existence of obesity, type 2 diabetes, cardiovascular disease, and related metabolic disorders and cancers. As with caries, a substantial body of evidence connects these disorders to diet through microbial mediators.

Although not related to dental caries, an interesting review by Zmora et al[398] analyzes this concept in a modern and intelligent article as reflected in the title, "You are what you eat: Diet, health and the gut microbiota." Diffusing the culture of proper nutritional habits and the importance of the diet for overall general health, to maintain a proper equilibrium with the microbiota remains paramount. However, an extensive number of contradictory reports with conflicting results remain insurmountable obstacle to translating the diet-microbiome-host research into clinical use.

Let us consider as an example, L-carnitine present in red meat. According to some studies, its ingestion can increase the presence of *Bacteroides* in the human body, thus reducing the risk of cardiovascular disease. However, L-carnitine can also increase the presence of the *Prevotella* specie, that have been associated with an increased risk of cardiovascular disease. Nevertheless, if we focus only on studies that prove causation, or those involving humans rather than only animal models, some of these conflicts may be eliminated. Still, some nutrients and bacteria are indicated to be beneficial in some reports and detrimental in others. This may be due to confusion and lack of standardization in research or the result of an interindividual variation in response to the same stimulus. What is healthy for some individuals may be dangerous for others.

The authors conclude, "This emerging field bears the potential to revolutionize the perception of nutrition from uniform food-intrinsic guidelines to flexible person-specific and context-specific recommendations, which are designed to prevent or correct metabolic derangements and even ameliorate inflammatory and neoplastic processes." It is now clear how a proper diet (low in animal proteins and sugars) can lead to a longer life of the human cells and therefore of the human beings.[399,400] In addition, there is growing evidence that controlled fasting can improve healing of healthy tissues, apoptosis (elimination of unwanted cells), and the specificity and efficacy of some drugs (chemotherapies for cancer), as well as optimizing the healthy relationship with our commensal microbiota.[401,402]

Back to dentistry. Considering what diet can do to general health and knowing that without carbohydrates there is no caries, improving accessibility to healthy foods and stressing the importance of avoiding highly processed sugars should be a goal of every dentist. As dentists, we should remind our patients that no sugar equals no caries. The solution could actually be that simple! A return to a more primitive and unprocessed diet is likely to have significant health benefits by supporting microbial profiles with which we have a proper evolutionary relationship to fortify a mutualistic connection. This of course includes the microbial profiles on the tooth surface. For example, by simply giving advices on diet and feeding to caregivers with children up to the 1 year of age, there is moderate evidence that we may be able to reduce the risk of early childhood caries.[403]

Control measures: Fluoride

Fluoride treatments, including fluoridated toothpaste and drinking water, have been used to control dental caries since the late 1950s. Fluoride prevents and treats dental caries by stimulating favorable remineralization of enamel while interfering with bacterial metabolism.[404] Fluoride has proven to be effective for root caries, and high-fluoride toothpastes seem to be a more effective and feasible strategy for both prevention and remineralization in root dentin.[405,406]

Although efficacy of fluoride treatments is well-documented, the current prevalence of the disease illustrates that fluoride alone is insufficient to prevent dental caries in many situations.[407] A Cochrane review supports the benefits of using fluoride toothpaste in preventing caries when compared with nonfluoride

toothpaste.[408] However, the choice of fluoride toothpaste concentration for young children should be balanced against the risk of fluorosis. Especially during orthodontic treatment, to avoid an increased risk of caries, everyday use of high-fluoride toothpaste (5000 ppm fluoride) or mouth rinse (0.2% NaF) in combination with ordinary toothpaste is recommended.[409] Unfortunately, because of a limited number of clinical trials, a recent systematic review failed to identify the type of professional fluoride agent, the concentration of fluoride, and the frequency of applications for prevention or reversal of enamel white spot lesions in patients undergoing multibracketed fixed orthodontic treatment.[410]

The efficacy of fluoride varnish in preventing early childhood caries was tested in children at high risk of caries by using a randomized controlled trial with 504 participants (mean age 21 months at baseline) randomly allocated to a test and control group. The test group then received fluoride varnish applications every 3 months for a total of 24 months. Two years after beginning the trial, 427 children remained in the study. At 2 years, the percentage of caries-free participants in the 2 groups was 69.4% (test group) and 40% (control group). Researchers concluded that the application of fluoride varnish, 4 times a year, lessened the incidence and reduced the severity of caries in preschool children.[411]

Silver diamine fluoride

Although it is a relatively new product, fluoride combined with silver (silver diamine fluoride or SDF) has already been shown to be even more successful when dealing with the treatment of dental caries than fluoride alone.[412] SDF application does not influence the dentin bond strength of glass ionomer cement but does compromise the bonding of adhesive systems, especially in root caries.[413] When compared with other conservative treatments aimed at arresting caries lesion (such as atraumatic restorative treatment or ART) and considering patient anxiety, adverse effects, esthetic perception, and quality of life, SDF demonstrates similar clinical outcomes while requiring much less chair-time. Thus, it has become the treatment of choice.[280]

Seifo et al[414] reported on an umbrella review of several systematic reviews to summarize conclusions from a wide number of publications on SDF. The authors concluded that, while the number of clinical trials is somewhat lacking, there is a reliable and substantially strong body of research that supports the effectiveness of SDF in arresting coronal carious lesions in children in the primary dentition and arresting and preventing root carious lesions in older adults. More rigorous research is always welcomed. Additionally, too few studies and inadequate evidence exist to draw conclusions for the use of SDF on permanent teeth in children.

Another article published out of the University of North Carolina at Chapel Hill is a handy and practical study related to the treatment of children.[415] The authors proposed clear clinical guidelines for the using SDF in children. All practitioners that manage children are encouraged to review this article to gain insight into the proper handling of the material.

To summarize the procedure, the first step should be to isolate adjacent soft tissues with Vaseline to avoid staining and saliva contamination. Carious lesions (up to 5) should then be cleaned and dried with cotton pellets, gauzes, or dry microbrushes. Then, SDF is applied for 1-3 minutes with continuous scrubbing on the lesion for the duration of application. The SDF is then dried, and the excess removed with cotton pellets or gauze, but not by air spray to avoid dispersing the SDF onto soft tissues. For pediatric patients, fluoride varnish (5% NaF) is then applied over the entirety of SDF-treated teeth and all other teeth present.

In general, 2 SDF applications, 4-6 weeks apart, should be provided as part of an aggressive prevention plan that includes oral health education on optimal diet and hygiene. Finally, a check for caries arrest, by assessing hardness and dark stains, should be performed at the follow-up visits. The use of SDF for preventing dental caries has gained considerable attention because of recent regulatory clearance in the United States. Initially, publications on SDF focused on the arrest of caries lesions because of the material's capacity to noninvasively achieve this important clinical objective.

SDF has also demonstrated the capacity to act as a preventive agent in decreasing the incidence of new caries lesions. Horst and Heima[416] reported an analysis of 9 clinical trials in children and found that SDF prevented 61% of new lesions compared with controls. A meticulous systematic review concluded that the preventive effect of SDF seems to be both immediate and lasting.[417] Direct comparisons of SDF applied once per year with alternative treatments revealing SDF to be more successful than topical fluorides placed 2-4 times per year and more cost-effective than dental sealants. When comparing enamel with dentin lesions, enamel caries appears to be even more responsive to SDF than cavitated dentin lesions. In conclusion, annual application of SDF to high-risk surfaces in all individuals seems to be our most cost-effective approach to preventing dental caries. At the present, SDF is unfortunately an underutilized evidence-based preventive agent for dental caries.

The World Health Organization advocates that all countries need to embrace strategies for improving the oral health of elderly populations and recognizes that there is a universal need for the prevention of oral diseases such as root caries. This is due, in part, to demographic transitions and enhanced oral health behavior

that have resulted in increased tooth retention in elderly individuals. As a consequence, the risk of root caries is increasing secondary to the age-associated gingival recession and exposure of cervical root dentin.[407] Root caries is challenging to repair because of its complex etiology and dentin structure. Recovery of dentin quality depends not only on remineralization but also on intact dentinal organic matrix and the organic-inorganic interfacial structure, which contribute to the unique biomechanics of dentin.

Although in vitro in design, Cai et al[418] reported on the effect of a crosslinking agent, proanthocyanidin (PA), used in conjunction with SDF and potassium iodide (SDF/KI) to stabilize the organic dentinal framework and to strengthen collagen-mineral phase interactions in root caries. The success of this strategy was evaluated 24 hours after application for distribution of ion uptake and microstructure of dentin, as well as analysis of the nanomechanical properties. The results indicated that, compared with the controls treated with deionized distilled water, the use of SDF/KI significantly improved surface microhardness and integrated mineral density up to 60-μm depth. The combined treatment of PA and SDF/KI attained a more homogenous mineral distribution throughout the lesions than SDF/KI alone. Specifically, PA+SDF/KI resulted in significant improvement in microhardness, elastic modulus, and recovery of creep behavior in the demineralized dentin.

Finally, an interesting article by Miller[419] poses an almost philosophical question. Open margins and marginal caries associated with indirect restorations are the bane of every restorative dentist's existence. Assessing marginal integrity is a subjective task with limited interoperator agreement. Immediate replacement of restorations with defective margins is suggested to be the standard of care. However, repair and monitoring of these margins is a viable option that has more recently become available.

SDF provides a new option in the management of defective restorative margins because it is inexpensive, easy to apply, kills pathogens, and hardens softened dentin making it more acid and abrasion resistant. Additionally, SDF does not stain sound dentin, enamel, or porcelain but does stain carious lesions black. It remains a clinical judgment whether to pursue restoration replacement or margin repair and reseal. The latter approach has been made practical and possible by SDF and is particularly useful for patients with medical or financial constraints that cannot undergo the replacement of restorations with defective margins.

Preventive approaches: Prebiotics

Prebiotics are food or supplements administered to modulate the microbiome for the benefit of the host.[420] Arginine has demonstrated success as a prebiotic used to prevent dental caries.[421] Arginine can be metabolized by commensal arginolytic species (*Streptococcus sanguinis* and *Streptococcus gordonii*) to produce ammonia, an alkaline molecule that buffers the organic acids in dental plaque. These reactions are achieved through an arginine deiminase system (ADS).[422] Furthermore, arginine has been shown to reduce the growth, pathogenic potential, and stress response mechanisms of *S. mutans*, thus inhibiting caries formation through multiple mechanisms.[423] Dentifrices containing both fluoride and arginine, although likely more effective in preventing caries, have not become widely available because of higher production costs[424] and due controversy surrounding the protective effects of arginine based on the reliability of several associated clinical trials.[425] As laboratory evidence for the protective effects of arginine continues to accumulate, more rigorous clinical trials may lead to widespread availability of arginine-containing commercial therapeutics.

Recent studies have identified several other compounds such as N-acetylglucosamine (GlcNAc) and glucosamine (GlcN) as prebiotic candidates for caries prevention. These amino sugars are able to improve the competitiveness of *S. gordonii* against *S. mutans*. In a study by Chen et al,[426] the mechanism of interaction of these amino sugars was studied by using a dual-species biofilm model. Compared with glucose, growth on GlcN or GlcNAc significantly reduced the quantity of *S. mutans* in cocultures with most commensals, changing the relative percentages of species. One reasons for this result was the increased production of hydrogen peroxide in most commensals when growing on amino sugars and the consequent inhibition of *S. mutans*, which is known to be sensitive to H_2O_2. All commensals, with the exception of *Streptococcus oralis*, had higher arginine deiminase activities when grown on GlcN, and in some cases, GlcNAc. In ex vivo biofilms derived from human saliva, the proportions of *S. mutans* were drastically diminished when GlcNAc was the primary carbohydrate. Increased production of H_2O_2 could account in large part for inhibitory effects on biofilms. Therefore, dental caries is determined by dysbiosis of oral biofilms in which dominance by acid-producing and acid-tolerant bacteria produces loss of tooth structure. Amino sugars GlcNAc and GlcN promote the antagonistic activity of health-associated oral bacteria, *Streptococcus gordonii in primis*, which compete with *S. mutans*.

An interesting cohort study investigated the relationship between ADS activity (that can potentially reduce the cariogenicity of oral biofilms by neutralizing glycolytic acids that cause tooth demineralization) and bacterial profile changes of supragingival biofilms among children with caries.[427] Seventy-nine children aged 2-7 years at baseline were followed up every 6 months for a period of 18 months. Children were divided in 3 groups:

caries free (CF), caries active with enamel lesions (CAE), and caries active with dentin lesions (CAD). Supragingival plaque samples were collected, and ADS activity was measured by monitoring citrulline production from arginine and compared with ribosomal 16S rRNA-derived taxonomic profiles for the same samples. During the observation period, ADS activity was significantly higher in the CF group than in the CAD group ($P<.001$), and ADS activity in plaque from CF samples was significantly higher than plaque in CAE and CAD samples ($P<.001$). Statistical analysis indicated that the bacterial communities could be differentiated when plaque samples are grouped into levels of high and low ADS activity.

The authors concluded that there is a positive correlation between caries activity and low arginolytic capacity of the oral biofilms. As a direct consequence, measurements of arginine metabolism, through ADS, could be a useful tool to discriminate the caries risk of different individuals and tooth surfaces. New strategies for caries risk assessment and prevention could be developed starting from these findings.

Exploiting oral immunology

Over the past 40 years, many attempts have been made to develop a vaccine against dental caries. Focus has been on different virulence determinants of *S. mutans*, such as Ag I/II, known to stimulate antigen-specific immune response related to adherence on surfaces, glucosyltransferase, production of glucan and glucan-binding protein, and attachment of glucan to surfaces. The levels of salivary IgA against immunogenic *S. mutans* epitopes have been shown to be inversely related to colonization of *S. mutans* and caries prevalence. An excellent review by Patel[428] discusses where research on a caries-vaccine currently stands. Recent studies have explored vaccination by using a fusion anticaries DNA vaccine (PAcA-ctxB) developed by fusing a cell surface protein PAc (PAcA) coding gene of *S. mutans* with cholera toxin B subunit coding gene (CTB).[429] The plasmids were then integrated into tomato genomes through agrobacterium-mediated plant transformation technology. The results generally indicated that transgenic tomatoes may offer a valuable system for the creation of human caries antigens.

Most protein antigens elicit low immune responses without the support of a potent mucosal vaccine adjuvant. Therefore, new mucosal adjuvants have been investigated to enhance specific IgA response in oral fluids to better protect against caries. For example, flagellin as the ligand of toll-r-like receptor 5 (TLR5) has been demonstrated to be a successful mucosal adjuvant and could stimulate evident systemic and mucosal immune responses. Liu et al[430] investigated whether the recombinant FimH-S.T protein could modulate immune response to anticaries vaccine in vitro and in vivo by using recombinant FimH protein derived from Salmonella as FimH is a great candidate as a mucosal adjuvant and has been used to stimulate immune responses and immune-protection of the novel FimH-CS-pVP1 oral vaccine against coxsackievirus B3 (CVB3)-induced myocarditis. The study, carried out on mice, confirmed that PAc+FimH-S.T decreased the caries lesions formation, which provided high protective efficacy against dental caries. The mice immunized with the mixture of FimH-S.T and PAc significantly enhanced the PAc-specific antibodies in the serum. Therefore, it could be concluded that recombinant FimH-S.T might enhance specific IgA responses and protection of anticaries vaccine, possessing mucosal adjuvant ability.

The same research group in a different report investigated the effect of 2 additional adjuvants, a combination of chitosan plus Pam3CSK4 and of chitosan plus monophosphoryl lipid A.[431] A significantly higher PAc-specific antibody concentration was found in serum, and saliva. *S. mutans* colonization onto the tooth surfaces was inhibited. The overall caries protection was definitely more efficacious when the 2 adjuvants where used than when using PAc alone. The authors concluded that chitosan-Pam3CSK4 and chitosan-MPL combinations are promising for anticaries vaccine development.

Unfortunately, regardless of the interesting and even promising research results being made available, past, present, and likely future, attempts to bring anticaries vaccine research into clinical trials face significant regulatory and investment obstacles because dental caries is a non–life-threatening disease. The outcome is that no licensed vaccines to prevent dental caries currently exist.

Salivary flow and saliva constituents significantly impact which taxa are able to endure in the oral environment and which are cleared. It is well known that a diminished salivary flow increases the prevalence of caries. Therefore, treatments that are able to increase the salivary flow are expected to help in buffering acids, supply antimicrobial peptides and antibodies, and prevent dysbiosis and caries from occurring. Chewing gums containing polyols (xylitol or erythrol) and also possess antimicrobial properties provide a salivary stimulus without fermentable carbohydrates. A systematic review, that included 12 acceptable studies, concluded that sugar-free gums reduced caries incidence by 28%. However, the authors pointed out that there is a considerable degree of variability in the effect between published reports, and the trials included were generally of moderate quality.[432]

Recently, an interesting report was published demonstrating a positive correlation between β-glucosidase activity in human saliva and the presence of oral biofilm.[433] It appears that β-glucosidase activity is vital for the formation of biofilm in the oral cavity. The same

report showed that xylitol inhibits β-glucosidase activity in human saliva. As this enzyme is important in the process of biofilm formation, the authors suggested that the reported inhibition of β-glucosidase activity by xylitol is one possible mode of action of xylitol for biofilm control.

PROBIOTICS

Probiotics participate in the prevention of dental caries through 2 mechanisms. First, they contribute to the health-associated taxa in reinforcing the capacity of the microbiome to oppose dysbiosis. Second, they replace cariogenic strains with modified mutants that are competitive but less pathogenic. Many studies have investigated the use of *Lactobacillus* and *Bifidobacterium*, the most common microorganisms used for probiotic activity in the digestive tract, in the prevention of dental caries.[434,435] Despite some promising reports, there is a general growing skepticism regarding the use of these bacteria as anticaries probiotics. Both *Lactobacillus* and *Bifidobacterium* are acidogenic and aciduric and capable of contributing to caries formation under the proper conditions. A concern supported by several studies.[436,437]

The best microorganism capable of competing effectively with *S. mutans* are found in the healthy oral cavity. Research has demonstrated that the best probiotics for preventing the growth of a specific pathogen reside in the same ecological niche as the pathogen and synthetize compounds that directly antagonize the pathogen. *Streptococcus dentisani* and *Streptococcus* A12 are 2 recently described species that show particular promise as potential probiotics.[438,439] Both genera colonize the tooth surface, are able to increase the pH of dental plaque through the arginolytic pathway, and prevent growth of *S. mutans*. Lee et al[438] described *Streptococcus.* A12 and the mechanism by which it competes with *S. mutans.* By using various bioinformatic tools, a distinct set of genes, that encode factors that could increase the ability of A12 to compete with *S. mutans*, were identified and labeled as pcf genes. This study focused on all mechanisms by which this competition occurs.

The results indicated that A12 is able to disrupt the quorum-sensing mechanism (the intercellular pathways) by which *S. mutans* communicate with each other to form a biofilm. Additionally, A12 is capable of detecting and resisting antimicrobial peptides present in the oral environment, similar to the antibiotic nisin. Furthermore, A12 harbors a gene that can produce a peptide that is part of an antimicrobial compound. The authors' working hypothesis was that this peptide may serve as a precursor to produce a mature antimicrobial peptide that may inhibit growth or metabolism of *S. mutans* and possibly other organisms in the oral microbiome.

A critical prerequisite for probiotic activity is the ability to colonize the human tissue on which the microorganism is expected to perform favorable action. Probiotic colonization has been demonstrated to be very limited, probably because of the exogenous nature of the microbe which must adapt on tissues with a resident microbiota and under the host-specific chemico-physical and immunological pressure. This general problem is increased in the oral cavity because most probiotics used to promote oral health are not oral bacteria but have either been isolated from dairy products or from the human or animal gut. In a clinical pilot trial, Ferrer et al[439] evaluated the colonization efficiency of *S. dentisani* under different dosing schedules and pretreatment conditions. *S. dentisani* was selected because of its ability to antagonize *S. mutans*. Additionally, it is a common constituent of the human oral bacterial flora, and therefore, it does not need to adapt to the oral environment. Promising results emerging from this human trial indicate that *S. dentisani* is able to colonize the oral cavity and that it buffers the oral pH, especially after multidosing. Similar results were reported in another research publication that investigated *S. dentisani 7746* (AB-Dentisanium).[440]

Attempts have been made to enhance the effects of probiotics with prebiotics. Nunpan et al[441] found that the growth rate of *S. mutans* was significantly retarded when cocultured with *Lactobacillus acidophilus* (a probiotic) and the proper concentration of galactooligosaccharides and fructooligosaccharides (prebiotics). These prebiotics have the potential for clinical application to activate natural intraoral *L. acidophilus* to inhibit *S. mutans*. Although the use of acid-producing bacteria to produce an anticaries effect has been seriously questioned, the idea of combining prebiotics and probiotics could be a new and interesting trend for future research.

Another major probiotic strategy used in caries prevention is replacement of the native strain of *S. mutans* with *S. mutans* strains engineered for low pathogenicity. Castillo Pedraza et al[442] used a rodent model to investigate a parental strain of *S. mutans* UA159 and derivative strains carrying single gene deletions to alter the formation of exopolysaccharides. Fewer carious lesions were observed on both smooth surfaces and dental fossae of the enamel and dentin of rats infected with the modified strain versus the parental strain. These findings indicate that inactivation of specific genes can alter *S. mutans* cariogenicity and virulence in vivo.

Tang et al[443] showed that *S. mutans* cas3 deletion strain formed less biofilm and became less competitive when cocultured with *S. sanguinis* under fluoride treatment. In addition, expression levels of virulence genes were significantly downregulated.

Antimicrobial peptides or STAMPs

Specifically targeted antimicrobial peptides (STAMPs) were developed as a very selective antibiotic therapy. They are synthetic peptides containing a targeting

domain to specifically bind to a single microorganism and a killing domain that exerts antimicrobial activity against the targeted species. Several interesting articles[444-447] have been published in 2019 on STAMPs and other antimicrobial peptides, some of which also possess remineralizing potential.[448] The most important publication of the Dental Caries and Cariology section of this review was published by Baker et al.[449] This report investigated C16G2, a STAMP designed to specifically kill *S. mutans*. Several previous studies demonstrated that C16G2 is capable of selective killing of *S. mutans* while leaving commensal streptococci intact. This small peptide is made of 2 parts: a "G2" killing domain consisting of a 16-residue segment of the well-characterized antimicrobial peptide novispirin G10 and a "C16" targeting domain consisting of the 16 C-terminal residues of the *S. mutans* pheromone CSP. Moreover, C16G2 is capable of remodeling the composition of the bacterial community, eliminating *S. mutans*, and permitting the growth of organisms associated with health. C16G2 eradicates *S. mutans* through membrane disruption as it induces membrane permeability and depolarization, as well as intracellular metabolite leakage. It is important for its efficiency that the cytotoxic effect of C16G2 works extremely fast. The elimination of *S. mutans* occurs within less than 1 minute of exposure, therefore making it suitable for application as an oral care product. The STAMP is also soluble in water, therefore appropriate for solutions to be used directly in the oral cavity in a rinse formulation. Finally, C16G2 has insignificant adverse effects on human cells in vitro, and it is stable in both phosphate-buffered saline and human saliva.

Several other STAMPs, particularly from China, have been described in previous years; however, only C16G2 has progressed to clinical trials in a number of formulations, the results of which are of significant interest. After a large preclinical examination, C16G2 progressed to phase I clinical trials. The randomized, double-blind, placebo-controlled studies included a dose-escalation period and focused on evaluating safety and pharmacokinetics. A total of 127 participants were included, and no C16G2-related events or severe adverse events were reported in the study. Several formulations were tested, including a mouth rinse, an oral gel, a varnish, and a tooth strip. A single varnish application outperformed multiple tooth gel applications delivered by dental tray or brushing. The varnish formulation is a product candidate for in-office treatment to be performed by dentist and dental hygienists, similarly to fluoride varnishes, and is therefore mostly well suited for the treatment of high-risk caries-prone populations.

In phase II trials completed in 2016, the C16G2 varnish achieved significant decrease in *S. mutans* count, and no adverse effects were reported. The tooth strip application was intended as a convenient, at-home application for multiple treatments. Additional phase II clinical trials of C16G2 are ongoing. Although not all the details of the phase I and II clinical trials have been included here, the anticipation, these authors have reported the first clinical in vivo efficacy data for a STAMP ever published. The authors suggest, "C16G2 represents an exciting advance in precision therapeutics, with the ability to selectively eliminate a pathogen, causing remodeling of a dysbiotic microbial community to one rich in health-associated species. Dental caries remains a serious public health concern and one that could strongly benefit from a precision therapeutic, such as C16G2, to supplement current recommended fluoride and hygienic regimens. Beyond dental caries, the opportunities to use STAMP technology to treat other diseases and advance research of complex bacterial communities, such as that of the human microbiome, are vast and await discovery."

Small molecules

Similar to STAMPs, several small molecules have been proposed as agents to prevent caries through disruption of *S. mutans* biofilms. These small molecules represent an interesting new field of research, although preliminary research seems to indicate a tendency toward transient effects requiring continuous reapplication of the therapeutic media. A new compound, called ZY354, was developed and tested by Zang et al[450] for cytotoxicity in human oral keratinocytes (HOKs), human gingival epithelial cells (HGEs), and macrophages (RAW) and for antimicrobial activity against selected oral streptococci in both planktonic cultures and multispecies biofilms. ZY354 demonstrated good antimicrobial activity against oral streptococci while showing low cytotoxicity to human oral cells. In addition, it stopped development of oral streptococcal biofilms as well as halting the biofilm-mediated demineralization process in enamel.

Other new nanotechnology-based compounds, that have been developed to disrupt or modify the biofilms, need to be subjected to laboratory protocols and clinical trials. Unfortunately, these compounds remain untested and far from the necessary further development.[451,452]

Considerations and perspectives

As a key pathogenic specie, *S. mutans* plays a leading role in the development of dental caries. Therefore, most efforts to develop innovative caries therapies focused on *S. mutans* and its unparalleled ability to form insoluble glucans from sucrose. It is equally important to understand that *S. mutans* is not the only etiologic factor of the disease, and caries does occasionally develop without detectable *S. mutans* levels.

Research has clearly demonstrated that a dramatic reduction in the prevalence of dental caries through the

current modalities (fluoride and dietary changes alone) is unlikely to be routinely achieved. Fortunately, evolution has designed territorial commensal taxa that antagonize cariogenic species. Direct support of the dominant commensal taxa with simultaneous selective killing of their pathogenic competitors is a promising path for therapeutic development. Appropriately designed and rigorously controlled human trials are needed to confirm the encouraging results that these approaches have demonstrated. However, the high costs of needed research represent a significant deterrent to rapid development.

Nevertheless, as concluded by Baker and Edlund,[397] "There is room for optimism, as it appears evolution may have already provided the best tools in the form of our commensal defenders and their natural products."

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