

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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PROSTHODONTICS

In 2018, the professional literature pertinent to the clinical practice of prosthodontics was voluminous. Carefully selected articles from well over 50 professional journals make up the current review, which is intended to provide readers with a clinically practical update in prosthodontics and restorative dentistry. For convenience, the subject has been divided into 8 subtopics: general prosthodontic considerations, conventional removable complete prosthodontics, conventional removable partial prosthodontics, conventional fixed prosthodontics, general implant prosthodontic considerations, implant removable prosthodontics, implant-fixed prosthodontics, and prosthodontic materials. In addition to articles selected for review, a sizable number of excellent general reviews, systematic reviews, meta-analyses, and helpful clinical technique articles were also published on topics

ABSTRACT

This comprehensive review of the 2018 dental literature is provided to inform busy dentists about progress in the profession. Developed by the Committee on Scientific Investigation of the American Academy of Restorative Dentistry, each author brings discipline-specific expertise to one of the 8 sections of the report including (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 that will likely influence day-to-day treatment decisions. Each review is not intended to stand alone but to update interested readers so that they may visit source materials if greater detail is desired. As the profession continues its march toward evidence-based clinical decision-making, an already voluminous library of potentially valuable dental literature continues to grow. It is the intention of this review and its authors to provide assistance in navigating the extensive dental literature published in 2018. It is our hope that readers find this work useful in the clinical management of patients moving forward. (*J Prosthet Dent* 2019;122:198-269)

germane to prosthodontics. Although it is impractical to provide detailed commentary on this supplemental material, it is listed here for the reader's convenience: clinical techniques,¹⁻¹⁶ conventional complete dentures,^{17,18} conventional fixed prosthodontics,¹⁹⁻²⁸ diagnosis and treatment planning,²⁹⁻³⁴ digital dentistry,³⁵⁻³⁹ esthetics,⁴⁰⁻⁴⁶ ethics,⁴⁷ evidence-based dentistry,^{48,49} geriatrics,⁵⁰⁻⁵² implants treatment planning,⁵³⁻⁶² implant-supported fixed prosthodontics,⁶³⁻⁶⁷ implant-assisted

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removable prosthodontics,⁶⁸⁻⁷⁰ implant surgery,⁷¹⁻⁸³ peri-implant conditions,⁸⁴⁻⁸⁸ temporomandibular disorders (TMDs) and orofacial pain,⁸⁹⁻⁹⁴ mastication,⁹⁵ bruxism,⁹⁶⁻⁹⁸ maintenance,^{99,100} pathology and disease,¹⁰¹⁻¹⁰⁸ oncology^{109,110} (including a full issue of the Journal of Dental Research on "precision medicine"¹¹¹), pharmacology,¹¹²⁻¹¹⁵ radiology,¹¹⁶⁻¹¹⁸ anatomy and physiology,¹¹⁹⁻¹²¹ materials science,¹²²⁻¹²⁷ and statistics.¹²⁸⁻¹³⁰

General prosthodontic considerations

Although intraoral scanners claim increased patient satisfaction, reduced procedural time, and ability to archive and readily retrieve digital information as advantages, a concern largely remains regarding the accuracy of the resultant digital scan when compared with conventional methods. Malik et al¹³¹ investigated this concern in an in vitro study that looked at the degree of accuracy with conventional and digital scans. Authors defined accuracy in terms of precision and trueness, where precision indicates the repeatability of sequential measures and trueness signifies closeness to the object of interest.

The protocol incorporated complete-arch impressions of a reference model made by using either a conventional polyvinyl siloxane (PVS) material (Aquasil Ultra; Dentsply Sirona) or one of 2 intraoral optical scanners (TRIOS; 3Shape or CEREC Omnicam; Dentsply Sirona). The model was a roughened surface (50- μ m glass beads), silver-plated replica of a maxillary dental cast incorporating 7 teeth surrounding 5 anterior and posterior reference points.

Reference scanning of the model was accomplished by using a contact laboratory scanner (Incise; Renishaw PLC). Then 5 scans of the model were made by using each of the experimental scanners, and the resulting digital files were converted to the standard tessellation language (STL) format. The next 5 conventional scans were made by using 2 PVS viscosities and tray adhesive in a custom impression tray. Resulting casts (Type IV dental stone) were scanned by using the reference scanner, and the scans obtained were converted to the STL format. Finally, reference scanning of the model was again accomplished to ensure model stability.

A surface matching software program (Geomagic Control; 3D Systems) superimposed scans within groups to determine mean deviations in precision and trueness as calculated for each group and compared statistically. Qualitative analysis was carried out from 3D maps of differences between scans.

Results indicated mean deviations in precision for conventional, TRIOS, and Omnicam groups to be 21.7 \pm 5.4, 49.9 \pm 18.3, and 36.5 \pm 11.12 μ m, respectively. Mean deviations in trueness were 24.3 \pm 5.7, 87.1 \pm 7.9, and 80.3 \pm 12.1 μ m, respectively. Conventional impression showed

significantly better mean precision ($P < .006$) and mean trueness ($P < .001$), and no significant differences were identified in precision or trueness between the digital scans. Qualitative analysis revealed local errors along palatal surfaces of molars and along incisal edges.

Within the in vitro limitations of this study, conventional complete-arch PVS impressions exhibited the best mean accuracy, while the digital scanning systems investigated did not show significant differences.

Defining optimal dentofacial esthetics is challenging, particularly when one considers the point of reference, that is, the patient, the practitioner, or the public. Regardless of all, the smile contributes significantly to facial esthetics, and dental restoration of anterior teeth must be carefully considered to optimize outcomes. Determination of the optimal tooth form has been related to sex, age, gingival architecture, facial form, dental arch form, and patient's temperament/emotions, among other factors. Mahn et al¹³² reported on an observational investigation designed to evaluate the anterior maxillary tooth outline form relative to sex and basic descriptive shapes. Additionally, investigators calculated the percentage of correct sex identifications made by lay people, dentists, and dental students, relative to the observed anterior tooth form.

Four hundred sixty randomly selected individuals, possessing no anterior dental restorations, were enrolled in the study. Standardized anterior dental photographs (anterior maxillary teeth without facial structures) were made and analyzed by 3 experts who categorized participants based on outline forms: oval (O), triangular (T), square (S), rectangular (R), oval-rectangular (OR), triangular-rectangular (TR), triangular-oval (TO), square-oval with flat lateral incisors (SOF), or square-oval with scalloped lateral incisors (SOS). Then, 10 dentists, 10 dental students, and 10 lay people studied the same photographs to ascertain the sex of the individuals depicted.

The results suggested that pure anterior tooth outline forms (O, T, S, and R) were less prevalent in the population studied than hybrid forms (OR, TR, TO, SOF, and SOS). The most prevalent ones were TO (20.87%), SOS (20.65%), and OR (19.57%), suggesting the appearance of an oval component to prevalent anterior tooth outline forms. Furthermore, observers, regardless of professional dental exposure and experience, were unable to assess the sex of individuals photographed beyond mere chance (approximately 50% were correct assessments).

The authors concluded that the use of sex to define the appropriate anterior maxillary tooth outline form might not be reliable. Perhaps consideration of patients' wishes when determining the anterior tooth shape for esthetic restorative dentistry is at least as important as other factors.

Masticatory performance is an important objective therapeutic parameter in restorative dentistry and prosthodontics. Previous reports indicate that the number of posterior dental units (premolars and molars) may influence masticatory performance, particularly on the patient's preferred or habitual chewing side. To clarify if the numerical status of available posterior teeth affects masticatory performance in elderly adults, Tanaka and Shiga¹³³ performed a well-developed *in vivo* study.

One hundred forty-nine independently living elderly women (age range: 65-89 years, mean age: 72.3 years) were asked to chew a gummy jelly (14×10-mm cylinder weighing 2 g) on their preferred chewing side, and the amount of glucose extraction was measured as the parameter for indicating masticatory performance. The participants were divided into 5 groups depending on available occlusal units on the preferred chewing side: no posterior teeth (G1); first premolar only (G2); first and second premolars only (G3); premolars and first molar only (G4); or premolars, first molar, and second molar (G5). Authors noted if participants were wearing removable dentures. If so, participants were asked to chew using the denture. The amount of glucose extraction was compared among the 5 groups and between participants with and without removable dentures.

In general, results demonstrated that the amount of glucose extraction progressively increased with increasing number of posterior teeth, with significant differences between G1-4, G1-5, G2-5, G3-5, and G4-5. There were no fixed tendencies between age and glucose extraction, when the number of posterior teeth was taken into account. The amount of glucose extraction of participants without removable dentures was significantly greater than that of participants with removable dentures (210.0 mg/dL vs. 162.1 mg/dL, respectively). It was also found that 67% of participants with removable dentures were within the normal range when normal was set based on G5 data.

Although data indicate masticatory performance in elderly women decreases with loss of posterior teeth, the authors suggested that removable dentures appear to permit significant performance recovery for many to expected levels when all natural teeth are present.

Conventional removable complete prosthodontics

It is generally understood that computer-aided design and computer-aided manufacturing (CAD-CAM) processes lead to accurately fitting acceptably retentive complete denture bases. However, optimally successful complete denture fabrication must also yield prostheses with limited or no denture tooth movement during processing. With this in mind, Goodacre et al¹³⁴ assessed denture tooth movement associated with 5 processing techniques (compression molding, fluid resin, injection molding, CAD-CAM milled base/bonded teeth, and

CAD-CAM milled base/teeth) and various materials to identify best accuracy and reproducibility.

A master maxillary complete denture was laser scanned, resulting in a standard tessellation language (STL) format file for import into the CAD processes. Ten complete dentures replicating master denture contours, in terms of dimensions and tooth positions, were fabricated on standardized casts by using each of the 5 experimental processing techniques, for a total of 50 experimental dentures. After fabrication, dentures were hydrated for 24 hours, and the cameo surfaces were laser scanned. Preprocessing and postprocessing scan files of each denture were superimposed by using a surface-matching software program (Geomagic Control; 3D Systems). Measurements were made at 64 common loci, permitting evaluation of buccal, lingual, mesial-distal, and occlusal denture tooth movement.

The authors defined accuracy as the capacity of a processing technique to produce dentures with minimal tooth movement. Accuracy was represented by the median value. A reproducible technique creates an accurate denture each time, which was represented by the interquartile range. An optimized combination of accuracy and reproducibility indicated the processing technique that performs best.

With respect to denture tooth movement, the results indicated that the CAD-CAM milled base/teeth technique was the most accurate, followed by fluid resin, CAD-CAM milled base/bonded teeth, compression molding, and injection molding. The CAD-CAM milled base/teeth technique was the most reproducible one, followed by compression molding, CAD-CAM milled base/bonded teeth, injection molding, and fluid resin. Techniques involving compression during processing (compression molding and injection molding) showed increased positive occlusal tooth movement (increasing the occlusal vertical dimension) compared with techniques not involving compression. In general, posterior teeth tended to move more than anterior teeth, and teeth predominantly moved in a lingual direction.

Goodacre et al¹³⁴ concluded that the CAD-CAM milled base/milled teeth technique produced the best combination of accuracy and reproducibility of the techniques investigated. The results demonstrated that varying amounts of tooth movement should be expected based on the processing denture technique used. However, the clinical significance of these differences remains unknown.

The re-establishment of adequate masticatory performance is an important therapeutic objective in restorative dentistry and prosthodontics. Oral health-related quality of life (OHRQoL) is widely recognized as an important outcome of dental therapy, while Oral Health Impact Profile (OHIP) is used to assess the effect of dental care. The loss of teeth has been associated with

a decline in masticatory performance, and prosthodontic management can bring about improvements in this regard. To clarify the relationship between masticatory performance and OHRQoL before and after complete denture treatment, Yamamoto and Shiga¹³⁵ published results of a clinical trial.

Thirty patients (15 men and 15 women, age range: 68-82 years, mean age: 74.7 years) wearing complete dentures participated. Each had worn complete dentures for at least 3 years but required new prostheses. Additionally, each was able to identify a preferred chewing side. Participants were instructed to chew a gummy jelly (14×10-mm cylinder weighing 2.3 g) on their preferred chewing side, and the amount of glucose extraction was measured as the parameter for indicating masticatory performance. Participants also completed the Japanese version of the OHIP questionnaire consisting of 49 questions related to oral problems (functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap). Total scores were calculated and used as parameters of OHRQoL. These records were obtained before and 3 months after treatment. Parameters of masticatory performance and OHRQoL were compared before and after treatment. Relationships between masticatory performance and OHRQoL were investigated by using a stepwise multiple linear regression analysis.

The results identified that both masticatory performance and OHRQoL were significantly improved after treatment and that masticatory performance was significantly correlated with some parameters of OHRQoL. Regression analysis indicated functional limitation and pain to be important factors affecting masticatory performance before treatment. Functional limitation was indicated to be an important factor affecting masticatory performance after treatment.

The authors concluded that participants experienced an improvement in masticatory performance and OHRQoL after treatment with new complete dentures and that there is a close relationship between these 2 therapeutic parameters. Data also suggested that functional limitation in these edentulous participants was the most important factor limiting the optimal masticatory performance.

Maxillary conventional complete dentures occasionally require reinforcement because of repeated fracture, desired thinness, or patient preference. The use of dental cobalt-chromium alloy for the fabrication of denture base reinforcements is currently the standard but may be objectionable for patients who demonstrate metal sensitivity. Nishiyama et al¹³⁶ published the use of a new-generation zirconia (ceria-stabilized zirconia/alumina nanocomposite; Panasonic Healthcare), manufactured via CAD-CAM technology, as an alternative.

A convenience sample of 29 patients (16 men and 13 women, age range: 59-89 years, mean age: 75 years) completed the study, with 10 participants receiving prostheses reinforced by zirconia frameworks (ZrCD) and 19 receiving conventional acrylic resin complete dentures (CCDs). All patients were free of orofacial pain and acute oral disease. For the ZrCDs, the CAD-CAM frameworks were incorporated into maxillary acrylic resin prostheses after media blasting with silane coupling (Rocatec Plus; 3M ESPE) and treatment by using 10-methacryloyloxydecyl dihydrogen phosphate. Patient satisfaction (specifically general satisfaction, comfort, denture stability, chewing ability, ability to speak, esthetics, and ease of cleaning) was evaluated before and 12 months after prosthesis placement by using the McGill Denture Satisfaction Instrument. Score differences were statistically compared within and between experimental groups.

The results indicated that during follow-up periods of up to 2 years (mean 32 months for ZrCD and 29 months for CCD), no denture fractures were observed in either group. Additionally, all aspects of patient satisfaction improved, and no significant group differences were found between groups.

The authors suggested that, within the limitations of this study, maxillary complete dentures incorporating nano-zirconia frameworks might be an acceptable alternative prosthetic treatment option. Advantages cited included ease of fabrication within a common digital workflow, acceptable alternative for patients with metal sensitivities, proven reinforcement capabilities, light weight compared with metal alternatives, and ability to be relined via chemically assisted acrylic resin bonding.

Conventional removable partial prosthodontics

Accurate fit is a standard objective when clinically assessing the metal framework for a removable partial denture (RPD). Clinical factors that may affect the fit of the RPD framework include, but are not limited to, impression material used, impression tray type, and type of partial dentulism (Kennedy classification). To investigate these clinical factors and their effect on the fit accuracy of cobalt-chromium (Co-Cr) RPDs, Baig et al¹³⁷ reported on a retrospective study accomplished in a dental school setting.

Electronic treatment records of 120 partially edentulous patients who were provided Co-Cr RPD treatment for one or both arches were examined. Data retrieved for each patient included demographic information, Kennedy classification, impression material used, impression tray type used, and the number of fabrication attempts needed to yield a satisfactory RPD framework for each dental arch included in the study. All providers followed a standard clinical protocol for patient treatment and fit assessment, and all frameworks were fabricated by a

single laboratory by using a conventional lost-wax casting technique.

Clinical procedures included 117 alginate impressions, 26 polyvinyl siloxane impressions, 123 impressions made by using metal stock trays, and 20 impressions made with custom trays. Alginate impressions made by using metal stock trays were the most frequent ones. Accurate framework fit was judged to have occurred in 124 participants (87%), while a second framework fabrication was needed for 19 participants (13%). In no participant was a third fabrication needed. Statistical analysis of data derived from 143 dental arches (69 maxillary and 74 mandibular) revealed no significant correlation between impression material, impression tray type, or Kennedy classification and the number of framework fabrication attempts for the pooled or individual arch data ($P > .05$).

Based on the data collected in the retrospective study, the authors concluded that alginate was as suitable for definitive impressions to fabricate an RPD metal Co-Cr framework as polyvinyl siloxane. Fit assessment of RPD frameworks did not appear to be influenced by the Kennedy classification of the partially edentulous arch. Finally, metal stock trays and alginate impression material can be used quite successfully in place of custom trays when making definitive impressions for the fabrication of Co-Cr RPD frameworks.

The 2 base metal alloys most frequently used in the fabrication of RPDs are cobalt-chromium (Co-Cr) and nickel-chromium (Ni-Cr). These alloys generally have acceptable physical properties for intended clinical applications and perform well under expected functional conditions. However, metal alloys used in dental restorations have been reported to leach heavy metals into the saliva, a phenomenon that may be pH-dependent and element-specific. For patients with gastroesophageal reflux disease (GERD), oral pH conditions may facilitate such heavy metal release. Therefore, Borg et al¹³⁸ studied surface microstructural changes and the release of ions from metal alloys used in RPDs, as well as potential exacerbating effects of acidic reflux in patients with GERD on this release.

This cross-sectional case-controlled clinical trial included 37 patients suffering from GERD. Data were gathered through a questionnaire and clinical examination, including presence of a denture and materials involved, presence of joint replacement and materials involved, presence of oral piercings, and details/conditions related to GERD diagnosis. GERD was confirmed by using the validated GerdQ questionnaire. Metal alloy specimens (both unused and from dentures) and patients' saliva were collected. Metal specimens were characterized by scanning electron microscopy and energy dispersive spectroscopy. Saliva samples were tested for trace chromium, cobalt, molybdenum, and nickel ions by using inductively coupled plasma. For comparison,

participants were assigned to 1 of 4 experimental groups: study group (metal denture and symptomatic GERD, $n=5$); control group 1 (metal denture and controlled GERD, $n=8$); control group 2 (no metal denture and symptomatic GERD, $n=11$); or control group 3 (no metal denture and controlled GERD, $n=13$).

The results demonstrated an etched appearance to the nickel-chromium alloy surface, while cobalt-chromium alloy exhibited no noticeable surface microstructural changes. The presence of nickel, cobalt, chromium, and molybdenum was identified in all participants. Significantly greater mean salivary levels of chromium and cobalt were associated with wearing metal-based dentures. Significantly higher chromium and nickel levels were associated with wearing Ni-Cr prostheses. No differences were found in salivary metal ion levels of patients suffering from GERD.

The authors concluded that the nickel-chromium alloy appears generally prone to acid etching in the oral cavity, while the cobalt-chromium alloy seems significantly more resistant. Cobalt, chromium, and nickel leached into the saliva of patients using cast removable prostheses. Within the current experimental protocol, GERD appeared to have a little impact on salivary ion release and alloy surface etching. However, GERD is not a static disease and the limited perspective provided here may inadequately represent dynamic clinical conditions. Therefore, the impact of gastric acid on metal ion release from dental metal alloys deserves further long-term investigation.

The application of CAD-CAM processes in RPD fabrication has to date been mainly focused on the design and fabrication of metal frameworks. Polyetheretherketone (PEEK) has recently been widely used in a number of dental applications including implant restorations, overdenture attachments, maxillary obturators, fixed interim restorations, and RPD frameworks. This material is thought to possess optimal physical properties that match with those of the tissues it is intended to replace (human bone, enamel, and dentin). Ye et al¹³⁹ reported on a preliminary laboratory trial incorporating a novel CAD-CAM process to produce 1-piece RPDs fabricated by using PEEK. Fit of the PEEK RPDs was assessed on a standardized model and compared with the fit of traditional cast metal framework RPDs.

A total of fifteen 1-piece RPDs were designed by using a commercial dental CAD software program (Dental System; 3Shape) and a reverse engineering software program (Geomagic Studio; 3D Systems) and then fabricated by using PEEK. Design differences related to the physical properties of PEEK included clasp tips-engaged 0.5-mm undercuts, and cross-sectional dimensions of clasps and connectors were generally greater than those of metal counterparts to provide adequate

retention and strength. Denture teeth and denture bases were created separately and exported as STL files. The final digital RPD assembly was accomplished and exported (STL file) for milling purpose. A second group of 15 RPDs was produced on the same standardized cast by using conventional processes. All RPDs were placed on replicas of the standardized cast. Fit assessment was carried out by visual inspection, manual manipulations, and digital assessment of the silicone material fit disclosure.

Objective results indicated that average thicknesses of silicone between elements of the RPDs (occlusal rests, major connectors, denture bases, and prosthesis entirety) and the standardized casts were significantly less for PEEK RPDs than those of RPDs fabricated by using conventional materials and processes. Visual assessment indicated that PEEK RPDs exhibited satisfactory subjective retention force, strength, and esthetics.

The authors concluded that RPDs can be designed by digital methods and fabricated in PEEK. The *in vitro* fit of prostheses so manufactured appears to be better than that of traditional metal framework RPDs with acrylic resin bases and denture teeth. Ye et al¹³⁹ encouraged further investigation into the mechanical properties and long-term performance of PEEK in this novel application.

Conventional fixed prosthodontics

Although not always well tolerated by patients, the definitive impression procedure is a critical step in the provision of all indirect dental restorations. Patients are now demanding less time-consuming and more comfortable procedures in the modern dental practice, and patient-reported outcome measures (PROMs) are of great interest to the savvy practitioner. Unfortunately, limited evidence is available comparing digital scanning versus conventional impressions from the point of view of patients' preference. With this in mind, Gallardo et al¹⁴⁰ systematically reviewed available professional literature to identify and summarize the status of patient-centered outcomes for digital scanning versus conventional impression techniques.

The population, intervention, comparison, outcome study (PICOS) question developed was, "Does the digital impression technique offer results comparable with those of the conventional impression technique with respect to patient centered outcomes?" From 1955 to July 2016, the databases Medline, Cochrane, Science Direct, Scopus, and Embase were electronically and then hand searched. Reports involving both implant- and tooth-supported restorations were included. Initially 2943 articles were identified as relevant to the question posed. After article screening and the application of inclusion and exclusion criteria, only 5 studies were included in this review.

Qualitative analysis results revealed that 4 studies compared patient-reported outcome measures (PROMs)

between conventional impressions and digital scans and indicated that the digital technique was more comfortable and caused less anxiety and nausea sensation. One study reported no difference between digital scanning and conventional impression techniques relative to patient comfort. Two studies reported a shorter procedure for the conventional technique while 3 studies reported a shorter procedure for the digital scanning technique. Because of the heterogeneity of experimental designs and treatments, only descriptive data could be presented in the review. According to the Newcastle-Ottawa scale, the methodology of the included studies was assessed to be of medium quality. According to Cochrane recommendations, the 3 randomized controlled trials (RCTs) included in this review presented a high risk of bias due to the lack of examiner blinding.

Although high-quality data are lacking, the authors offered 2 conclusions. Time efficiency of digital scanning and conventional definitive impression-making appears to be similar. Clinical studies addressing PROMs related to digital prosthodontics are generally lacking. However, current evidence seems to suggest that patients are more likely to prefer digital scanning procedures than conventional impression techniques.

With advancing popularity of CAD-CAM restorative dentistry and the total digital workflow, the accuracy (trueness and precision) of intraoral scanners must be questioned. Trueness refers to agreement between the arithmetical mean of a large number of test results and the true or accepted reference value. Precision refers to the agreement among test results. The precision and trueness of intraoral scanners have been measured while scanning the single model, multiunit model, complete-arch model, and edentulous jaw model. *In vivo* studies have evaluated the precision of intraoral scanners for quadrant scans and complete-arch scans. However, evidence is lacking relative to the accuracy of intraoral scanners in the acquisition of a complete-arch model that includes different cavity preparations. Therefore, Kim et al¹⁴¹ evaluated the trueness and precision of complete-arch digital scans made by using 9 intraoral scanners and a superimposition method.

Nine intraoral scanners obtained 10 STL data sets, each from a bimaxillary complete-arch model with various cavity preparations. Inlay, post-and-core, and complete coverage preparations were distributed across the model. CEREC Omnicam (Dentsply Sirona), CS 3500 (Carestream Health), E4D Dentist (E4D Technologies), FastScan (IOS Technologies), iTero First Generation (Align Technologies), PlanScan (Planmeca), TRIOS Second Generation (3Shape), True Definition Gold-Nine Version (3M ESPE), and Zfx IntraScan (Zfx GmbH) intraoral scanners were evaluated. After superimposition of data sets, comparison to the reference scan yielded estimates of trueness, while intragroup comparisons

resulted in precision. Scanners were also compared based on data capture principle and mode and the need for powder coating. Surface smoothness and sharp edge reproducibility of the digital images were compared with assess scan quality.

The results revealed the lowest median precision values for TRIOS (average: 34.70 μm ; maximum: 263.55 μm) and highest for E4D (average: 357.05 μm ; maximum: 2309.45 μm). The lowest median average trueness values were for TRIOS (42.30 μm) and highest for Zfx IntraScan (153.80 μm). The lowest median maximum trueness values were for CS 3500 (450.75 μm) and highest for E4D (2680.55 μm). Individual image and video sequence data captures showed similar median average trueness values ($P > .05$), while median maximum individual image trueness values were higher than those of the video sequence ($P < .05$). Swept source optical coherence tomography (SS-OCT) exhibited higher trueness values than other scanning principles ($P < .05$). The FastScan (IOS Technologies, Inc) and True Definition (3M ESPE), which require powder coating, showed significantly better trueness than other scanners that did not require powdering ($P < .05$). The E4D, PlanScan, and Zfx IntraScan had increased tendency to produce images with imperfect surface features and rounded rather than sharp edges.

Within the limitations of the in vitro protocol, the authors concluded that E4D and Zfx IntraScan scanners were inferior to the other intraoral scanners tested for complete-arch digital scanning of complicated tooth preparations. The data capture principle of SS-OCT and the individual image acquisition mode exhibited inferior trueness, whereas scanners that required powder coating offered better trueness (FastScan and True Definition). Finally, qualitative features varied among the investigated scanners in terms of polygon shapes, sharp-edge reproducibility, and surface smoothness. The authors cautioned that the protocol was specifically established to eliminate potential confounding variables typically present in a clinical setting, for example, saliva, crevicular fluid, blood, breathing moisture, patient movement, and involvement of the tongue, lips, and cheeks. Therefore, the results presented should be carefully interpreted.

While every dentist learns the basic fixed prosthodontic impression technique in dental school, not all dental schools teach the same fundamental procedures, and technology and materials change rapidly. Clinicians may gain valuable insights into improved clinical technique by better understanding what techniques are reported to be favorable by other likeminded practitioners. With this in mind, McCracken et al¹⁴² compiled survey results aimed at determining which impression and gingival displacement techniques practitioners use for single crowns on natural teeth and which, if any, dentist

or practice characteristics are significantly associated with the use of specific techniques.

This study was based on 2 surveys completed by dentists in the National Dental Practice-Based Research Network (PBRN). The network is a consortium of dental practices and dental organizations focused on improving the scientific basis for clinical decision-making. The first survey was the enrollment questionnaire, which covered demographic information on the dentist, his/her practice, and the patient population. The second survey was the clinical techniques questionnaire developed to measure current practices in treatment planning, preparing, and fabricating single crowns on natural teeth. The surveys specifically included questions regarding gingival displacement and impression techniques. Survey responses were statistically compared for dentist and practice characteristics.

The results revealed a response rate of 83% (1777 of 2132 dentists eligible for the survey). Most respondents were male practice owners who worked full-time, and many had been practicing for over 20 years. Regarding gingival displacement, most clinicians reported using either a single cord (35%) or dual cord (35%) technique. About 16% of respondents preferred an injectable retraction technique (for example, Expasyl). Only 4 clinicians reported gingival troughing (for example, electrical or laser soft tissue removal). Dentists reported using chemical agents for hemostasis on 57% of impressions. Thirty-seven percent of respondents use these agents more than 90% of the time while 22% use them less than 10% of the time.

The dentist who prepared the tooth made the impression 98% of the time, while a dental auxiliary or assistant made the definitive impression 2% of the time. Some clinicians used a single impression material and technique all the time, while others indicated using various materials and techniques based on clinical circumstances. The most frequently used materials were polyvinyl siloxane (77%), polyether (12%), optical or digital scanning (9%), and hydrocolloid (1%). Regarding dual-arch impression trays, 23% of practitioners reported they typically use a metal frame tray, 60% use a plastic frame, and 16% did not use a dual-arch technique. Most clinicians (57%) used a heavy body material in the tray, while others (34%) used a medium body material. Most clinicians (77%) indicated using a light-viscosity impression material to syringe material around the tooth preparation, while 12% syringed ultra-light viscosity and 8% syringed medium-viscosity material for this purpose.

Eight percent of respondents used optical scan impressions most (75% or more) of the time, while 6% used optical scanning over 90% of the time. Two percent of clinicians used optical scanning techniques exclusively. Comparing dentist characteristics, white dentists, private practice owners, and dentists who reported being less busy were significantly more likely to report using optical scanning more than 90% of the time.

The dentist who prepared the tooth made the interim restoration 49% of the time, and an assistant made the interim restoration 50% of the time.

This study documents current techniques for gingival displacement and making impressions for single crowns by a specific subset of dentists. While this represents a limitation of the report, the primary limitations may be the self-reporting of data, which may differ from actual clinical behavior during treatment. The authors indicated that certain dentist and practice characteristics appear to be associated with the use of specific impression materials and techniques.

General implant prosthodontic considerations

The primary objective in dental implant surgical placement is to provide the ideal foundation for the planned prosthesis. This objective necessitates completion of prosthodontic planning before the consideration of surgical planning, giving rise to the concept of prosthetically driven implant placement. To optimize this approach, the provider must acquire clear and anatomically correct 3D visualization of the planned prosthesis accurately positioned within a 3D radiographic image (cone beam computed tomography or CBCT) of the foundational hard and soft tissues and other critical anatomic structures. Basically 3 approaches to prosthetically driven implant planning have been suggested: (1) a radiographic approach that involves the use of a radiographic template to register the planned restoration during CBCT imaging; (2) a laboratory approach that involves merging an indirect surface scan of a cast carrying planned prosthesis with the CBCT scan; and (3) an intraoral approach that involves merging a direct intraoral surface scan with the CBCT scan. Jamjoom et al¹⁴³ studied the accuracy and validity of these diagnostic planning approaches by using a well-designed in vitro protocol.

A dentate mandibular master model with radiopaque teeth served as reference. The master model was surface scanned (intraoral direct approach) by using an intraoral scanner (TRIOS; 3Shape), and the scans obtained were exported as STL files. Three dental stone duplicates of the master model were surface scanned (laboratory indirect approach) by using a laboratory scanner (D900; 3Shape), and the scans obtained were exported as STL files. A clinical simulation was developed by removing the left first molar from the reference model and subjecting the resultant clinical simulation model to 3 CBCT scans. Intraoral and laboratory surface scan STL files were merged with CBCT scans for comparison. Then, 3 radiographic templates were fabricated for the clinical simulation model, and the model was subsequently CBCT scanned with each radiographic template in place. A metrology software program (Geomagic Control X; 3D Systems) was used to assess the accuracy of each planning approach by measuring 3D deviation on STL files

generated from the CBCT scans against an STL file of the dentate master model generated from a CBCT scan.

The results indicated that the planning approach had a significant effect on deviation from the dentate master model ($P=.004$). The overall mean 3D deviation was 0.04 mm for intraoral (direct) surface scan approach, 0.03 mm for laboratory (indirect) surface scan approach, and 0.33 mm for radiographic templates. Radiographic templates were significantly less accurate than both surface scan methods ($P<.001$). No significant difference in accuracy was found between intraoral and laboratory surface scan techniques ($P=.94$).

The authors concluded that intraoral and laboratory surface scan migrations with CBCT scans were comparable with each other and more accurate than the use of radiographic templates for prosthetically driven dental implant planning. These conclusions should be interpreted with caution given that this in vitro protocol did not incorporate complicating clinical scanning factors (for example, saliva, patient movement, and involvement of the tongue, lips, and cheeks) and the sample size was small.

Many diverse factors influence success in implant dentistry. One risk factor repeatedly presented is implant location in the maxilla versus mandible. With this in mind, Jemt¹⁴⁴ analyzed implant failures in an exceptionally large number of edentulous patients, focusing on the dental arch treated and implant surface roughness.

This study includes all edentulous patients consecutively treated with dental implants from 1986 to 2015 at a single clinic (Branemark Clinic, Public Dental Care, Region of Vastra Gotaland, Sweden). A total of 3493 arches were treated with 19 338 turned surface implants by using a 2-stage surgical approach between 1986 and 2002. A total of 1092 arches were treated with 5443 moderately rough surface implants by using either a 1- or 2-stage surgical approach between 2003 and 2015. All implant failures were consecutively identified during routine follow-up. A multivariate logistic regression analysis was applied to assess implant failure relative to dental arch and implant surface.

For turned surface implants, overall cumulative survival rates (CSRs) were 75.7% for the maxillary arch and 94.6% in the mandible. For moderately rough surface implants, the corresponding 10-year CSRs were 91.9% and 96.1%, respectively. The strongest significant association ($P<.05$) with risk for implant failure was found to be of placement in the maxilla, which was more pronounced for turned surface implants. Age at implant placement, implant surgeon, year of surgery, and follow-up time also had significant associations with the risk of implant failure ($P<.05$).

This long-term follow-up study involving a large edentulous patient population demonstrated that the risk for implant failure was significantly higher in the maxilla,

but this risk decreased significantly when moderately rough implants were used. The impact of surface characteristics was not as obvious in the mandible. The risk for late (after first year) implant failures was lower for moderately rough implants in the maxilla. The risk for late failure in the mandible seemed comparable for both surfaces.

Despite improvements in the design of implant components, screw joint mechanical failures remain a significant concern. Stability of the preloaded screw joint and maintenance of the seal between clamped components is intimately related to screw insertion torque, component design and manufacture, and physical interfacial relationships between mating surfaces. Seloto et al¹⁴⁵ investigated on improvement of the interfacial relationship within the implant screw joint and maintenance of preload by application of screw thread sealing agents.

Forty experimental samples (n=10/group) were developed by screw fastening an external hexagon implant to a prefabricated abutment (cobalt-chromium alloy collar/base). Three experimental groups were designed, each involving a different thread sealing agent: an ASMT group that included an anaerobic thread sealing agent for medium torque, an ASHT group that included an anaerobic thread sealing agent for high torque, and CYAB group that used a cyanoacrylate-based bonding agent as the thread sealer. A control group (CG) with no thread sealer was also included.

All abutments were attached to their respective implants by using 32 Ncm torque. For experimental groups, the assigned thread sealer was applied by using a syringe to standardize the amount of sealer incorporated into the screw joint. After 48 hours from initial assembly, loosening torque (or detorque) was measured by using a calibrated digital torque wrench.

The results indicated significant differences between insertion torque (32 Ncm) and removal detorque values in all groups ($P < .05$). Detorque values for CG (24.6 ± 1.5 Ncm) and ASMT (24.3 ± 1.1 Ncm) groups were significantly less than the insertion torque value. However, detorque values for ASHT (51.0 ± 7.4 Ncm) and CYAB (47.7 ± 15.1 Ncm) groups were significantly greater than the insertion torque value. The detorque values for CG and ASMT groups were statistically similar but significantly lower than detorque values for ASHT and CYAB groups. The ASHT and CYAB groups displayed statistically similar detorque values.

The authors concluded that ASHT was more efficient than the other thread sealing agents, increasing the remaining preload (or detorque value) by 58.88%. Although the cyanoacrylate-based bonding agent also generated high detorque values (an increase of 47.7%), an associated high standard deviation in this investigation suggested lower reliability of this application.

Implant removable prosthodontics

The use of the LOCATOR Attachment System (Zest Anchor) for implant-assisted overdentures remains popular. Clinically, the retentive force of this attachment can reduce significantly over time as an indication of wear affecting both the abutment and the nylon inserts. In an effort to characterize this clinical predicament, Hahnel et al¹⁴⁶ investigated mechanical properties and wear characteristics of nylon inserts and abutments in LOCATOR-retained, implant-assisted overdentures (L-IODs).

This cross-sectional clinical study included 16 patients (8 men and 8 women; mean age: 69 years; age range: 39-89 years) who received 15 mandibular and 1 maxillary L-IODs from 2008 to 2016. Two calibrated dentists independently qualitatively rated clinical wear of inserts and abutments. Nylon inserts were carefully removed and subjected to microscopic analysis, differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA). New, unworn nylon inserts from the same retention categories were used as reference for comparisons.

Review of treatment records indicated that the pink nylon inserts and corresponding abutments had been in clinical service for 10 months (n=5, service range: 7-70 months), the green inserts for 43 months (n=5, service range: 33-52 months), and the clear inserts for 60 months (n=5, service range: 5-100 months). Wear was identified affecting almost all inserts and abutments. Of the removed nylon inserts, 62.1% displayed heavy wear and 37.9% displayed moderate wear. For abutments, 61.8% showed signs of heavy wear, 20.6% demonstrated moderate wear, and 14.7% revealed no wear. More than 80% of the oral surfaces and approximately 70% of the vestibular surfaces of the abutments showed signs of wear, while only 50% of the mesial and distal abutment surfaces were worn.

These direct clinical observations were corroborated by DSC and TGA analyses, which showed significant mechanical deterioration of the inserts. Microscopic analysis of the worn inserts revealed relevant signs of material deterioration.

The authors concluded that, for the L-IOD patient population studied, most LOCATOR abutments and all nylon attachment inserts displayed clear signs of wear. This level of component deterioration highlights the need for regular follow-up and maintenance appointments with a carefully calculated and systematic replacement of deteriorating components. Most importantly, patients should be informed of the need for follow-up and the cost of maintenance before accepting this means of prosthodontic management of edentulism.

An interesting investigation to juxtapose against the Hahnel et al¹⁴⁶ study was published by Choi et al.¹⁴⁷ This research group performed an in vitro investigation to compare the retentive properties of an implant

attachment system that incorporates a nylon insert (LOCATOR, Zest Anchor; Zest Dental Solutions) and an attachment with a polyetherketoneketone (PEKK) insert (CM LOC, Cendres+Metaux) on 2-implant mandibular overdentures during simulated masticatory loadings and insertion and removal cycles.

Two edentulous resin mandibular models with 4 mm of resilient material (Gi-Mask; Coltène) overlying the edentulous ridges served as experimental models. Implant analogs were placed in the canine regions of the models at interimplant angulations of 0 and 20 degrees. LOCATOR and CM LOC abutments were attached to the models as needed.

Attachment systems investigated offer inserts with varying retentive capacities. The LOCATOR system offers 3 standard nylon inserts (designated nylon/low, nylon/medium, and nylon/high), and the CM LOC system offers 4 PEKK inserts (designated PEKK/x-low, PEKK/low, PEKK/medium, and PEKK/high). To accommodate all inserts for both attachment systems and both implant angulations, 140 overdentures were fabricated to fit the experimental models (10 overdentures for each insert at each angulation).

Experimental mastication included 400 000 repeated loadings in a dental mastication simulator (R&D Inc) by using 70-N compressions to represent 1 year of mastication. One year of typical prosthesis insertion/removal was simulated in a universal testing machine (MTS Systems Co) set to deliver 1080 cycles at a crosshead speed of 50 mm/min. The resulting wear patterns and deformations on the attachment surface were analyzed by scanning electron microscopy.

At 0 and 20 degrees, the nylon/high insert had the greatest initial retentive force and PEKK/x-low had the lowest. PEKK/high and PEKK/medium had the highest final retentive force at 0 and 20 degrees, respectively, whereas the PEKK/x-low had the lowest at both angulations.

At 0 degrees, nylon/low, nylon/medium, PEKK/x-low, and PEKK/low displayed a significant increase in retention ($P < .05$), while the nylon/high and PEKK/medium displayed a significant decrease in retention ($P < .05$). The PEKK/high displayed no decrease ($P > .05$).

At 20 degrees, nylon/low and PEKK/x-low increased retention significantly, while the nylon/medium, nylon/high, PEKK/low, PEKK/medium, and PEKK/high decreased retention significantly ($P < .05$).

Abutments of both attachment systems barely showed detectable abrasion, while inserts revealed severe wear and surface deformation. Nylon inserts displayed greater wear and deformation than PEKK inserts.

The authors concluded that, within the limitations of this investigation, the attachment system with PEKK inserts resulted in less abrasion and fewer retention changes than the attachment system incorporating a

nylon insert, for both paralleled implants and axially angled implants under 400 000 repeated loadings and 1080 insertion/removal cycles. Although direct comparison of these different attachment systems must be cautiously considered, improved physical properties of PEKK (high chemical and mechanical wear resistance; high fatigue, flexural, and tensile strength; and high compressive strength) may prove beneficial when developing new implant overdenture attachment systems.

Although implant-supported fixed dental restorations are routinely incorporated into modern dental treatment plans, this use of removable alternatives may be more appropriate for a variety of reasons (for example, patient age, esthetics, treatment cost, oral hygiene access, bone resorption, or available restorative space). Strategic placement of a limited number of dental implants to support and retain an RPD may be the most appropriate option for some patients. Unfortunately, there seems to be a lack of robust clinical research analyzing treatment outcomes for implant-assisted removable partial dentures (IARPDs). Therefore, Bassetti et al¹⁴⁸ conducted a critical review to assess clinical efficacy and effectiveness of IARPDs by using the outcome measures of implant survival and failure rates, biologic and technical complications, maintenance, and patient satisfaction.

For the period January 1980 to May 2016, a search of the databases Medline (PubMed), Embase (OVID), and the Cochrane Library (CENTRAL) and a manual search of related articles were completed. Initially 2581 articles were identified as relevant to the study subject. After article screening and the application of inclusion and exclusion criteria, 9 studies were included in this review. A quality assessment of these articles was performed to assess the risk of bias and to evaluate heterogeneity.

Overall, 236 IARPDs in 227 patients with 130 in the maxilla and 106 in the mandible were included and analyzed in the 9 studies selected. None of these studies were RCTs, and all studies demonstrated high risk of bias. The mean observation period ranged from 1 to 12.2 years, and only 4 studies included at least 1 control group. The studies reported implant survival rates of 91.7% to 100%, abutment tooth survival rates of 79.2% to 100%, and prosthesis survival rates of 90% to 100%. Peri-implant crestal bone level changes ranged from -0.17 to -2.2 mm. IARPDs were associated with far greater frequency of technical complications and maintenance interventions (for example, clasp adjustment, denture base adjustment, relining, occlusal adjustment, or prosthesis tooth wear replacement) than biologic complications (for example, peri-implant mucositis, peri-implantitis, mucosal/gingival hyperplasia, caries, periodontitis). Only 2 questionnaire-based studies assessed patient satisfaction before and after treatment, and both reported marked improvement. A meta-analysis was not

possible because of substantial heterogeneity in study design.

Limited availability of robust publications related to this review topic precluded scientifically compelling conclusions. Current knowledge regarding efficacy and effectiveness of IARPDs is unfortunately based on scientifically weak evidence. Nonetheless, the authors suggested that preliminary evaluation of available literature indicates the use of IARPDs to be a straightforward and cost-effective treatment that achieves symmetric and substantial prosthesis support and stability with good patient satisfaction. More scientifically robust, well-designed, long-term studies are needed to confirm this conclusion.

Implant fixed prosthodontics

Achieving a passive fit of a multiple implant-fixed prosthodontic restoration is considered important to the long-term biological and mechanical success of the restoration. Achieving a passively fitting multiple implant restoration typically begins with an accurate impression. To assess alternative impression procedures, Alshawaf et al¹⁴⁹ designed an in vitro study to compare the accuracy of printed implant casts fabricated from digital scans made by using 2 intraoral scanners with stone casts fabricated from conventional impressions.

A mandibular stone master cast with Kennedy class II partial edentulism (missing molars and premolars) was fabricated incorporating 2 dental implants (Replace Select RP; Nobel Biocare) in the second molar and second premolar locations with 30 degrees of relative occlusal divergence. Digital scans ($n=10$) were made by using a white light (WL) intraoral scanner (CEREC Omnicam; Dentsply Sirona) and active wavefront sampling technology (AWST) intraoral scanner (True Definition; 3M ESPE). The resulting STL data sets were used to print implant casts. Conventional casts ($n=10$) were produced by using the splinted open tray impression technique, polyether material, and Type IV dental stone. The master cast and all experimental casts were scanned by using a laboratory reference scanner (Activity 800; Smart Optics). STL data sets from the experimental casts were superimposed onto the master cast STL data set, and an inspection software program (Geomagic Control; 3D Systems) calculated root-mean-square error.

The 3 experimental groups (conventional impression, WL intraoral scanner, and AWST intraoral scanner) were compared statistically. The conventional group displayed the lowest 3-dimensional mean deviation ($53.49 \pm 9.47 \mu\text{m}$), followed by the WL group ($108.09 \pm 9.59 \mu\text{m}$) and AWST group ($120.39 \pm 5.91 \mu\text{m}$). One-way ANOVA and Tukey test demonstrated statistically significant differences among all groups ($P < .001$).

The authors concluded that printed casts generated from digital scans of partially edentulous posterior

mandibular arches had inferior accuracy than conventional stone casts fabricated from splinted, open-tray, polyether impressions. The printed casts from the WL intraoral scanner had better accuracy than casts generated from AWST intraoral scans. Again, the authors caution that the presence of saliva, blood, lips, tongue, and cheeks in a clinical setting may influence the results.

Peri-implantitis affects a surprising number of implant patients, up to 45% after 9 years of implant function in some reports. Risk indicators may include poor oral hygiene, history of periodontitis, history of cigarette smoking, and diabetes. Additionally, crown margins within 1.5 mm of the bone and excess intracrevicular cement have also been cited as risk factors. Katafuchi et al¹⁵⁰ expressed the concern that overcontoured restorations, defined as having an excessive emergence angle and/or convex emergence profile, might increase the risk for peri-implantitis. Therefore, they designed a study to analyze cross-sectional data comparing healthy implants with those diagnosed with peri-implantitis to determine the impact of emergence angle and emergence profile on the prevalence of peri-implantitis.

A data set consisting of 96 patients (48 men and 48 women, age range: 34 to 86 years, mean age: 68 years) with 225 implants treated in a university setting from 1998 to 2003 with 10.9 years (mean) follow-up was investigated. All patients presented for follow-up examination immediately before enrollment in the trial. Implants were divided into bone-level and tissue-level groups. Radiographs were analyzed to determine the restoration emergence angles (angle between long axis and emerging restorative surface) and restoration profiles (convex, straight, or concave emerging restorative surface). Peri-implantitis was diagnosed based on bleeding on probing and/or suppuration, 2 mm of detectable bone loss after initial remodeling, and probing depth ≥ 4 mm. Associations between peri-implantitis and emergence angles/profiles were assessed by using generalized estimating equations.

Eighty-three patients with 168 implants met inclusion criteria for radiographic analysis (bone-level group: 59 patients with 101 implants; tissue-level group: 27 patients with 67 implants). The prevalence of peri-implantitis was significantly greater in the bone-level group when the emergence angle was >30 degrees on at least one proximal surface compared with an angle ≤ 30 degrees (31.3% versus 15.1%, $P=.04$). In the tissue-level group, no correlation between peri-implantitis and emergence angle was found. For bone-level implants, a convex profile combined with an emergence angle >30 degrees resulted in a 37.8% prevalence of peri-implantitis, with a statistically significant interaction between emergence angle and emergence profile ($P=.003$).

The authors concluded that an emergence angle >30 degrees appears to be a significant risk indicator for peri-

implantitis and that a convex profile creates an additional risk for bone-level implants, but not for tissue-level implants. For tissue-level implants, neither emergence angle nor emergence profile was associated with an increased prevalence of peri-implantitis. The authors also indicated that this may be the first cross-sectional investigation to assess the relationship between restoration emergence contours and the prevalence of peri-implantitis.

Achieving ideal soft tissue integration around a single implant restoration in the esthetic zone is often challenging, particularly in interproximal areas. It is generally believed that when the vertical distance between the proximal contact point and the bone crest is ≤ 5 mm, the papilla will be available to fill the gingival embrasure. However, the availability of credible data to support this claim has been called into question. To investigate this subject, Rocuzzo et al¹⁵¹ posed the PICO question, "Does the vertical distance from the base of the interproximal contact point to the crest of bone, at a single implant adjacent to teeth, affect the interproximal papilla height."

For the period January 2000 to January 2017, a search of the databases Medline (PubMed), Embase (OVID), and the Cochrane Library (CENTRAL) and a manual search of related articles were completed. Targeted were human trials that included 10 or more patients, with at least 12 months follow-up, who received an implant-supported restoration of a maxillary incisor, canine, or premolar in the esthetic region. Inclusion criteria dictated that studies had to provide both radiographic and clinical data regarding the distance between the interproximal bone levels and the base of prosthetic contact points. Initially 157 articles were identified as relevant to the study question. After article screening and the application of inclusion and exclusion criteria, 12 publications were included in this review (0 RCT, 3 retrospective trials, 6 prospective trials, and 3 cross-sectional clinical studies).

The 12 publications included 485 patients (age range: 18-78 years) and 531 implants from various manufacturers. Less than half of the studies addressed or accounted for smoking habits, and 9 of 12 did not report the patients' periodontal status. Most studies reported on bone-level implants, while one addressed both bone-level and tissue-level implants. The timing of load application varied among reports. All studies used peri-apical radiographs for assessment; however, measurement reference points differed among the studies.

The results appeared to indicate that when vertical distance between the interproximal bone level and the base of the prosthetic contact point ranged from 2 to 11 mm, partial (half or more) or complete papilla fill (Jemt Papilla Index¹⁵² score 2-3) was observed in 56.5% to 100% of cases.

The authors concluded that the vertical distance from the base of the interproximal contact point to crest of bone seems to affect the interproximal papilla height. That is, the shorter this distance, the greater the percentage of papilla fill. Of the many clinical factors reported to influence papilla height (for example, integrity of adjacent PDL, implant diameter, implant collar, implant-tooth distance, prosthetic connection, facial-palatal position, bone thickness, tooth morphology and position, and gingival bio-type), this review suggests that complete embrasure fill between an implant restoration and the adjacent tooth seems to correlate with integrity of the adjacent periodontal ligament. Therefore, to reduce the risk of esthetic failures, interproximal probing on the adjacent teeth is encouraged before implant placement.

The authors expressed concern that a variety of nonstandardized bone measurement reference points are currently being used in the literature, including bone peak, bone level at adjacent tooth, defined reference point, and bone level at implant. Additionally, one of the most critical radiographic measurement issues is the precise location of the interproximal contact point. This identification is confounded by the varying radiolucent nature of ceramic materials. As a consequence of these metrological heterogeneities, it remains impossible to combine data for statistical evaluation.

Prosthetic materials

Recently, monolithic zirconia was reported to be the most prescribed material for posterior single crowns, and lithium disilicate the most prescribed material for anterior single restorations. Dentists appear to favor the desirable mechanical properties of zirconia (3 mol% yttria-stabilized tetragonal zirconia polycrystal or 3Y-TZP) and the esthetic translucency of lithium disilicate. With the development of 5 mol% yttria-stabilized zirconia polycrystal (5Y-ZP, referred to as "translucent zirconia"), the possibility of forming a material with the strength of zirconia and the translucency closer to that of lithium disilicate now exists. To evaluate this claim, Kwon et al¹⁵³ compared the flexural strength, translucency parameter, bond strength, and enamel and material wear of 5Y-ZP (Katana UTML) to those of 3Y-TZP (Katana HT) and lithium disilicate (e.max CAD) by using an *in vitro* protocol.

Three-point bend flexural strength bar specimens ($n=10$, $25 \times 4 \times 2$ mm) were sectioned, sintered or crystallized, polished, and loaded to failure in a universal testing machine at 1 mm/min. Translucency specimens ($n=10$, 1 mm thick) were fabricated. Their $L^*a^*b^*$ values were obtained against a black-and-white background by using a spectrophotometer (CM-700d; Konica Minolta), and ΔE_{00} was calculated.

Shear bond strength specimens ($n=10/\text{group}$) were prepared by sectioning ceramic into blocks, sintering or crystallizing, and polishing. Lithium disilicate specimens were etched (IPS Ceramic Etching Gel; Ivoclar Vivadent AG). Zirconia specimens were airborne-particle abraded (10 sec, 50 μm alumina, 0.2 MPa). A primer containing silane and MDP (CLEARFIL Ceramic Primer; Kuraray Dental) was applied to pretreated surfaces. A Tygon tube (internal diameter: 1.5 mm) filled with resin cement (PANAVIA SA) was fixed to ceramic surfaces and light polymerized. After 1 or 150 days of water storage, the resin cement was debonded in a macroshear test.

Ceramic wear specimens ($n=8$) were prepared by sectioning ceramic into blocks, sintering or crystallizing, and polishing with 1200-grit silicon carbide paper. Enamel specimens ($n=8$) were obtained from flat labial enamel surface of freshly extracted maxillary central incisors. Opposing enamel cusps (antagonists) were prepared from the mesobuccal cusps of extracted caries-free mandibular molars standardized to cones (diameter=5 mm, height=2 mm) with rotary instrumentation. Wear testing was performed (20 N, 300 000 cycles, in 33% glycerin) by using a wear machine in the University of Alabama at Birmingham. Volumetric wear of zirconia, lithium disilicate, enamel, and opposing enamel were subjected to contact measurement profilometry.

The results revealed no significant differences between bond strengths ($P=.155$) or the opposing enamel wear ($P=.533$) for the ceramics tested. Significant differences were found between flexural strengths ($P<.001$, e.max LT<5Y-ZP<3Y-TZP) and translucency parameters ($P<.001$, 3Y-TZP<5Y-ZP<e.max LT<e.max HT). No wear was detected on zirconia materials, while wear on enamel was less than wear on e.max LT.

The authors concluded that 5Y-ZP lies between 3Y-TZP and lithium disilicate in terms of flexural strength and translucency. With the application of MDP-containing primer and when treated according to manufacturer's recommendations, both short-term and long-term bond strengths of 5Y-ZP and 3Y-TZP were similar to those of lithium disilicate. No measurable material wear was demonstrated by 5Y-ZP, and wear on opposing enamel was similar to that associated with other materials tested. The authors recommended that future studies be conducted to compare the strength and durability of these materials in clinically relevant environments, geometries, and bonding conditions. Such studies will help to determine minimum restoration dimensions and optimal bonding protocols for 5Y-ZP.

The prevalence of metal allergies in dentistry is low but may rise to the level of concern when susceptible individuals contact specific metal alloy elements, such as nickel, palladium, chromium, cobalt, and tin. Titanium is considered minimally allergenic due to its inherent chemical stability, low erosive potential, and high

biocompatibility. However, suspected cases of titanium allergy have been reported and are of concern to the dental community for obvious reasons. To clarify the relationship between titanium allergy and dental implants, Hosoki et al¹⁵⁴ presented a detailed discussion of patients who suffered allergic symptoms after receiving dental implants.

Two hundred seventy patients (61 male and 209 female, age range: 7-85 years, mean age: 54 years) who visited the Dental Metal Allergy Clinic at Tokushima University Hospital with a tentative diagnosis of dental metal allergy from April 2010 to March 2014 comprised the cohort for this cross-sectional observational study. Patch testing with 28 types of metal allergens was undertaken. These allergens were specifically selected to match the main elements of alloys typically used in dentistry and included 4 titanium allergens.

The results indicated that 217 patients (80.4%) exhibited allergy-positive reactions to at least 1 of the 28 metal allergens. Mercury, palladium, chromium, and nickel exhibited the highest prevalence of allergy-positive reactions. Sixteen patients (7 men and 9 women, age range: 57-79 years, mean age: 65 years) presented with allergic symptoms after receiving dental implants. Eleven of those patients (68%) exhibited allergy-positive reactions to at least one of the metal allergens, and 4 patients exhibited allergy-positive reactions to titanium allergens. Patients with dental implants displayed a significantly greater prevalence of reaction to tetrachloride titanium (TiCl_4 , $P=.01$) than patients without implants. The total number of allergy-positive reactions for titanium allergens among all 270 patients was 17 (6.3%). No patient exhibited a positive reaction only for the titanium allergen.

The authors concluded that the prevalence of allergy-positive reactions to titanium allergens was lower than that for other metal allergens but also that titanium allergy does exist. Therefore, it was suggested that an examination, specific for metal allergens, be performed for potential dental implant patients with a history of metal hypersensitivity.

Cobalt-chromium (Co-Cr) alloys possess excellent mechanical properties, corrosion resistance, and biocompatibility and are increasingly used for metal-ceramic and implant-supported restorations in prosthodontics. Co-Cr alloy prostheses may be fabricated by using several processes, including conventional lost-wax casting (CAST), computer numerical controlled (CNC) milling, and selective laser melting (SLM). The mechanical properties of Co-Cr alloys are strongly associated with materials' microstructure, which varies according to the manufacturing technique. Limited information is available regarding the variability of microstructure and mechanical properties of dental Co-Cr alloys prepared by using different laboratory processes. In

an effort to better understand this variability and to provide basic information on material preparation and clinical applications, Zhou et al¹⁵⁵ conducted an in vitro investigation addressing the microstructures and mechanical properties of dental Co-Cr alloys fabricated by using CAST, CNC, and SLM technologies.

Each group (n=6) of 50-mm-long, Co-Cr alloy, dumbbell-shaped specimens (reduced section: 25×5×2 mm; gauge length 20 mm) was fabricated by using CAST, CNC, and SLM techniques. For each technique, the commercial alloy used was Wirobond 280 (CAST, BEGO GmbH), Gialloy CB Blank (CNC, BK Giulini GmbH), and Wirobond C+ (SLA, Bego GmbH).

Mechanical properties were evaluated by tensile testing (ISO Standard 6892), including 0.2% yield strength, ultimate tensile strength, elongation, and fracture analysis. Microhardness was measured via Vickers hardness. Specimen microstructure was evaluated by metallurgical microscopy, X-ray diffraction, and scanning electron microscopy.

The results indicated that the SLM microstructure exhibited homogeneously distributed fine grains, dispersed second-phase particles, and few defects. SLM X-ray diffraction showed a predominant α -Co phase, minimal ϵ -Co phase, and no harmful needle σ phase. SLM mean 0.2% yield strength was 790 ±11 MPa and ultimate tensile strength was 1072 ±18 MPa. These values exceeded those of CAST and CNC groups by approximately 50% ($P<.05$). The SLM group showed the highest microhardness (475.3 ±10.2 HV), followed by CNC (325.2 ±17.8 HV) and CAST (323.7 ±27.2 HV) groups. Additionally, SLM ductility and toughness were better than those of the other groups. No significant differences in mechanical performance between CNC and CAST groups were identified ($P>.05$).

The authors concluded that the microstructure and mechanical properties of Co-Cr dental alloys were indeed dependent on the fabrication techniques. SLM specimens exhibited 50% higher strength, 40% greater microhardness, and improved ductility and toughness when compared with CNC and CAST specimens. The authors emphasized that improvement in mechanical properties of this important dental alloy is significant because of its wide application in dentistry. For example, a high 0.2% yield strength can prevent permanent deformation of a restoration, especially in a fixed partial denture framework.

PERIODONTICS, ALVEOLAR BONE, AND PERI-IMPLANT TISSUES

This year's review covered topics relating to the assessment, prevalence, and treatment regimens of periodontal disease; systemic health conditions affecting the periodontium; medication-related osteonecrosis of the jaw

and bone biology; periodontal regeneration; soft tissue health and procedures adjacent to teeth and implants; alveolar ridge preservation and alveolar bone augmentation techniques; and peri-implant diseases.

Periodontal disease prevalence, etiology, and treatment

In 2017, the World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions developed new case definitions and established a systematic methodology for the classification of these diseases.¹⁵⁶ Their goal was to review evidence and rationale for a revision of the current classification and to provide a framework for case definition that can be implemented in clinical practice, research, and epidemiologic surveillance. The periodontitis case definition system is based on staging and grading. Stage I to IV of periodontitis is defined based on severity (primarily periodontal breakdown with reference to root length and periodontitis-associated tooth loss), complexity of management (pocket depth, infrabony defects, furcation involvement, tooth hypermobility, masticatory dysfunction), and the extent (localized or generalized). The grade of periodontitis is estimated with direct or indirect evidence of progression rate in 3 categories: slow, moderate, and rapid progression (grade A–C). The use of pretreatment attachment level measures and radiographs is now essential in the establishment of a grade assessment. Risk factor analysis is used as grade modifier. This system is believed to be a distinct improvement on prior classification systems as the rate of progression of the disease is now taken into consideration.

Aggressive periodontitis (AgP) is characterized by an early age of onset, high rate of disease progression, and absence of systemic diseases that compromise the host. If left untreated, it can lead to early tooth loss. These patients have a hyper-inflammatory response. Studies have shown that the subgingival microbiota can affect the gene expression in the adjacent gingival tissues of patients with periodontitis. Gene expression profiles of gingival tissue adjacent to the periodontal pocket or gingival sulcus may reflect the inflammatory process activated by subgingival microbiota rather than biologic differences. Therefore, the examination of the host response must include an examination of the gene expression profiles of tissues, which have not been affected by subgingival microbiota. Taiete et al¹⁵⁷ compared gene expression profiles of patients with a history of generalized AgP (GAgP) and chronic periodontitis (CP) with those of patients who had not experienced any destructive periodontitis (H), through transcriptomic analysis of healthy gingival tissues from edentulous sites by using microarray and quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis. Healthy gingival tissue from edentulous

sites was obtained from GAgP (n=12), CP (n=12), and H (n=12) patients. Genes that were differentially expressed and showing a significant role on altered pathways were validated by qRT-PCR analysis on 12 specimens per group. Natural killer cell receptors and other genes related to the immune system were upregulated in GAgP, while genes with functions in neural processes and in proliferation or differentiation of keratinocytes were underexpressed. CP was characterized by the increased expression of genes related to responses to external stimuli and an underexpression of immune system-related genes. This study demonstrated differences in the transcriptome of healthy gingival tissues from edentulous sites from GAgP when compared with that of patients with H or CP. These findings validate clinical impressions that patients with aggressive periodontitis present with more periodontal tissue destruction despite minimal biofilm accumulation.

Epidemiological studies have associated chronic periodontal inflammation with an increase in the incidence of vascular disease. The mechanism for this association is not entirely clear. *Porphyromonas gingivalis* (Pg), a pathogen intimately associated with the onset and progression of periodontitis, can activate platelets, thus linking periodontal disease with vascular stasis. Wild-type Pg strains are characterized by major genetic heterogeneity, and the commonness of platelet-activating Pg strains in patients with periodontitis is unknown. Jockel-Schneider et al¹⁵⁸ evaluated the platelet-activation capacity of wild-type Pg isolates sampled from patients with aggressive periodontitis to study their effect on platelet aggregation. The extent and velocity of platelet aggregation were determined by light transmission aggregometry. Platelet surface expression of P-selectin was measured by flow cytometry, activation of p38 MAP kinase, and protein kinase C by Western blot by using phospho-specific antibodies. Pg isolates displayed high variability regarding extent and velocity of platelet activation, as well as the involved activating pathways. Of clinical importance was that some isolates induced platelet aggregation even in the presence of potent therapeutic platelet inhibitors. Chronic bacteremia involving specific, platelet-activating Pg strains may constitute a substantial hazard for the integrity of cardiovascular health even with patients who are taking anticoagulants.

The use of lasers in the treatment of periodontitis remains controversial. A recent systematic review by Chambrone et al¹⁵⁹ involved a best evidence review assessing the efficacy of infrared laser therapy. Randomized clinical trials (RCTs) with a follow-up duration ≥ 3 months that evaluated root surface debridement to laser therapy alone or to laser therapy plus treatment of adult patients (aged ≥ 18 years) with moderate to severe aggressive or chronic periodontitis

were considered eligible for inclusion. Of the 475 potentially eligible articles, 28 were included in the review. Individual study outcomes and 7 sets of meta-analysis (1 for the nonsurgical treatment of AgP and 9 for nonsurgical and surgical treatment of CP) showed a benefit of laser therapy in improving clinical attachment level (CAL) and probing depth (PD). However, the comparative differences in clinical outcomes were modest (<1 mm), and the level of certainty for different therapies was considered to range from low to moderate. In patients with moderate to severe periodontitis, the nonsurgical treatment of AgP and CP by SRP plus infrared diode laser and the surgical treatment of CP by Er:YAG laser therapy alone may promote statistically significant improvements in PD and CAL. However, these gains are relatively small (<1 mm) and provide modest clinical relevance compared with SRP alone. It is important to note this systematic review focused on nonsurgical, that is, no elevation of a surgical flap, use of laser therapies in comparison to SRP therapies.

Local delivery of statins, such as simvastatin, as an adjunctive therapy to SRP, has been shown to be effective. Ambrosio et al¹⁶⁰ conducted a systematic review of the use of statins with SRP therapies. This review evaluated if adjunctive local delivery of statins is more effective than SRP alone. Randomized clinical trials that presented a test group evaluating local delivery of statins as adjuncts in healthy, diabetic, and smoking patients were included. Medline and the Cochrane library databases were searched up to November 2016. Most of the trials reported additional clinical benefits in the groups that were treated with adjunctive local delivery of statins. Pooled calculations showed that local delivery of statins resulted in additional reduction of pocket depth and clinical attachment gain in healthy people, smokers, and patients with diabetes. Local statins may offer additional clinical benefits to SRP, even in smokers and diabetics.

Another nonsurgical therapy that seems to demonstrate advantages over traditional SRP therapies is photodynamic therapy. Chambrone et al¹⁶¹ conducted a systematic review that evaluated the efficacy of antimicrobial photodynamic therapy (aPDT), as an adjunct to nonsurgical or surgical therapy. The principles of aPDT involve the use of a nontoxic light-sensitive dye called a photosensitizer (PS) combined with harmless visible light (low energy) of the appropriate wavelength to match the absorption spectrum of the PS. This procedure stimulates the dye to form free radicals of singlet oxygen that will act as toxic agents to the bacteria/cell. Randomized controlled trials (RCTs) with a follow-up duration ≥ 3 months that evaluated SRP versus SRP plus aPDT for the treatment of adult patients with CP, AgP, or peri-implantitis were eligible for inclusion. Of 729 potentially eligible articles, 28 articles (26 studies) were included in the review. Individual study outcomes and 4

sets of meta-analysis showed a potential statistically significant benefit of aPDT in improving the clinical attachment level (CAL) (nonsurgical treatment of AgP) and probing depth (PD). However, the comparative differences in clinical outcomes were modest (<1 mm), and the level of certainty for different therapies was considered to range from low to moderate. The authors concluded that aPDT may provide similar clinical improvements in PD and CAL when compared with conventional periodontal therapy for both patients with periodontitis and peri-implantitis.

Patients sometimes present with the need for both periodontal and orthodontic therapies. Traditionally, periodontal therapies aimed at the resolution of the inflammatory lesion(s) were performed before orthodontic therapy was initiated. Zasciurinskiene et al¹⁶² examined the validity of the assumed order of therapies. They compared 2 treatment strategies regarding the effect of orthodontic treatment on periodontal status in patients with plaque-induced periodontitis. Fifty periodontal patients were randomly assigned to the test or control groups according to periodontal treatment timing. All patients received supragingival and subgingival debridement after baseline examination. The control group patients received cause-related periodontal treatment before the start of orthodontic treatment, and this was performed simultaneous to orthodontic treatment for the test group patients. They found no difference between the test and control groups regarding the change of the CAL after periodontal-orthodontic treatment. However, fewer sites with an initial pocket depth (PD) of 4 to 6 mm healed after periodontal-orthodontic treatment in the test group (20.5%) in comparison with controls (30.4%). Anterior teeth and teeth in male patients had a greater chance for PD improvement ≥ 2 mm. As expected, the total periodontal-orthodontic treatment duration was significantly longer for the control group. Both groups showed a gain of CAL and a reduction in sites with PD of ≥ 4 mm. This study supports the simultaneous use of orthodontic treatment and the periodontal treatment in sites with moderate PD in the routine treatment of patients with plaque-induced periodontitis.

Relationships between periodontal and systemic health

Evidence for psychological stress as a risk factor for periodontitis has been inconclusive as many studies rely on either questionnaire-based input or biomarker studies. Haririan et al¹⁶³ studied the brain-derived neurotrophic factor, substance P, vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), calcitonin gene-related peptide, and adrenomedullin as well as cortisol in saliva and serum in patients demonstrating periodontal health and those with periodontal disease with different aspects

of stress. Fifty-six patients with aggressive and chronic periodontitis and 44 healthy controls were screened by ELISA and mass spectrometry for the presence of neuropeptides and cortisol in saliva and serum. Psychological stress was evaluated by using validated questionnaires. All substances were explored for a possible relationship to periodontitis, clinical parameters, and stress. This study demonstrated that only VIP and NPY were in significantly higher levels in the saliva but not in the serum of patients with periodontitis. These neuropeptides correlated with the extent, severity, and bleeding on probing scores in patients with periodontitis. The enhanced release of these neuropeptides was limited to saliva and was independent of stress levels or coping strategies. Future detection of these markers in the saliva may aid in the diagnosis of active periodontal disease.

Cross-sectional studies have shown that cognitive impairment (CI) and Alzheimer disease (AD) have been associated with periodontal disease. Studies using an animal model of periodontitis and human postmortem brain tissues from participants with AD strongly suggest that a gram-negative periodontal pathogen, *Porphyromonas gingivalis* (Pg) and/or its product gingipain, is/are translocated to the brain. Ilievski et al¹⁶⁴ tested the hypothesis that repeated exposure of mice to orally administered Pg results in neuroinflammation, neurodegeneration, microgliosis, astrogliosis, and formation of intracellular and extracellular amyloid plaque and neurofibrillary tangles (NFTs) which are pathognomonic signs of AD. Experimental chronic periodontitis was induced in 10 mice by repeated oral application, and another 10 mice received vehicle alone (control group). Brain tissues were collected, and the presence of Pg was determined by immunofluorescence (IF) microscopy, confocal microscopy, and quantitative PCR (qPCR). The hippocampi were examined for signs of neuropathology related to AD: Pg was detected in the hippocampi of mice in the experimental group by immunohistochemistry confirming the translocation of orally applied Pg to the brain. Pg was localized intranuclearly and perinuclearly in microglia, astrocytes, and neurons and was evident extracellularly. In addition, microgliosis and astrogliosis were evident in the experimental group but not in the control group. Neurodegeneration was evident in the experimental group based on a fewer number of intact neuronal cells. Finally, phospho-Tau (Ser396) protein was detected, and NFTs were evident in the experimental group but not in the control group. Although this animal study has limitations, it is the first to show neurodegeneration in young adult WT mice after repeated oral application of Pg. The neuropathological features observed in this study strongly suggest that low-grade chronic periodontal pathogen infection can result in the development of neuropathology that is consistent with that of AD.

The association between alcohol consumption and periodontitis has not been defined. Gay et al¹⁶⁵ conducted an examination of a large database to assess the association between alcohol consumption and periodontitis. A total of 7062 adults, aged 30 years or older, who participated in 2009-2010 and 2011-2012 cycles of the National Health and Nutrition Examination Survey (NHANES) were the study participants. Alcohol consumption measurement included self-reported average number of alcoholic drinks per week over the previous 12 months and was categorized into 4 groups (0, <1, 1-8, and ≥ 8 drinks per week). Participants were categorized by using surveillance case definitions for periodontitis, which included both clinical attachment level (CAL) and periodontal probing depth (PD) measurements. The association between alcohol consumption and chronic periodontitis was evaluated by multivariable regression analyses adjusting for age, sex, race/ethnicity, education level, income-to-poverty ratio, smoking, self-rated overall oral health, and HbA1c. The odds ratio (95% confidence interval) of having severe periodontitis was 1.9 (1.2-3) among participants who reported alcohol consumption of ≥ 8 drinks compared with participants consuming some alcohol but <1 drink per week on average. Participants who consumed ≥ 8 drinks per week, on average, also had higher mean PD, percentage of sites with PD ≥ 4 mm, mean CAL, and percentage of sites with CAL ≥ 3 mm than participants reporting consumption of <1 drink per week. The authors concluded that alcohol consumption was associated with an increase in the likelihood of having periodontitis, particularly severe periodontitis.

Rheumatoid arthritis (RA) has also been associated with the incidence of periodontal disease. Often, these patients are being treated with immunosuppressive medications, which may exacerbate the extent of the periodontal destruction. Ziebolz et al¹⁶⁶ conducted a cross-sectional study, investigating the clinical periodontal findings as well as prevalence of selected potentially periodontal pathogenic bacteria in patients with RA treated with different immunosuppressive rheumatic medications. They examined 168 patients with RA taking different immunosuppressive medications. Subgroups were developed according to medication taken in the past 6 months, to include nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids combined, and the following different disease-modifying antirheumatic drugs (DMARDs): (1) methotrexate designated MTX; (2) leflunomide; (3) MTX and TNF-alpha antagonists combined; (4) interleukin-6, designated IL-6, antagonist; (5) MTX and rituximab combined, and (6) combination therapies of more than 2 of these DMARDs. Periodontal examination consisted of papilla bleeding index (PBI), periodontal status with periodontal probing depth

(PD), bleeding on probing (BOP), and clinical attachment loss (AL). Periodontitis was classified as none/mild, moderate, or severe. Samples obtained from gingival crevicular fluid were analyzed for the presence of 11 periodontal pathogenic bacteria. The authors demonstrated that patients undergoing MTX plus TNF-alpha antagonists therapy showed higher PBI and BOP values than leflunomide and higher BOP than MTX plus rituximab. *Porphyromonas gingivalis*, *Treponema denticola*, *Fusobacterium nodatum*, and *Capnocytophaga* species were associated with the medication subgroup. RA medication is associated with periodontal inflammation, without differences in periodontal disease severity. They also identified that the combination of MTX plus TNF-alpha shows an increased potential to periodontal inflammation. Close evaluation of the periodontal status and frequent supportive periodontal recall appointments are indicated with these RA patients.

According to the World Health Organization, Global Report on Diabetes, the number of individuals with diabetes worldwide has quadrupled from 108 million in 1980 to 422 million in 2014, which is largely due to the increase in overweight and obesity. In 2014, over 1.9 billion adults were overweight, and over 600 million were obese. Obesity, especially abdominal obesity, has been associated with insulin resistance (IR), a precursor of type 2 diabetes, and with periodontitis. Andriankaja et al¹⁶⁷ evaluated whether insulin resistance (IR) predicts the risk of oral inflammation by assessing the number of sites with bleeding on probing (BOP) and number of teeth with probing pocket depths (PPDs) ≥ 4 mm and BOP. The authors examined the data on 870 overweight or obese diabetes-free adults, aged 40 to 65 years, from the San Juan Overweight Adults Longitudinal Study over a 3-year period. Baseline IR, assessed using the Homeostasis Model Assessment of IR (HOMA-IR) index, was divided into tertiles. BOP was assessed at buccal and lingual sites, and PPD at 6 sites per tooth. Negative binomial regression was used to estimate the risk ratios (RRs) for oral inflammation adjusted for baseline age, sex, smoking status, alcohol intake, education, physical activity, waist circumference, mean plaque index, and baseline number of sites with BOP or number of teeth with PPD ≥ 4 mm and BOP. The potential impact of tertiles of serum TNF-alpha and adiponectin on the IR-oral inflammation association was also assessed in a subsample of 597 participants. Participants in the highest HOMA-IR tertile at baseline had significantly higher numbers of sites with BOP and number of teeth with PPD ≥ 4 mm and BOP at follow-up than individuals in the lower 2 HOMA-IR tertiles. IR or prediabetes significantly predicts gingival and/or periodontal inflammation in this population.

When addressing the periodontal needs of the patient with diabetes, adequate glycemic control has long been a goal of treatment. Likewise, it has been suggested that local periodontal therapies may be an adjunct for maintaining good glycemic control. Vergnes et al¹⁶⁸ conducted a study assessing whether periodontal treatment can lead to clinical glycemic control and quality of life improvements in metabolically unbalanced diabetic patients (type 1 or type 2) diagnosed with periodontitis. In this open-labeled RCT, diabetic participants (n=91) were given “immediate” or “delayed” periodontal treatment (complete-mouth nonsurgical scaling and root planing, systemic antibiotics, and oral health instructions). The main outcome was the effect on glycated hemoglobin (HbA1C) and fructosamine levels. The General Oral Health Assessment Index and the SF-36 index were used to assess quality of life (QoL). Periodontal health significantly improved after periodontal treatment as expected, but unfortunately, periodontal treatment had no significant effects on glycemic control based on HbA1C and fructosamine levels. There was no obvious evidence of improvement in general QoL after periodontal treatment. However, there was a significant improvement in oral health-related QoL.

Platelets and their activation state are of pivotal importance to the onset and exacerbation of atherosclerosis. As discussed earlier in this review, patients with periodontitis show elevated platelet activation. As it is currently unknown whether periodontal treatment reverses platelet hyperreactivity, Laky et al¹⁶⁹ investigated the role of periodontal treatment on platelet activation. In a prospective controlled therapeutic trial, 52 patients were enrolled and randomly selected for periodontal treatment or monitored without treatment for 3 months. Patient’s blood was analyzed by flow cytometry for platelet activation markers and for platelet aggregation in response to prothrombotic stimuli. Platelet activation in the control group aggravated over the observation period of 3 months, whereas patients who underwent periodontal treatment showed unchanged levels of platelet activation, measured by surface expression of CD62P, CD40L, generation of reactive oxygen production, activation of GPIIb/IIIa, and fibrinogen binding. Moreover, platelet turnover, measured by platelet RNA content and platelet aggregation in response to collagen, differed significantly between patients who were treated and those who were untreated. This finding is significant as it demonstrates subgingival debridement reduces the risk of aggravated platelet activation and therefore might potentially diminish subsequent diseases such as cardiovascular disease in periodontal patients. It is possible that if a patient is currently taking an antithrombotic medication, their dose may be lowered as a result of improved periodontal health. However, more studies are indicated to support this concept.

Periodontal regeneration

A relatively new approach for periodontal regeneration involves the use of adult mesenchymal stem cells (MSCs). Adult stem cells are undifferentiated cells found in the specialized tissues and organs of adults which can differentiate into multiple, but limited, number of cell lines. Teeth represent an important source of MSCs niche because of their embryogenic origin. MSCs have been isolated from exfoliated deciduous teeth, apical papilla of immature permanent teeth, dental follicle, the periodontal ligament, and the dental pulp. Ferrarotti et al¹⁷⁰ performed a study evaluating if dental pulp stem cells (DPSCs) delivered into intrabony defects embedded within a collagen scaffold would enhance the clinical and radiographic parameters of periodontal regeneration. In this randomized controlled trial, 29 patients with chronic periodontitis presenting with 1 deep intrabony defect and requiring extraction of 1 vital tooth were consecutively enrolled. Defects were randomly assigned to test or control treatments which both consisted of the use of a minimally invasive surgical technique. The dental pulp of the extracted tooth was mechanically dissociated to obtain micrografts rich in autologous DPSCs. Test sites (n=15) were filled with micrografts seeded onto a collagen sponge, whereas control sites (n=14), with a collagen sponge alone. Clinical and radiographic parameters were recorded at baseline, 6, and 12 months, postoperatively. The test sites exhibited significantly more probing depth (PD) reduction (4.9 mm versus 3.4 mm), clinical attachment level (CAL) gain (4.5 mm versus 2.9 mm), and bone defect fill (3.9 mm versus 1.6 mm) than controls. Moreover, residual PD <5 mm (93% versus 50%) and CAL gain \geq 4 mm (73% versus 29%) were significantly more frequent in the test group. The application of DPSCs significantly improved clinical parameters of periodontal regeneration and remained stable after one year of treatment.

The minimally invasive surgical technique, known as MIST, has been demonstrated to be effective in controlled surgical and postsurgical clinical environments. De Bruyckere et al¹⁷¹ conducted a study with the primary objective of examining the 5-year clinical outcome of regenerative periodontal therapy (RPT) by using MIST and a collagen-enriched bovine-derived xenograft (Bio-Oss Collagen; Geistlich Pharma North America, Inc) and to identify predictors for clinical attachment level (CAL) gain and vertical radiographic bone (RB) gain. Ninety-five nonsmoking patients with \leq 25% complete-mouth plaque and bleeding, presenting \geq 6 months after initial periodontal therapy with \geq 1 isolated interdental infrabony defect, were recruited. The MIST approach and a collagen-enriched bovine-derived xenograft were used in all patients. Patients were surgically treated by the same clinician and evaluated by using up to 5 years of follow-up. Multivariate analyses were used to identify predictors for

CAL gain and RB gain. Before surgery, the mean probing depth (PD) was 7.8 mm, CAL was 10.0 mm, and defect depth amounted to 5.2 mm. Seventy-one patients were available for evaluation at 5 years. Mean PD reduction was 3.3 mm, CAL gain was 3.0 mm, and RB gain was 57%. Forty-five percent showed ≥ 4 mm of CAL gain, whereas 24% were considered failures (≤ 1 mm of CAL gain). Forty-eight percent showed considerable RB gain ($\geq 75\%$). Regression analyses showed that plaque was a significant predictor for CAL gain and RB gain. Patient compliance had a significant impact on RB gain. Owing to the high failure rate seen with patients who demonstrated poor compliance, only patients with perfect oral hygiene and excellent compliance should be considered for RPT.

Bone grafts, or artificial bone, are commonly used for alveolar bone regeneration therapy. These therapies usually require surgical procedures, which are associated with patient morbidity. The development of alveolar bone regeneration techniques that do not require surgical procedures is a therapeutic ideal. It is well documented that bone morphogenetic protein (BMP) strongly induces differentiation of mesenchymal stem cells (MSCs) into bone cells. The most common application of recombinant BMP protein is in bone induction that requires biomaterial-based carriers via a surgical approach. Gene therapies are an alternative to surgical interventions. Gene therapies transfer, or infect, DNA into the host tissue and recruit the cellular machinery of the cell to produce the protein prescribed by the DNA. A common way of introducing this DNA is by the use of a virus as the vector of transmission. Animal studies have been carried out attempting to deliver the BMP-2 gene to skeletal muscles of rats by using an adenoviral expression vector. Unfortunately, the BMP-2 adenoviral gene expression vector induced an immune response, thus failing to induce ectopic bone formation. A model of ectopic bone formation in skeletal muscles of rats was constructed by using a BMP-expressing nonviral plasmid vector via *in vivo* electroporation. In this technique, an electrical current facilitates the gene transfer. Kawai et al¹⁷² conducted a study that uses this technology and is based on the concept that exogenous BMPs derived by gene transfer into periodontal tissues can promote differentiation of the endogenous MSCs into osteogenic cells. They hypothesized that transfer of the BMP-2/7 gene into periodontal tissues via *in vivo* electroporation induces exogenous BMP production and induces stem cells in the periodontal tissues to differentiate into osteogenic cells, enabling the generation of new alveolar bone. The BMP-2/7 gene expression vector was introduced via electroporation into the target site in the periodontal tissues of the first molar of the rat maxilla. Exogenous BMP-2 and -7 were detected in the target areas, and the growth of new alveolar bone tissue was

observed 5 days after gene transfer. On day 7, the new alveolar bone tissues were found to connect to the original bone tissues. Moreover, the mineral apposition rates of the alveolar bone after BMP-2/7 gene transfer were significantly higher than those in the control group after lacZ gene transfer. These findings indicate that a combination of the BMP-2/7 nonviral vector and *in vivo* electroporation represents a promising nonsurgical option for alveolar bone regeneration therapy.

Soft tissues adjacent to teeth and implants

The coronally advanced flap (CAF) has long been considered as one of the most predictable and versatile root coverage procedures. However, the long-term stability of the results gained from this procedure has been questioned. Pini Prato et al¹⁷³ examined the long-term outcomes after CAF in the treatment of gingival recession (GR) and explored the tooth- and patient-related factors on the stability of surgical gingival result at 5, 10, and 20 years after surgery. Ninety-four patients with 97 GRs (73 Miller class I and 24 Miller class III) were treated with CAF in a private practice between 1984 and 1996. Recession depth (RD), probing depth (PD), keratinized tissue (KT) width, and patient- and tooth-associated variables were recorded for each GR at baseline, 1 year, 5 years, 10 years, 15 years, and 20 years after surgery. A total of 72 patients with 72 GRs were available for analysis at the 20-year follow-up examination (dropout rate=23.4%). Statistically significant improvements were found for RD at all time points. Little more than a half (56%) of the sites treated with CAF did not display RD changes between the short-term (that is, 1 year) and long-term (that is, 20 years) examinations. Overall, the mean root coverage (MRC) decreased from 68.59% to 56.11%. The achievement of complete root coverage (CRC) 1 year after treatment was associated to GR not presenting interdental tissue loss, the lack of noncarious cervical lesion, an attached KT band ≥ 2 mm, and baseline RD. GR recurrence seemed to be influenced by age, RD at 1-year follow-up, sites displaying an attached KT < 2 mm, and interdental tissue loss. The aging process, the condition of the interdental periodontal tissue, and the presence of an attached KT band < 2 mm seem to be negative factors influencing the stability of the gingival margin during the 20-year observation period.

This same group¹⁷⁴ evaluated the long-term results by using a coronally advanced flap in combination with a subepithelial connective tissue graft (SCTG plus CAF), often considered one of the best and most predictable root coverage procedures. The aim of this study was identical to the previous study examining the CAF alone. Forty-five patients with 45 maxillary GRs (Miller class I or III) were treated with SCTG plus CAF in a private practice between 1990 and 1997. The same outcome

measurements and time frames were used. A total of 21 Miller class I (44.67%) and 24 class III (53.33%) GRs were treated. Considering all the 45 GRs, statistically significant improvements were found for RD in all evaluations compared with baseline data. Over the course of the study, mean root coverage (MRC) decreased from 74.23% (1 year) to 67.69% (20 years). Within maxillary class I defects, complete root coverage (CRC) at 1-year follow-up was 57.14% (n=12) and 47.62% (n=10) at the end of study period, whereas MRC decreased from 82.37% to 77.62%, respectively. Within maxillary class III recessions, CRC of 20.83% (n=5) was found at both 1-year and 20-year follow-ups. However, MRC decreased from 66.55% to 58.18%. The results of logistic regression analysis showed that the achievement of CRC was associated with sites not presenting interdental tissue loss, whereas GR recurrence appeared to be associated with sites with attached KT of <2 mm (that is, 5-, 10-, 15- and 20-year follow-ups), to teeth presenting root steps (that is, 10- and 20-year follow-ups), and smoking (that is, 15-year follow-up). The authors concluded that positive RD reduction and KT improvements achieved by SCTG plus CAF at short term might be preserved for a long term with the majority of the treated sites not displaying relapse of the gingival margin. Teeth lacking a minimal 2-mm width of attached KT and presenting noncarious cervical lesions were more prone to develop an apical shift of the gingival margin during a 20-year follow-up period.

A similar study by Rasperini et al¹⁷⁵ examined the long-term stability of the results obtained in a RCT comparing CAF to SCTG plus CAF. This study examined Miller class I and II defects after 9 years. Twenty-five gingival recessions were randomly treated with CAF plus SCTC or CAF alone. Outcomes included complete root coverage (CRC), recession reduction (REC), keratinized tissue (KT) gain, and dentin hypersensitivity and were evaluated at 6 months, 1 year, and 9 years. The chance to gain and preserve CRC over time is equal to 70% in the CAF plus CTG group. Using the CTG, an increase in KT was recorded 9 years after the surgery. An odds ratio (OR) of 0.12 ($P=.022$) of not achieving CRC was observed in patients with noncarious cervical lesions (NCCLs) compared with patients without NCCL. Both treatment modalities demonstrated stability over time. Additional use of CTG provided a greater increase in KT. As cited in the previous studies, the presence of NCCL negatively affected CRC and REC.

Acknowledging the negative effect of an NCCL on the ability to maintain the long-term result of gingival recession correction procedures, Santamaria et al¹⁷⁶ conducted a study examining the efficacy of combining gingival grafting procedures with a small class V restoration which has been placed presurgically. Forty patients presenting 40 Miller class I or II GR defects associated

with gingival recession and a tooth cervical defect were randomly allocated to one of the following treatments: test group (n=20), partial restoration (PR) of the NCCL, in which the apical border of the restoration was placed 1 mm beyond the cement-enamel junction estimation, and connective tissue graft (CTG plus PR) and control group (n=20), odontoplasty of the NCCL and connective tissue graft (CTG). Clinical, esthetic, and patient-centered outcomes were evaluated. After 12 months, CD coverage rates were 75.3% for CTG plus PR and 74.6% for CTG. The estimated complete root coverage was 60% (n=12) for CTG plus PR and 70% (n=14) for CTG. CTG plus PR resulted in significantly better dentin hypersensitivity (DH) reduction. Both groups resulted in esthetic improvements; however, the CTG plus PR group showed better gingival contour results, albeit subjectively assessed.

The efficacy of root coverage procedures can be correlated to many factors. One of these factors is the extent of the gingival recession into the alveolar mucosa (Miller class III). These defects, especially in the mandibular anterior region, are difficult to treat. Sculean and Allen¹⁷⁷ described a novel surgical technique that addresses the treatment of deep isolated recession defects in the mandibular anterior. This technique is described as the laterally closed tunnel (LCT). A total of 24 healthy patients exhibiting one single deep mandibular Miller class I (n=4), II (n=10), or III (n=10) gingival recession lesion ≥ 4 mm were consecutively treated with LCT in conjunction with an enamel matrix derivative (EMD) and palatal subepithelial connective tissue graft (SCTG). The primary outcome variable was complete root coverage (CRC). The postoperative morbidity was low, and no complications, such as bleeding, infections/abscesses, or loss of SCTG, occurred. At 12 months, CRC was obtained in 17 of the 24 defects (70.83%), while in the remaining 7 defects, RC amounted to 80% to 90% in 6 patients and 79% in 1 patient. With respect to defect type, CRC was found in 3 of the 4 Miller class I, 8 of the 10 class II, and in 6 of the 10 class III defects. This study suggests that the LCT is a valuable approach for the treatment of deep isolated mandibular Miller class I, II, and III gingival recessions.

Establishing a zone of keratinized mucosa (KM) around implants has been associated with less discomfort during brushing and improved esthetic outcomes. This perceived need has been the basis for performing mucogingival procedures adjacent to dental implants. Bonino et al¹⁷⁸ systematically assessed and compared discomfort during brushing, patient's soft tissue esthetic satisfaction, and other clinical parameters between implants with and without KM. They divided patients into 2 groups; group 1 patients had implants surrounded by KM, whereas patients in group 2 had no KM around implants. Patient discomfort during brushing and

esthetic satisfaction was measured by using a visual analog scale and compared between the 2 groups by using a mixed model. Clinical width of KM, probing depth, peri-implant recession, plaque index, and bleeding on probing were compared within and between groups 3 and 6 months after implant restoration. Twenty-four patients (12 in each group) were evaluated at the 3- and 6-month follow-up visits. Patients without peri-implant KM were less satisfied with the esthetics of the soft tissue around their implants. An unexpected finding was that the lack of KM was not associated with discomfort during brushing. In group 1, the width of KM was significantly increased after 6 months, and there was greater recession around implants without KM after 3 months, but not after 6 months. Patients reported that presence or absence of keratinized mucosa did not affect discomfort associated with brushing. Yet, esthetically, patients preferred implants with a zone of keratinized mucosa.

Numerous investigators have shown the positive effect of peri-implant mucosal thickness (PMT) on the maintenance of peri-implant bone levels. Placement of a subepithelial connective tissue graft (sCTG) or collagen matrix graft adjacent to the implant is a documented method that would increase the PMT. Hutton et al¹⁷⁹ investigated the efficacy of an acellular dermal matrix (ADM) as a material for mucosal augmentation. Twenty patients who could benefit from peri-implant mucosal augmentation at the time of implant placement were recruited. Participants were randomized to the control (simultaneous sCTG) or test (simultaneous ADM) group. The primary outcome in this study was changes in PMT between baseline and 16 weeks later. Keratinized mucosal width (KMW) changes, modified wound healing index (MWHI) variations, and patient-reported outcome measures (PROMs) were recorded, as well. There were no statistically significant differences between groups at baseline for any of the parameters analyzed. The gain in PMT at 1 mm, 3 mm, and 5 mm from the expected mucosal margin was 0.44 ± 2.04 mm, 1.20 ± 1.48 mm, and 1.20 ± 0.89 mm, respectively, in the sCTG group, and 0.05 ± 1.57 mm, 0.85 ± 1.29 mm, and 1.45 ± 1.17 mm, respectively, in the ADM group. No statistically significant differences in terms of PMT, KMW, or MWHI changes were observed among groups. However, as expected, the perceived discomfort was higher at 2 and 4 weeks for patients in the sCTG group. ADM should be considered a viable alternative to sCTG for the enhancement of soft tissue thickness if used at the time of implant placement.

The placement of an sCTG in conjunction with immediate implant placement is often dictated by the gingival biotype or the thickness of the gingival tissues before extraction. Zuiderveld et al¹⁸⁰ studied the effect of placing an sCTG and placement of an interim restoration

at the time of immediate implant placement upon the midbuccal mucosal level (MBML). Sixty patients with a failing tooth were provided with an immediately placed implant and interim restoration. During implant placement, patients randomly received either a connective tissue graft from the maxillary tuberosity ($n=30$, test group) or no graft ($n=30$, control group). Follow-up visits were at 1 (T1) and 12 months (T12) after definitive crown placement. The primary outcome measure was any change in MBML compared with the preoperative situation. In addition, gingival biotype, esthetics (using the Pink Esthetic Score-White Esthetic Score), marginal bone level, soft tissue peri-implant parameters, and patient satisfaction were assessed. The mean MBML change at T12 was -0.5 ± 1.1 mm in the control group and 0.1 ± 0.8 mm in the test group. No significant differences regarding other outcome variables were observed, neither was gingival biotype associated with a gain or loss in MBML. This 1-year study showed that connective tissue grafting in single, immediately placed, and interim-restored implants led to less recession of the peri-implant soft tissue at the midbuccal aspect, irrespective of the gingival biotype.

Although the location of the mucosal tissue is a prime endpoint in the evaluation of the esthetic outcome of immediate implant procedures, the volume of residual tissue also has an impact on the esthetic outcome. A subanalysis of the previous study conducted by van Nimwegen et al¹⁸¹ examined the volumetric outcomes of sCTG grafting at the time of immediate implant placement. Using the same patient population, clinical parameters, digital photographs, and conventional impressions were obtained before extraction (Tpre) and at 12 months after definitive crown placement (T12). The casts were digitized by using a laboratory scanner, and a volumetric analysis was performed between Tpre and T12. Twenty-five patients in each group were available for analysis at T12. The volumetric change, transformed to a mean (\pm SD) change in thickness, was -0.68 ± 0.59 mm (test) and -0.49 ± 0.54 mm (control), with a nonsignificant difference between groups. The midfacial mucosa level was significantly different between both groups, with a mean (\pm SD) change of 0.20 ± 0.70 mm (test) and -0.48 ± 1.13 mm (control). The Pink Esthetic Score was similar between both groups. The use of a CTG in immediately placed implants with interim restorations in the esthetic zone did not result in less mucosal volume loss after 12 months, leading to the assumption that a CTG cannot fully compensate for the underlying facial bone loss, although a significantly more coronally located mid-facial mucosa level was found when a CTG was performed. The implications of this study suggest that if no loss of tissue volume is the clinician's goal, augmentation of the bone or the use of a larger connective tissue graft should be considered.

Bone biology and medication-related osteonecrosis of the jaws (MRONJ)

Predicting which patients will develop MRONJ is significant in the treatment of at-risk populations. Soundia et al¹⁸² explored the radiographic appearance of stage 0 MRONJ and examined 5 radiographic parameters (trabecular sclerosis, cortical erosion, periosteal reaction, sequestration, and crater-like defect) as predictors of progression to bone exposure. Twenty-three patients with a history of antiresorptive therapy, no bone exposure, and nonspecific signs and symptoms were included. Intraoral photographs, panoramic, and cone beam computed tomography (CBCT) images at initial visit and follow-up intraoral photographs were reviewed. Three patients had dental disease (DD), 10 patients had stage 0 MRONJ that did not progress to bone exposure (NBE), and 10 patients progressed to bone exposure (BE). Radiographic parameters were scored as absent (0), localized (1), or extensive (2), and their sum formed the composite radiographic index (CRI). The patients with DD demonstrated minimal radiographic findings, and their CRI was significantly lower than that of NBE and BE patients. Additionally, BE patients demonstrated a higher radiographic index than NBE patients. Intriguingly, sequestration was observed in the initial CBCT of 9 (90%) of 10 BE patients, whereas 80% of NBE patients showed absence of sequestration at the initial CBCT examination. CBCT imaging can aid in the differentiation of stage 0 MRONJ from dental disease. Radiographic sequestration at initial presentation can serve as a predictor of future bone exposure in patients with stage 0 MRONJ. The use of CBCT as a screening tool for patients taking antiresorptive drugs (ARDs) can be justified.

Clinicians often counsel patients taking ARD regarding the risk of implant failures or complicated bony healing. Stavropoulos et al¹⁸³ conducted a systematic review exploring the question: "In patients with systemic intake of ARDs, what is the outcome and complication rate of implant therapy including associated bone grafting procedures comparing to patients without systemic intake of ARDs?" Original studies fulfilled predefined inclusion criteria. Various patient-, medication-, and intervention-related parameters (that is, implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, medication-related osteonecrosis of the jaws designated MRONJ, and peri-implantitis) were extracted, and meta-analyses and quality assessment were performed. Twenty-four studies on bisphosphonate (BP) intake (mainly low dose for osteoporosis treatment) and 7 studies on hormone replacement therapy (HRT), including ≥ 10 patients and controls not taking the medication, were identified. Seven studies on MRONJ associated with implants were included. Meta-analyses showed no significant differences in terms of implant loss between patients on BPs

(mainly low dose for osteoporosis treatment) and controls. Furthermore, low-dose BP intake did not compromise peri-implant marginal bone levels. Based on 2 studies, no negative effect of HRT was observed on the implant level, while HRT appeared to exert a marginally significant negative effect regarding implant survival on the patient level and regarding peri-implant marginal bone levels. However, based on 6 studies reporting single-patient data, MRONJ in patients on BP for osteoporosis appeared in 70% of the patients at >36 months after the start of drug intake, while in patients with cancer, MRONJ appeared in 64% of the patients at ≤ 36 months after first BP intake. The authors concluded that low-dose oral BP intake for osteoporosis treatment does not compromise implant therapy. There is little information available on the possible effect of implant therapy of high-dose BPs or other widely used ARDs (for example, denosumab) or on the success or safety of bone grafting procedures. Patients with high-dose ARD intake for the management of malignancies, patients on oral BP over longer periods of time, and patients with comorbidities should be considered as high-risk patients for MRONJ.

In addition to ARD, the use of other systemic medications has been associated with implant failures. Chappuis et al¹⁸⁴ published a systematic review and meta-analysis examining medication-related dental implant failures. Electronic and manual literature searches were conducted. Implant failure was the primary outcome, while biological/mechanical and the causes/timing associated with implant failure were set as secondary outcomes. A final selection of 17 articles was screened for qualitative assessment. Five studies focused on evaluating the association of implant failure with nonsteroidal anti-inflammatory drugs (NSAIDs), 2 on selective serotonin reuptake inhibitors (SSRIs), 2 on proton pump inhibitors (PPIs), 7 on bisphosphonates (BPs), and 1 on antihypertensives (AHTNs). For PPIs, the fixed-effect model estimated a difference of IF rates of 4.3%, indicating significantly higher implant failure rates in the test than those in the control group. Likewise, for SSRIs, the implant failure was shown to be significantly higher in the individuals taking SSRIs, with an estimated difference of 7.5%. No subset meta-analysis could be conducted for AHTN medications. None of the other medications yielded significance. Clinicians considering implant therapy should be aware of possible medication-related implant failures when patients are taking SSRIs or PPIs.

Alveolar ridge preservation, ridge and sinus augmentation

Numerous autologous blood products have been used in dentoalveolar surgery with success. Advanced platelet-rich fibrin (A-PRF) is one such product and recently being used in alveolar ridge preservation procedures. Clark

et al¹⁸⁵ conducted a multiarm parallel randomized controlled clinical trial to evaluate the efficacy of A-PRF alone or with freeze-dried bone allograft (FDBA) in improving vital bone formation and alveolar dimensional stability. Forty patients requiring extraction of nonmolar teeth and replacement with dental implants were randomized into 1 of 4 ridge preservation approaches: A-PRF, A-PRF+FDBA, FDBA, or blood clot. Nontraumatic extractions and ridge preservation were performed. After an average of 15 weeks of healing, bone core samples were harvested at the time of implant placement for micro-CT and histomorphometric analysis. Ridge dimensions were measured immediately after extraction and before implant placement. Significantly greater loss of ridge height was noted in the blood clot group (3.8 ± 2.0 mm) than in the A-PRF (1.8 ± 2.1 mm) and A-PRF+FDBA (1.0 ± 2.3 mm) groups. No significant differences in ridge width reduction were noted between groups. Significantly more vital bone was present in the A-PRF group ($46\% \pm 18\%$) compared with the FDBA group ($29\% \pm 14\%$). This study demonstrates A-PRF alone or augmented with FDBA is a suitable biomaterial for ridge preservation.

Despite the proven efficacy of many ridge preservation procedures, it is not clear what type of extraction sites will benefit the most from such procedures. Tomasi et al¹⁸⁶ examined if the characteristics of the fresh extraction socket site influenced subsequent dimensional alterations and whether or not the placement of deproteinized bovine mineral (BioOss Collagen) in the socket affected volumetric change during healing. Twenty-seven participants and 28 extraction sites were included. Immediately after the removal of the tooth and after 6 months of healing, stone and virtual casts of the jaw were produced. A cone beam computerized tomography scan was obtained immediately after extraction, and the thickness of the buccal bone wall at the extraction site was measured. Extraction sites were randomly assigned to the test or control group. In the test group, extraction sockets were filled with deproteinized bone mineral and covered with a collagen membrane. In the control group, only a collagen membrane was placed. The thickness of the buccal bone wall at the extraction site influenced the amount of volume reduction that occurred. Socket grafting influenced the degree of ridge diminution only at sites where the buccal bone wall was thin (≤ 1 mm). From these data, the use of a preoperative CBCT or bone sounding after tooth extraction may help the clinician decide if a socket grafting procedure is indicated.

Because volumetric changes after tooth extraction are common, lateral ridge augmentation is a common procedure prior or simultaneous to implant placement. Unfortunately, little is known about the dimensional remodeling after healing from lateral ridge augmentation procedures. Elnayef et al⁷⁸ conducted a systematic review

assessing the stability of bone grafting material between augmentation procedures and final healing. An electronic and hand literature search was conducted. Only randomized controlled trials (RCTs) with a mean follow-up of at least 6 months after implant placement aiming to evaluate the stability of grafting material for lateral ridge augmentation were included and quantitatively analyzed. A total of 35 articles were evaluated, with only 17 RCTs meeting the inclusion criteria. The estimated overall mean horizontal bone gain at the time of regeneration was 3.71 ± 0.24 mm, with 4.18 ± 0.56 mm for the block graft technique and 3.61 ± 0.27 mm for guided bone regeneration (GBR). The estimated overall net bone gain at final reevaluation (11.9 ± 7.8) was 2.86 ± 0.23 mm. The estimated mean (\pm SD) resorption after 6 months was 1.13 ± 0.25 mm, with 0.75 ± 0.59 mm for the block graft technique and 1.22 ± 0.28 mm for GBR. Regardless of the material used for regeneration, different degrees of graft resorption should be expected. The resorption of the xenograft group was inferior compared with the combination of xenograft and autologous bone groups. Overcorrection of the horizontal defects should be performed to compensate for the resorption of the grafting materials.

The reported rate of developing soft tissue complications or flap opening, which accompany GBR procedures, varies widely, from 0% to 45%. It is commonly believed that these surgical complications can have a significant impact on the efficacy of the GBR procedure.¹⁸⁷ Lim et al¹⁸⁸ published a systematic review investigating the rate for resorbable versus nonresorbable membranes and the timing of soft tissue complications. Two independent reviewers conducted electronic and manual literature searches in several databases. Overall, 21 and 15 articles were included in the qualitative and quantitative synthesis, respectively. The weighted complication rate of the overall soft tissue complications, including membrane exposure, soft tissue dehiscence, and acute infection/abscess, into the calculation was 16.8%. When considering the complication rate based on the membrane type used, resorbable membrane was associated with a weighted complication rate of 18.3% and nonresorbable membrane, with a rate of 17.6%. Moreover, soft tissue lesions were reported as early as 1 week and as late as 6 months based on the included studies. Soft tissue complications after GBR are very common (16.8%), and the membrane type did not appear to significantly affect the complication rate. Technique sensitivity and the surgical skill of the operator may still be regarded as the main components to influence the success of bone regenerative therapy.

As the addition of autologous blood products improves outcomes in socket graft, these products may also enhance alveolar ridge augmentation. Cortellini et al¹⁸⁹ performed a single cohort observational study

evaluating the outcome of the leucocyte- and platelet-rich fibrin (L-PRF) block for horizontal bone augmentation in the maxilla. The L-PRF block is prepared by mixing a particulated biomaterial with chopped L-PRF membranes at a 50:50 ratio and adding liquid fibrinogen to glue all together. Horizontal augmentation was assessed linearly and volumetrically immediately after surgery and 5 to 8 months later by matching consecutive CBCTs. Ten patients representing 15 sites with horizontal alveolar deficiencies were included. Superimposition of preoperative and posthealing CBCT scans showed an average linear horizontal bone gain of 4.6 mm (± 2.3), 5.3 mm (± 1.2), and 4.4 mm (± 2.3), measured at 2, 6, and 10 mm from the alveolar crest, respectively. The volumetric gain was 1.05 cm³ (± 0.7) on average. Of note is that the resorption rate after 5-8 months was 15.6% (± 6.7) on average. This is less than that described in most GBR procedures.

Schwarz et al¹⁹⁰ described a novel approach for lateral alveolar ridge augmentation. In this technique, the roots of impacted or retained third molars are harvested, trimmed, and fixed to the deficient alveolar ridge before coverage with a collagen barrier. They conducted a study assessing the efficacy and safety of autogenous tooth roots (TRs) compared with autogenous bone blocks (ABs) for lateral alveolar ridge augmentation and 2-stage implant placement. A total of 30 patients in need of implant therapy and lateral ridge augmentation were allocated to parallel groups receiving either (1) healthy autogenous tooth roots (for example retained third molars or impacted teeth) ($n=15$) or (2) cortical autogenous bone blocks harvested from the retromolar area. After 26 weeks of submerged healing, the primary endpoint was defined as the crestal ridge width (mm) (CW26) being sufficient to place an adequately dimensioned titanium implant at the respective sites. Soft tissue healing was uneventful in both groups. CW26 at visit 6 allowed for a successful implant placement in all patients of both groups. Mean CW26 values amounted to 10.06 \pm 1.85 mm (median: 11.0) in the TR group and 9.20 \pm 2.09 mm (median: 8.50) in the AB group, respectively. The difference between both groups did not reach statistical significance. This technique serves as a good alternative to support lateral alveolar ridge augmentation and 2-stage placement.

The increasingly common use of short implants has impacted the need for sinus augmentation procedures. Thoma et al¹⁹¹ reported the 5-year results comparing the implant survival rate between short dental implants and standard-length implants placed in combination with sinus bone grafting. This multicenter study enrolled 101 patients (137 implants) with a posterior maxillary bone height of 5 to 7 mm. Patients randomly received either short implants (6 mm; GS) or long implants (11 to 15 mm) with sinus grafting (GG). Six months later, implants

were loaded with single crowns, and patients were reexamined at 1, 3, and 5 years of loading. At 5 years, 90 patients (124 implants; GS: 60; GG: 64) were reexamined (drop-out rate 10%). Patient-level implant survival rates were 98.5% (GS; 1 implant failure) and 100% (GG; $P=.49$). Mean marginal bone levels were 0.54 mm \pm 0.87 (GS) and 0.46 mm \pm 1.00 (GG). Biological and technical parameters were not significantly different. Both treatment modalities were suitable for implant therapy in the atrophied posterior maxilla revealing no differences in terms of survival rates, marginal bone level changes, patient-reported outcomes, and technical/biological complications. However, it is important to note that the short implants were placed in locations adjacent to natural teeth, and this scenario may have a positive impact on the success rate of the short implants.

Peri-implant health and disease

Many local and systemic factors may influence the incidence of peri-implantitis. Dreyer et al¹⁹² conducted a systematic review and meta-analysis to assess the prevalence, incidence, and risk factors of peri-implantitis. An electronic search was performed to identify publications from January 1980 until March 2016 on 9 databases. Heterogeneity analysis and random-effect meta-analysis were performed for selected potential risk factors of peri-implantitis. The search retrieved 8357 potentially relevant studies. Fifty-seven studies were included in the systematic review. Overall, the prevalence of peri-implantitis on implant level ranged from 1.1% to 85.0% and the incidence from 0.4%, within 3 years, to 43.9%, within 5 years. The median prevalence of peri-implantitis was 9.0% for regular participants of a prophylaxis program, 18.8% for patients without regular preventive maintenance, 11.0% for nonsmokers, 7.0% among patients representing the general population, 9.6% for patients provided with fixed partial dentures, 14.3% for patients with a history of periodontitis, 26.0% for patients with implant function time ≥ 5 years, and 21.2% for patients with implant function time ≥ 10 years. On a medium and medium-high level of evidence, smoking, diabetes mellitus, lack of prophylaxis, and history or presence of periodontitis were identified as risk factors of peri-implantitis. There is medium-to-high level of evidence that patient's age, sex, and maxillary implants are not related to peri-implantitis. Currently, there is no convincing or low level of evidence available that identifies osteoporosis, absence of keratinized mucosa, implant surface characteristics, or edentulism as risk factors for peri-implantitis. However, based on the data analyzed in this systematic review, insufficient high-quality evidence is available to the research question. Very few studies have been designed to evaluate the incidence of peri-implantitis.

Some of the difficulties in determining the true prevalence of peri-implantitis are the lack of an accepted definition of the disease and the validity of biologic diagnostic markers, which accurately correspond to implant survival and peri-implantitis prevalence. Doornewaard et al¹⁹³ evaluated whether commonly used biologic diagnostic parameters correspond to implant survival and peri-implantitis prevalence. Publications from 2011 to 2017 were selected by an electronic search. Prospective and retrospective studies with a mean follow-up time of at least 5 years and reporting prevalence of peri-implantitis as well as mean bone loss and standard deviation were selected. The correlation between reported prevalence of peri-implantitis and reported implant survival, mean follow-up time, mean bone loss, mean probing depth, and mean bleeding on probing was calculated. Mean bone loss and standard deviation were used for estimation of proportion of implants with bone loss exceeding 1, 2, and 3 mm. The overall mean weighted survival rate was 96.9% (89.9% to 100%), and the reported prevalence of peri-implantitis ranged between 0% and 39.7%, based on 15 different case definitions. The overall weighted bone loss was 1.1 mm based on 8182 implants and an average mean loading time ranging from 5 to 20 years. No correlation was found between mean bone loss and the reported prevalence of peri-implantitis. The estimated prevalence of implants with bone loss exceeding 2 mm was 23%. The overall weighted mean probing depth was 3.3 mm, and mean weighted bleeding was 52.2%. Only a weak correlation was found between survival and function time ($r=-0.49$). There was no relation between the probing depth or bleeding and the mean bone loss, mean follow-up time, or reported prevalence of peri-implantitis. Biologic parameters mean probing depth and mean bleeding on probing do not correlate with mean bone loss, irrespective of follow-up. Case definition for peri-implantitis varied significantly between studies indicating that an unambiguous definition based on a specified threshold for bone loss is not agreed upon in the literature. These findings present major difficulties for practicing clinicians as they have the responsibility to diagnose a disease, which has no consistent definition and no accepted clinical parameter for detection. These difficulties may in part explain the wide variation in the prevalence of peri-implantitis.

The influence of undetected submucosal dental cement is commonly thought to be a major risk factor for the development of peri-implantitis. However, what is not clear is the effect of the specific type of cement used with implant restoration. Korsch et al¹⁹⁴ conducted an observational study investigating the impact of 2 different cements on the peri-implant biofilm and inflammation. The suprastructures of 34 patients with cemented fixed implant-supported restorations were revised. A

methacrylate cement (Premier Implant Cement [PIC]), in 20 patients, and a zinc oxide eugenol cement (Temp Bond [TB]), in 14 patients, were used. After revision, TB was used for recementation. During revision and follow-up after 1 year, microbial samples were obtained. Excess cement was found in 12 (60%) of the 20 patients with PIC. Suppuration was observed in 2 (25%) implants with PIC without excess cement (PIC-) and in all 12 (100%) implants with PIC and excess cement (PIC+). Implants cemented with TB had neither excess cement nor suppuration. The taxonomic analysis of the microbial samples revealed an accumulation of periodontal pathogens in the PIC patients independent of the presence of excess cement. Significantly, fewer oral pathogens occurred in patients with TB than in patients with PIC. TB was used in all cases (PIC and TB) for recementation. In the follow-up evaluation, suppuration was not found around any of the implants with PIC-, only around 1 implant with PIC+, and around 1 implant with TB. Bacterial species associated with severe periodontal infections that were abundant in PIC- and PIC+ samples before the revision were reduced after 1 year to levels found in the TB samples. The revision and recementation with TB had a positive effect on the peri-implant biofilm in patients with PIC. This study suggests the type of cement used is a significant factor in the prevalence of peri-implantitis.

The most effective treatment of peri-implantitis and peri-implant mucositis is controversial. The use of dental lasers has been suggested as acceptable treatment modality. Lin et al¹⁹⁵ and the American Academy of Periodontology published a best evidence review on the use of laser therapy for the treatment of peri-implantitis. An electronic search of 3 databases and a hand search of peer-reviewed journals for relevant articles published from January 1980 to June 2016 were performed. Human clinical trials of ≥ 10 patients with peri-implant diseases, treated with surgical or nonsurgical approaches and laser therapy, and a follow-up period of ≥ 6 months were included. From 22 articles selected, 11 were included in the meta-analyses. The outcomes of using lasers as a monotherapy could not be evaluated as no controlled studies were identified. Therefore, all reported results were the outcomes of applying lasers as an adjunct to surgical/nonsurgical treatment. For the nonsurgical approach, WMD of probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI), marginal bone level (MBL), and recession (REC) was 0.15 mm ($P=.50$), -0.10 mm ($P=.32$), 21.08% ($P=.02$), -0.07 ($P=.002$), -0.22 mm ($P=.04$), and -0.11 mm ($P=.34$), respectively. For the surgical approach with a long-term follow up, WMD of PD, CAL, BOP, and PI was 0.45 mm ($P=.11$), 0.22 mm ($P=.56$), 7.26% ($P=.76$), and -0.09 ($P=.84$), respectively. Current evidence shows laser therapy in combination with surgical or nonsurgical therapy provided minimal benefit in PD reduction, CAL

gain, amount of REC improvement, and PI reduction in the treatment of peri-implant diseases. Lasers, when used as an adjunct to nonsurgical therapy, might result in more BOP reduction in short term.

IMPLANT DENTISTRY

Abutment height and prosthetic interface

Blanco et al¹⁹⁶ address the historical recommendation of the Brånemark group to use transmucosal abutments between implant and prosthesis. Here, the authors focus on abutment height (1 and 3 mm) and compare peri-implant marginal bone remodeling over the short term (3 and 6 months after surgery). Twenty-two healthy patients were randomly allocated 2 abutments. Marginal bone levels were measured and correlated to abutment height. At both 3 and 6 months, the marginal bone remodeling was significantly greater in association with 1-mm abutments (0.83 mm and 0.91 mm), as to 3-mm abutments (0.14 mm and 0.11 mm). Given the small sample size, these statistically significant differences speak strongly in favor of taller abutments when considering the amount of early marginal bone loss.

Using a meta-analytical approach, Caricasulo et al¹⁹⁷ suggested that the implant internal connection was more favorable to marginal bone levels than the implant external hexagonal connection. The comparison between implant internal and implant conical connections was not clear. Platform switching seemed to have a positive effect per se on bone levels, when the type of abutment-implant connection was disregarded.

Implant size, number, and angulation

Several investigators have attempted to evaluate shorter and/or narrower implants as a treatment alternative to bone augmentation despite resultant unfavorable crown-to-root (C/I) ratios. Hadzik et al¹⁹⁸ designed a study to compare traditionally favorable and unfavorable C/I ratios involving shorter and longer implants in the posterior maxilla. Short implants (6 mm×4 mm diameter) were placed without sinus lift and augmentation procedures, while the longer implants (11 or 13 mm×4 mm diameter) required sinus augmentations. C/I ratios were 1.06 with longer implants group and 1.63 with shorter implants. Both experimental groups contained 15 patients. Implants were loaded 6 months after surgical placement. Marginal bone levels, at 36 months, were statistically similar for short implants (0.34 mm) and longer implants (0.22 mm). The authors concluded that C/I ratios did not influence peri-implant marginal bone outcomes up to 36 months in the patients investigated.

Taschieri et al¹⁹⁹ compared short (6.5 or 8.5 mm) and standard (≥ 10 mm) implants in the posterior maxilla, in a parallel group design, when 4 to 7 mm of residual bone height was available. Twenty-five patients received 58

standard-length implants with sinus augmentation by using inorganic bovine bone, and 27 patients received 65 short implants. Various clinical and radiographic outcomes were recorded at 1 and 3 years. Immediate and early patient symptoms as well as treatment time were significantly more favorable in the short implant group due primarily to reduced surgical trauma. Other variables were comparable. Despite the short clinical follow-up duration, this report is a valuable comparison favoring short implants and reduced surgical invasiveness.

Felice et al²⁰⁰ conducted bilateral evaluations of atrophic maxillae and mandibles in 20 patients over 3 years. A minimum of 6 mm in the mandible and 7 mm in the maxilla was needed to allocate patients to 2 different procedures in a split-mouth design. One side received a conventional approach involving bone augmentation and delayed implant placement (4 months after augmentation). The opposite side received short implants (6 mm) without augmentation or delayed implant placement. At 3 years, implant and prosthetic failures were not significantly different between experimental groups. Eighteen complications occurred in 13 patients with augmented sites, while 4 complications were registered in 3 patients with short implants. At 3 years, augmented implants lost 1.54 mm in the mandible and 1.50 mm in the maxilla. Nonaugmented short implants lost 1.25 mm and 1.28 mm in mandibles and maxilla, respectively. Bone loss differences between augmented and nonaugmented sites were statistically significant.

Gastaldi et al²⁰¹ performed a similar study comparing conventional 10-mm implants in augmented posterior maxillae or mandibles and 5-mm calcium-incorporated titanium surface implants without augmentation. Complications were significantly more in augmented sites (17 in mandibles and 6 in maxillae) than in nonaugmented sites (8 in mandibles and 2 in maxillae).

de Souza et al²⁰² treated 22 patients in a split-mouth study to compare narrow diameter (3.3 mm) and regular diameter (4.1 mm) implants supporting single crowns in the posterior mandibles and the maxillae. Forty-four implants were placed, 21 in premolar sites and 22 in molar sites. Marginal bone levels at 3 years were significantly similar. Overall, narrow and regular diameter implants yield similar outcomes in posterior areas.

Papaspyridakos et al²⁰³ accomplished meta-analysis of 10 randomized controlled trials (low heterogeneity) comparing outcomes of implants ≤ 6 mm with those >6 mm in function from 1 to 5 years. Outcomes were somewhat similar yet more predictable for longer implants. The risk ratio for short implant failure was 1.29-times greater than that of longer implants. This meta-analysis corroborates individual controlled trials in that similar success rates can be obtained but also indicates that the shorter implants may be at higher risk of failure. This result may indicate the steeper learning curve

associated with clinical procedures required for short implants.

Schiegnitz and Al-Nawas²⁰⁴ performed a meta-analysis to evaluate the survival of narrow-diameter implants. Implant diameters were categorized as <3 mm, 3 to 3.25 mm, and 3.3 to 3.5 mm. Implants with diameters <3 mm are primarily indicated in patients with extreme resorption and presented a survival rate of 94.7%, while diameters above 3 mm are associated with survival rates above 97%. This difference was statistically significant. This study confirmed that narrow-diameter implants can be used with high success rates despite being limited to patients with resorption.

Daudt Polido et al²⁰⁵ performed a meta-analysis to evaluate the use of fewer than 5 implants to support complete-arch fixed prostheses. In both arches, results were similar when 5 or fewer implants were used as compared with more than 5.

A meta-analysis was completed by Apaza Alccayhuaman et al²⁰⁶ to investigate the effect of implant angulation on implant failure and marginal bone levels after at least 3 years in function. Seventeen studies were included: 13 pertained to fixed complete dentures; 4 described fixed partial dentures; none were randomized; 8 were prospective; 9 were retrospective; and 14 presented a serious risk of bias. Survival rates ranged from 95% to 100% for tilted implants and 87.5% to 100% for straight implants. Marginal bone levels ranged from 0.4 to 2 mm for tilted implants and from 0.5 to 1.9 mm for straight implants. The extent of implant angulation was significantly associated with the amount of marginal bone loss (0.6 mm of bone loss for each additional 10 degrees of implant angulation).

Ceramic implant-supported fixed partial dentures

Sailer et al²⁰⁷ demonstrated that success at 5 years, albeit above 90%, was significantly lower for implant-supported zirconia-ceramic fixed partial dentures (FPDs) than for metal-ceramic FPDs. The authors accumulated 3 zirconia-ceramic FPD and 16 metal-ceramic FPD studies. Cumulatively, these studies represented 175 zirconia-ceramic restorations followed up for an average of 5.1 years and 932 metal-ceramic FPDs followed up for an average of 6.3 years. The 5-year survival rates (that is, still in situ with or without modifications during the observation period) were 93% for the zirconia-ceramic and 98.7% for the metal-ceramic FPDs. All zirconia-ceramic restorations encountered complications during the 5-year observation, while 84.9% of the metal-ceramic FPDs were without complications. Authors indicated, "... metal-ceramics is the 'gold standard' material of choice for the fabrication of multiple-unit, implant-borne FPDs." Limitations of this study were a greater number of metal-ceramic restorations as compared with zirconia-ceramic restorations. The

authors concluded that zirconia remains a novel material without a significant track record that requires further rigorous clinical investigation.

In a similar manner, Pieralli et al²⁰⁸ evaluated ceramic implant-supported FPDs corroborating, to a certain extent, results reported by Sailer et al.²⁰⁷ This meta-analysis involved studies with at least 12 months of functional loading, while Sailer et al²⁰⁷ had 3 years of functional loading as a minimum requirement. Additionally, Sailer et al²⁰⁷ avoided studies with significant numbers of complete arch restorations, while Pieralli et al²⁰⁸ included 7 reports addressing complete arch restorations and 4 studies looking at FPDs. The results indicated that implant survival was not influenced by restorative variables. Estimated survival rates at 5 years were 98.3% and 97.7% for FPDs and complete arch restorations, respectively. Fracture of veneering ceramic was observed in all studies. Estimated 5-year success rate for FPDs was 77.2% and that for complete arch restorations was 65.2%. Similar to Sailer et al,²⁰⁷ this study demonstrated a high incidence of chipping of the veneering material and pointed out that clinical evidence descriptive of monolithic zirconia restorations is lacking.

Digital versus conventional workflow

Mangano and Veronesi²⁰⁹ compared analog (conventional) and digital workflows for posterior single-unit implant-supported restorations (n=25). Implant and prosthodontic successes were evaluated, as well as radiographic marginal bone loss, patient satisfaction, cost, and time of therapy. Implant and prosthodontic failures and biological and prosthodontic complications were not significantly different between the 2 workflows. However, overall patient satisfaction was significantly greater with digital processes than with analog processes (93.5% and 83.6%, respectively) because of the discomfort of conventional impression making and gag reflex. Patients appreciated the shorter treatment time associated with the digital workflow and felt that the cost of therapy was more justified. With respect to production time, the digital workflow was statistically superior for scanning, interim crown fabrication, and definitive crown fabrication. The real cost of materials in the digital workflow was 277.3 euros (\$312 US) and 392.2 euros (\$441 US) in the analog workflow.

Flugge et al²¹⁰ reported on a meta-analysis of the literature addressing the accuracy of different impression techniques for implant-supported dental prostheses. Overall, 59 studies evaluated conventional impressions, 11 digital scans, and 9 compared both techniques. Most studies were in vitro. The level of evidence and insufficient quality of data reported did not permit clinical recommendations. Available information suggested that relative angulation of the implants had a negative impact on impression accuracy for conventional techniques.

Abduo and Yin²¹¹ compared the fit of zirconia implant abutments and frameworks fabricated by using different processes. Computer-assisted design and computer-assisted manufacturing (CAD-CAM) involves digital design and milling, while manual-aided design and manual-aided manufacturing (MAD-MAM) uses pantographic copying of a pattern for manufacturing. Seventeen studies comprising 7 manufacturing systems (7 CAD-CAM and 2 MAD-MAM) were included. Results related to abutments indicated the interfacial gap of metal abutments was significantly smaller than that of the zirconia abutments; CAD-CAM zirconia and metal abutment were similar in terms of rotational misfit; MAD-MAN zirconia abutment had a significantly smaller rotation misfit than metal abutments; and proprietary abutment demonstrated significantly smaller interface gaps than nonproprietary abutments. The meta-analysis could not demonstrate significant differences in fit between CAD-CAM and MAD-MAM zirconia frameworks compared with milled metal frameworks. Passivity of fit between complete and partial arch CAD-CAM frameworks was statistically similar.

Immediate and early loading

Early and immediate loading protocols have been discussed extensively in the literature. Even though the first year of loading is known to be critical with respect to biomechanical complications, it is always of interest to assess long-term follow-ups. Cannizzaro et al²¹² compared immediate and early loading of 6.6-mm-long single implants placed by using a flapless surgical procedure, over a 9-year follow-up period. Thirty patients were treated, by using a split-mouth design, with 2 single NanoTite External Hex (Biomet 3i) implants. To be included, implant placement had to achieve 40 Ncm of torque. Twenty-nine implants were loaded immediately. Thirty-one implants were loaded at 6 weeks (early loading group). Complications, implants loss, and peri-implant bone loss were not significantly different between the groups. This study tends to indicate that early and immediate loading, under conditions of the investigation, can be applied safely and be reliable over long term.

Surgical management of peri-implantitis

Rocuzzo et al²¹³ systematically reviewed treatment of peri-implantitis. An encouraging 75% of the studies had a low risk for bias. Reported implant survivals at 3, 4, 5, and 7 years ranged from 70% to 100%, indicating that surgical management of peri-implantitis should be considered a viable treatment option for infected implants.

Outcome assessments

Schimmel et al²¹⁴ accomplished a meta-analysis to evaluate the influence of systemic medical conditions on

dental implant survival in geriatric patients aged 75 years and older. The authors concluded that age did not influence implant survival rates, and the functional and psychosocial benefits of dental implant therapy in the geriatric population may outweigh risks associated with common medical conditions. Wittneben et al²¹⁵ applied systematic review and meta-analysis to evaluate perceived esthetics with patient-reported esthetic outcome measures (PROMs) for implant-supported FPDs. Patient evaluations, reported on visual analog scales, were favorable with a mean of 90.3%. Restorative material, implant design, and the use of fixed interim restorations had no effect on patients' ratings of the definitive FPDs. Papageorgiou et al²¹⁶ evaluated the number prevalence of infrapositioned implants and open contacts. Long-term studies were evaluated, and the prevalence for infrapositioned implants was 50.5%, with a mean infraposition of 0.58 mm. The prevalence of open contacts was 46.3%. The prevalence of open contacts of more than 1 mm was 20.8%.

DENTAL MATERIALS AND THERAPEUTICS

Opioids

During this past year, there has been a definite awakening in the dental profession about the national epidemic of prescription drug-related fatalities. Many have been personally impacted by this addiction, and it is taking a disproportionate toll on a sector of our society, that is, in its most formative and productive stage of life. The most recent and alarming indicator of the impact came in the form of the National Center for Health Statistics Data Brief No. 328, Mortality in the United States in 2017.²¹⁷ This report showed a continued trend in the reduction in life expectancy, which is now longer and larger than the combined impact of World War I and the influenza epidemic of 1918. While the leading causes of death have not changed, those with the largest increases in death rates were unintentional injuries, which include drug overdoses at 4.2% and suicide at 3.7%. Both have been trending with and linked to the current epidemic. The other compelling piece of data coming out of this report is that the age cohorts with the highest increase in death rates were 25 to 34 at 2.9% and 35 to 44 at 1.6%. Much like the HIV crisis of the 1980s, we are experiencing a disease that is striking down young people during their most productive years.

Early in 2018, the American Dental Association's Health Policy Institute published a comprehensive overview of opioid-prescribing practices looking at trends and patterns among dentists from 2010 through 2015.²¹⁸ While dentists made up a small percentage of overall opioid prescriptions, the trend over this period showed an increase in prescriptions per 1000 patients going from 130.58 in 2010 to 147.44 in 2015. More

importantly, the data showed that for the age cohort 11 to 18 years, the rate over this same period increased from 99.71 to 165.94. This is a very compelling finding as this age cohort represents mostly patients who are receiving a first-time prescription for opioids, and this is the cohort recognized to be most susceptible to prescription drug addiction. The median daily morphine dose equivalent in those prescriptions was also higher for this age cohort at 36.00 as compared with 33.33 for all age groups. Other findings reported in this article were that acetaminophen with hydrocodone was the most frequently prescribed combination at nearly 70%, followed by acetaminophen and oxycodone at 11%. Surgical dental visits accounted for 68% of prescriptions, and this increased to 89% for the age cohort of 11 to 18 years. This report led directly to the development of the American Dental Association New Policy to Combat Opioid Epidemic that was announced in March 2018 and distributed widely to policy groups and government agencies across the country.²¹⁹ This policy consisted of 3 position statements:

- The ADA supports mandatory continuation of education in prescribing opioids and other controlled substances.
- The ADA supports statutory limits on opioid dosage and duration of no more than 7 days for the treatment of acute pain, consistent with the Centers for Disease Control and Prevention evidence-based guidelines.
- The ADA supports dentists registering with and using Prescription Drug Monitoring Programs (PDMPs) to promote the appropriate use of opioids and deter misuse and abuse.

Another overview of dental prescribing patterns was published in August 2018 that looked at a large number of Medicare Part D prescriptions in 2014.²²⁰ This study found that of 6 724 372 dental prescription claims submitted, 1 312 796 or 19.5% of them were for opioids. The mean days' supply of opioids was found to be 3.6%, and 56.9% of dentists were prescribing over the recommended duration of 3 days for acute pain. At about this same time, another publication in the *Journal of the American Medical Association* focused on the use of opioids after wisdom tooth extraction between 2009 and 2015.²²¹ They found that of 56 685 patients who filled their opioid prescriptions, 1.3% went on to persistent opioid use. This percentage compares to 0.5% of the 14 256 third molar extraction patients who did not fill a prescription. The authors pointed out that while the numbers may seem small, with a high number of third molar extractions seen each year in an age demographic that is most susceptible to abuse, these data indicate that there are still a large number of young people being put at risk. Another factor cited was the propensity for more

than half of the pills prescribed for third molar extractions to remain unused and available for potential abuse.

Most recently, the *Journal of the American Dental Association* published a scoping systematic review of opioid analgesic literature from 2000 through 2017.²²² This review used a modified Preferred Reporting Items Systematic Reviews and Meta-Analysis methodology where 18 studies met the inclusion criteria. From these studies, 8 common areas or themes emerged. The first included 4 studies that described the impact of patient demographic characteristics on prescribing practices. The most compelling finding was that dentists rated pain intensity higher and were more willing to prescribe opioids to female patients. As compared with whites, African Americans were 1.29 times more likely, Asians 0.57 times more likely, and Hispanics 0.84 times more likely to receive opioid prescriptions. The second theme included 3 studies that described the prescribing patterns by different provider types. These studies showed that dentists generally prescribed under lower risk conditions and had much lower rates of patient hospitalization and mortality than other health-care providers. The third theme cited 3 articles looking at the quantity of opioids prescribed and consumed. It was noted that more than half of the opioids prescribed after tooth extraction were left unused and that the median consumption during the first 24 hours was 3 tablets. Total consumption over 7 days was 8 tablets. The fourth theme emerging from 9 studies was the types of opioids prescribed. These studies showed that 99.9% of dentist-prescribed opioids were immediate-release types and 96.2% were initial fill prescriptions. Hydrocodone made up 76.1% and oxycodone 12.2% of prescriptions. The fifth theme centered around 1 study that described dentist self-reported opioid prescription. This study indicated that most dentists surveyed did not screen for prior abuse, 38% had never accessed a PDMP, and only 4.4% consistently used a PDMP. The sixth theme also centered around a study that looked at the procedures associated with opioid prescriptions. The data confirmed that surgical procedures followed by endodontic and implant procedures had the highest rates of prescribing. The seventh theme included a study that looked at the impact of having pharmacy services integrated into dental delivery. While this is a relatively rare situation, the results indicated that dentists were 81% less likely to prescribe opioids when working in an integrated facility. The eighth and final theme identified was the implementation of risk mitigation strategies. A survey of the National Dental Practice-Based Research Network dentists found that opioids were most rarely prescribed for acute pain, the overall rate of PDMP use was low, and dentists rarely counseled patients on risk, storage, and disposal of opioids. Some of the major gaps identified in this scoping review were that the subject of analgesic prescribing in

dentistry is highly understudied, that the impact of the ADA policy on practitioner behavior is still unknown, that most studies were state-specific or regional in nature, and that none of the studies specifically focused on the most vulnerable teen and adolescent populations.

What is clear from this body of literature is that while we may be a small contributor to the overall prescribing burden with opioids, dentistry still has a critical role in addressing this epidemic. Every addiction starts with a first-time prescription, and most of our prescriptions are first time. Many of those first-time prescriptions are provided to our most vulnerable population of young patients. We know that alternative first-line analgesics such as nonsteroidal anti-inflammatories are effective pain relievers with fewer adverse effects. We have the opportunity and the professional obligation to assess patients' history and risk for addiction; counsel on proper use, storage, and disposal of prescribed drugs; and use the PDMP tools that are available to help identify and control abuse.

Silver diamine fluoride

Once again, 2018 experienced a flurry of publication activity related to silver diamine fluoride (SDF). The most significant of these was the publication of a practice guideline for the nonrestorative treatment of carious lesions.²²³ This guideline was the product of an expert panel convened by the American Dental Association that developed 11 clinical recommendations specific to lesion types, tooth surfaces, and primary or permanent dentitions. The critical pathways for decision support around each of those recommendations were also presented as flow diagrams. The most compelling recommendation for SDF was for advanced cavitated lesions on any coronal tooth surface of both primary and permanent teeth, where the use of a biannual application of 38% SDF was recommended as a first course of treatment over 5% NaF varnish placed once per week for 3 weeks. The second recommendation including SDF was for noncavitated and cavitated lesions on root surfaces, where the prioritized recommendations were 5000 ppm fluoride (1.1% NaF) toothpaste or gel at least once daily as the most effective, followed by 5% NaF varnish applied every 3 to 6 months as the next most effective, and finally 38% SDF applied annually. This guideline provides a logical sequence and pathway for decisions based first on coronal versus root surface, next on tooth surface, and then whether the lesion is cavitated or noncavitated, with a list of possible treatments under each outcome listed in their priority of effectiveness. The authors have distilled a huge amount of data and information into a comprehensive, understandable, and useful tool for clinical decision-making. A systematic review tied to this guideline summarized the supporting evidence for the recommendations.²²⁴ This review included 44 trials with 7378

participants and presented 4 network meta-analyses that provided the basis for both the treatment recommendations and the prioritization of those recommendations.

Three systematic reviews evaluated studies on the use of SDF in primary teeth. The first compared the efficacy of SDF to other active treatments or a placebo in arresting lesions.²²⁵ Eleven studies were included, 8 with primary teeth and 2 including permanent first molars. Six studies used 38% SDF, two 12% SDF, and one used a nanosilver fluoride combination. The authors concluded that SDF outperformed the other active treatments or placebos for arresting lesions in primary teeth, but there was not enough evidence to extend that conclusion to permanent molars. A second review and network meta-analysis included 15 studies that compared conventional restorative treatment by using several different composite resin materials and SDF on different lesion types.²²⁶ For occlusal lesions in the outer half of dentin, the authors concluded that conventional composite resin restorations were superior, with compomers performing better in deeper lesions. Stainless-steel crowns demonstrated best survival in occlusoproximal lesions, and SDF was found to perform best for nonrestorative arrest of lesions on both occlusal and smooth surfaces. The third systematic review looked at SDF use for prevention of caries in primary teeth.²²⁷ This review included 2 trials comparing SDF with no treatment, one comparing SDF with a placebo and NaF varnish and the other comparing SDF with glass ionomer cement. The conclusions were that SDF appears to effectively prevent new caries development when compared with no treatment, placebo, or fluoride varnish. The level of evidence for this effect, however, is relatively low, and better trials aimed specifically at preventive outcomes are needed.

Two systematic reviews looked at SDF for prevention and arrest of root caries in older adults. Three randomized controlled trials were included, and the preventive fraction for SDF was found to be 71% when compared against a placebo in a 3-year study and 25% in a 2-year study.^{228,229} SDF was found to be as effective as either chlorhexidine or sodium fluoride varnish in preventing new root caries, and it showed much higher caries arrest than the placebo control. No serious adverse effects were reported in any of the 3 studies, and few complaints about black staining were noted.

One study compared the effectiveness of 12% to 38% SDF at 2 different application frequencies, once and twice per year.²³⁰ The study included 888 children, 4220 teeth, and followed up the teeth for 30 months. Caries arrest rates were 55.2% for 12% SDF once per year, 58.6% for 12% SDF twice per year, 66.9% for 38% SDF once per year, and 75.7% for 38% SDF twice per year. These results confirmed that 38% SDF is more effective than 12% and that twice-yearly application is the preferred protocol. A second smaller study of 118 lesions assessed

whether 1 or 2 applications of 38% SDF could arrest caries and reduce subsequent pain and infection.²³¹ Nearly all lesions were arrested, but more importantly, there were no observed or reported incidents of pain or infection. Measuring patient-centered outcomes such as pain and infection get much closer to the true value of treatment. Another study of preschool children looked at both the impact of 38% SDF on arrest rates and resulting changes in the plaque flora.²³² Similar to related studies, caries arrest was confirmed, but the RNA sequencing of microbes indicated that there was no change in the relative abundance of caries-associated microbes after treatment. While the treatment did not appear to alter the plaque flora, it also did not lead to the emergence of antibiotic or metal-resistant gene expression in the organisms. Finally, one interesting clinical report looked at the histology of an extracted primary tooth with a deep carious lesion that had been treated with SDF 6 months earlier.²³³ Microscopy indicated that there was no carious pulp exposure, and tertiary dentin was present with silver deposits extending 1 mm into the intact dentin. There were no bacteria present in the dentin tubules and no signs of pulpal inflammation. When considered with the results of the study on plaque, it appears that any antimicrobial activity for SDF may be localized to the treated tissues and perhaps does not affect the surrounding plaque or salivary flora.

The growing body of evidence continues to overwhelmingly demonstrate the caries-arresting qualities of SDF in coronal lesions of primary teeth and root surface lesions of permanent teeth. There is a limited amount of evidence around primary prevention, but one factor that is very consistent among studies is the lack of adverse effects beyond lesion discoloration. Fortunately, this year's publication of a clinical guidance document should help clinicians better choose when and where to use this promising treatment option.

Sealants

In the "Evidence-Based Clinical Practice Guideline on Nonrestorative Treatment for Carious Lesions," the decision matrix pertaining to noncavitated lesions on occlusal surfaces lists sealants plus 5% NaF varnish as the highest priority recommendation for both primary and permanent teeth.²²³ In addition, for noncavitated approximal surfaces, sealants in the form of resin infiltration are listed as the second option behind 5% NaF varnish every 3 to 6 months. Once again, this document provides valuable guidance in selecting the most appropriate indications for use. One of the supporting documents associated with this guideline was a systematic review and meta-analysis that summarized the available evidence on arrest or reversal of noncavitated and cavitated lesions in primary and permanent teeth.²²⁴ Forty-four trials with 7378 participants were included, and

meta-analyses suggested that sealants plus 5% NaF varnish was most effective for arresting or reversing noncavitated occlusal lesions, resin infiltration plus 5% NaF was most effective in approximal lesions, and 5000 ppm F (1.1% NaF) toothpaste or gel were most effective for cavitated and noncavitated root surface lesions. All of these were reflected in the clinical guidance document.²²³

Two articles described studies evaluating fluoride-releasing sealants and provided differing results. The first was a 2-year split-mouth design where a resin-based sealant was compared both with and without fluoride on molar teeth to molar teeth with no sealant at all.²³⁴ Two years after sealant placement, the overall effect of it was an 83% reduced risk of developing a lesion. There was no significant difference in this performance with or without fluoride. In the second study, a fluoride containing flowable resin was compared with a conventional sealant in 76 patients by using a similar split-mouth design.²³⁵ At the end of 24 months, the flowable resin sealant had a moderately higher retention rate at 88.5% versus 73.1%, and the incidence of caries progression was significantly better for the fluoride-containing flowable resin at 7.7% versus 25.0% for the conventional sealant. This begs the question of whether the lower caries progression was because of the fluoride or the physical effect of improved retention.

Three articles reported on the use of glass ionomer cements as sealants. The first was a comparison of resin-based sealant to a glass ionomer sealant on the first permanent molars of 7- to 9-year-olds.²³⁶ A total of 419 participants were randomly divided into 3 groups for resin sealant, glass ionomer sealant, and no sealant as a control. After 5 years, 13.4% of resin-sealed teeth, 22.5% of glass ionomer-sealed teeth, and 34.5% of unsealed teeth developed cavitated lesions. While both sealants were more effective than no sealant, the resin-based sealant was significantly better than the glass ionomer one when not taking the control into account. The second study followed up 1736 newly erupted molars for up to 13 years after glass ionomer sealant placement.²³⁷ The mean follow-up duration was 5 years, but starting from the eighth year of follow-up, no completely retained sealant was observed, and by 13 years, 76% of sealants were completely lost. Even so, at 13 years, 65% of the occlusal surfaces were still caries-free. Finally, a systematic review of glass ionomers compared with resins as sealant materials summarized 20 studies on caries prevention and 28 studies on sealant retention.²³⁸ The meta-analyses showed that there were no significant differences between the materials for caries prevention (odds ratio=0.938; 95% CI=0.647-1.359; $P=.734$), while the results for retention showed the resin-based sealants had a significantly better performance (odds ratio=6.006; 95% CI=3.226-11.183; $P<.001$). These results may demonstrate a residual effect of fluoride release and

incorporation into the enamel long after the glass ionomer is no longer in place.

Two articles reported on the often-overlooked cost-effectiveness of pit and fissure sealants. The first quantified the impact of preventive dental services including sealants and topical fluoride in nearly a million Medicaid-enrolled children across 6 US states.²³⁹ In all 6 states, expenditures for children receiving topical fluoride and sealants before caries development were lower than those for other children. Savings on a per-member per-year basis ranged from \$88 to \$156 across the 6 states. As an example, this amounted to \$12.9 million/y in savings for the state of Texas at a 10% penetration level. A second study used a Markov model to simulate disease progression and cost impact over a period of 9 years.²⁴⁰ Both disease progression and sealant failure probabilities were derived from the literature, and 2 scenarios were tested based on the probability of replacing a failed sealant. In the scenario where 100% of failed sealants were replaced, the incremental cost-effectiveness ratio was \$156.87 per first episode of caries lesion averted. If the probability of replacing a failed sealant dropped to 50%, this ratio was still \$113.00 per caries lesion averted. It is interesting to see that these 2 studies using very different methodologies came to similar conclusions and similar savings estimations.

Composite resins

Literature related to composite resin materials has generally moved away from the focus on shrinkage and stress to more application-oriented studies of performance in pediatric settings and the development of antimicrobial additives. One article published in 2018 did use a meta-analysis to compare the clinical performance of conventional and low shrinkage composite resin formulations.²⁴¹ Twenty-one articles with follow-up times up to 60 months were included, and the only variable found to be significant was marginal adaptation after 12 months, which was actually better for the conventional composite resins. This analysis confirmed prior reports that there was no improved clinical performance for low shrinkage formulations such as silorane, ormocer, or bulk-fill modified systems. Another 5-year study compared a nanohybrid composite resin (ceram.x duo, Dentsply Sirona) with a nanofilled material (Filtek Supreme XT, 3M ESPE) in class IV restorations.²⁴² The study was relatively small with only 34 participants, and there was no difference in performance between these 2 classes of materials.

Several articles reported on the relative performance of composite resin restorations to other restorative options in treating lesions in primary teeth. The first compared conventional composite resin restorations to atraumatic restorative treatment (ART) restorations placed in children with disabilities and followed up over a period of 3 years.²⁴³ The findings from 66 patients

showed that the ART restorations had a cumulative survival rate of 94.8% \pm 2.1% (mean \pm SE) which was significantly better than that of the resin composite at 82.8% \pm 5.3%. Conventional composite resins were compared with stainless steel crowns (SSCs) for the restoration of class II lesions in high-risk patients.²⁴⁴ A total of 593 composite resin restorations and 243 SSCs were assessed for mean survival time, and failure rates were determined. While there was no significant difference in mean survival times at 41.3 months for composite resins and 45.6 months for SSCs, the failure rate for composite resin restorations was 22.6% with recurrent caries as the major cause and the failure rate for SSCs was 15.2% with the major cause being loss of the crown. A similar study followed up a total of 6288 primary molar teeth restored with either composite resin or SSC restorations where the primary outcome was time to a new restoration or crown on the same tooth.²⁴⁵ At 3 years, 1.5% of SSCs and 21% of 2- and 3-surface composite resin restorations required replacement resulting in a hazard ratio of 14.0 (95% CI=9-22, P <.001). In addition, 6.8% of the composite resin restorations required replacement with SSCs. A systematic review of materials used to restore primary teeth reviewed results for 12 047 restorations with an overall failure rate of 12.5% after at least 1 year of service.²⁴⁶ This review found that there was a high degree of variability in failure rates (0% to 29%) but also that SSCs had the highest success rate at 96.1% and that restorations placed under rubber dam fared better than those placed without a rubber dam. These studies continue to affirm the higher performance of SSCs in restoring multiple-surface lesions in primary molars.

The field of antimicrobial adjuncts to resin-based materials continues to grow, but as of yet, there are no clinical studies reporting their performance. One common antimicrobial being investigated is silver in various forms. A silver-doped sol-gel glass was incorporated into the filler phase of a composite resin at various concentrations from 5% to 15% and evaluated for growth inhibition of *Streptococcus mutans* and assessment of physical properties.²⁴⁷ When compared with a control material, the silver-doped composite resin achieved significant microbial inhibition after 3 months of simulated body fluid immersion while not compromising physical properties. In another silver adjunct, silver nanoparticles were generated by using a biofabrication process with 2 different organisms, *Bacillus amyloliquefaciens* and *Curcuma aromatica*.²⁴⁸ Polymer films incorporating both types of nanoparticles demonstrated more than 90% inhibition of *S. mutans*. Silver was not the only metal being studied. Another article described the use of zinc oxide nanoparticles as an additive to interim cement for antibacterial properties.²⁴⁹ Temp Bond NE was modified by incorporation of the zinc nanoparticles, resulting in

significant *S. mutans* growth inhibition at only 0.25% volume fraction while not compromising diametral tensile strength. Metal nanoparticles continue to be a promising antimicrobial for restorative materials of all types, but much needs to be done to evaluate factors such as duration of effect and the development of microbial resistance over time.

Bioactive adhesives were also investigated, with one incorporating a novel quaternary ammonium methacryloxy silane (QAMS) from 0% and 5% mass fraction.²⁵⁰ A dose-dependent relationship was found in the killing ability for both *S. mutans* and *Actinomyces naeslundii* exposed to the polymer films, but no data were provided on the duration of this effect. Duration was addressed in another adhesive containing dimethylaminohexadecyl methacrylate and 2-methacryloyloxyethyl phosphorylcholine after 6 months of water aging.²⁵¹ Both agents were added to Scotchbond Multi-Purpose Adhesive (3M ESPE) primer and adhesive and evaluated for biofilm inhibition and dentin bond strength. The combination resulted in no decline in bond strength after 6 months, and the polymer film continued to demonstrate a significant antibacterial activity that did not decline over that period.

Finally, an article described the use of triclosan-encapsulated halloysite nanotubes to dope a composite resin for microbiological inhibition.²⁵² In this case, the nanotubes proved to be too effective at encapsulating the triclosan as there was no antibacterial effect measured, proving that not every great idea pans out. While the entire field of incorporating antimicrobials continues, there remain many questions related to duration, microbial resistance development, maintenance of physical properties, host response, and likely route for regulatory approval for these combination materials.

Amalgam

While the use of dental amalgam continues to decline, the literature still reflects an interest in the safety and performance of this time-proven material. One study used a nationwide database of more than 88 000 young people to investigate the association between amalgam restorations and attention-deficit/hyperactivity disorder (ADHD).²⁵³ Children with one or more restorations and no ADHD history before 2001 were tracked through 2011 for a positive diagnosis of ADHD. In total, 2073 (2.4%) received a positive ADHD diagnosis yielding an incidence rate of 32.4 per 100 000 person-years, but there was no significant difference between those receiving amalgam and composite resin restorations. Those with 6 or more amalgam restorations showed a significant risk over composite resin in the unadjusted model, but once the model was adjusted for age, this difference disappeared. The overall conclusion was that there was no association between young patients having received

amalgam restorations and a future diagnosis of ADHD. A second study of ADHD investigated the association of prenatal exposure to mercury from the mother's amalgam restorations and symptoms related to ADHD.²⁵⁴ The study population was part of the Norwegian Mother and Child Cohort Study where data were collected on 42 163 children at 3 years of age and 23 392 children at 5 years of age. No significant association was identified between the number of teeth with amalgam fillings, amalgam fillings placed or removed during pregnancy, and symptoms related to ADHD in children at either age. A third study looked at prenatal mercury exposure and the risk of autism.²⁵⁵ This study compared 45 pregnancies resulting in children with a diagnosis of autism from a population of 3840 as associated with increased mercury exposure from fish consumption and dental amalgam. The only result of significance was the positive association of poor social cognition when the mother ate no fish (AOR=1.63, 95% CI=1.02-2.62, $P=.041$).

The clinical performance of amalgam was reported in 2 studies. The first looked at the timing of pulpal disease after restoration and its association with the material used for restoration.²⁵⁶ The data were drawn from the Oral Health Center of Western Australia from 2009 through 2013 and included restoration type, restored surfaces, tooth type, and dates of restoration and subsequent endodontic treatment or extraction. Three hundred thirty teeth met criteria requiring endodontic or extraction treatment, of which 26% were composite resin restorations, 24% amalgams, 36% glass ionomers, and 14% crowns. Teeth with crowns or 5-surface glass ionomer restorations were significantly more likely to require earlier endodontics or extraction than teeth with amalgam or composite resin, and premolars and anterior teeth were more likely to require earlier treatment than molars. A second study compared the performance of different treatment options performed under general anesthesia in pediatric patients from 2010 through 2013.²⁵⁷ Of 1155 primary teeth treated under general anesthesia, stainless steel crowns and amalgam had nearly identical failure rates of 5.26% and 5.33%, respectively, and composite resin failed at a rate of 9.63%.

Two articles reported on the use of adhesives with amalgam restorations. The first compared the frequency of postoperative sensitivity in amalgam restorations placed by using either copal varnish or a dentin bonding agent as cavity liners.²⁵⁸ Sixty patients with class I lesions were randomly assigned to 1 of the 2 liners and the teeth evaluated for sensitivity 1 month after restoration placement. The dentin adhesive outperformed the copal varnish in both the mean postoperative pain scores and the proportion of restorations experiencing no pain. A systematic review of bonded amalgam restorations included 170 articles of which 129 were in vitro

studies.²⁵⁹ The results of the clinical studies indicated a reduction in postoperative sensitivity with adhesives, but a lack of consistent evidence around other potential outcomes did not indicate any additional advantage for bonding amalgam restorations.

Finally, a very comprehensive assessment of the clinical performance and suitability of amalgam and composite restorations was published by the Canadian Agency for Drugs and Technologies in Health.²⁶⁰ This investigation included efficacy, safety, cost consequence, patient perspectives and experiences, implementation issues, environmental impact, and ethical considerations. The conclusions of the report stated that, "... compared with composite resin, amalgam restorations appear to be clinically efficacious and as safe, while also costing less. In addition, dental amalgam waste constitutes a small relative contribution to overall mercury contamination in the Canadian environment compared with other sources—largely owing to the judicious management of resultant mercury waste."

The authors went on to conclude that these findings suggest that there is a limited rationale for discontinuing the use of amalgam in Canada. While the conclusions of this report mirror others offered by many governmental agencies around the world, it is still doubtful that amalgam can weather the political, environmental, and societal pressures being placed upon it. Never has a material as historically influential for improving oral health and function been so unjustly maligned.

Restoration repair and replacement

Two articles published in 2018 reported on the teaching of repair and replacement of restorations in dental schools. The first was a follow-up survey of German dental schools that updated results from similar surveys done in 2000 and 2009.²⁶¹ Twenty-nine schools responded to the survey (97% response rate), and 90% of them reported teaching repair, which was similar to the 2009 results at 88% and greater than the 2000 results at 50%. The main reasons for teaching repairs were tooth tissue preservation (97%) and reduction of pulpal damage (79%), and the main clinical indications were marginal defects and secondary caries. The average expected longevity given for repairs was 7.4 ± 3.0 years. The second article was a systematic review and meta-analysis that attempted to identify barriers and facilitators for repairs.²⁶² Twenty-nine studies including 7228 dentists and 276 dental schools provided survey data, while treatment data were available for 30 172 restorations. The proportion of dentists stating that they performed repairs was 71.5% (95% CI=49.7% to 86.4%). Of the dental schools surveyed, 83.3% (95% CI=73.6% to 90.0%) taught repairs. The treatment data indicated that 31.3% (95% CI=26.3% to 36.7%) of failed restorations had been repaired, and amalgam restorations were repaired less

often than others. Facilitators for repair were employment in a public health dental practice and being the dentists who placed the original restoration. Barriers to repair were identified as financial aspects and regulations.

Another review mirroring one carried out in the 1998 looked in more detail at the reasons for placement and replacement of restorations.²⁶³ Twenty-five articles were included, with 12 being in the original review. In total, there were 86 720 restorations, with 37 016 (42.7%) being new placements and 49 704 (57.3%) being replacements. When comparing the pre-1998 to post-1998 review periods, the placement of amalgam restorations dropped from 56.7% to 31.2%, and there was a corresponding increase in placement of composite resin restorations going from 36.7% to 48.5%. The same comparison of pre-1998 to post-1998 reviews for restoration replacements shows an increase from 56% to 58.1%. Secondary caries was the most common reason for replacements at 59%. These data confirm that the proportion of amalgam restorations continues to decline, and unfortunately, the proportion of replacement restorations is increasing.

Three articles reported follow-up data on repaired restorations. The first looked at survival of anterior composite resin restorations over 15 years when repair was either considered a failure or not a failure.²⁶⁴ Records for 144 patients were reviewed from a private dental office that comprised 634 anterior composite resin restorations. For class III and class IV restorations, the survival rate was 69% over 15 years when repair was not considered a failure and 64% when repair was considered a failure. For direct veneers, survival dropped from 52% at 10 years when repair was not considered a failure to 38% when repair was considered a failure. Maxillary restorations had a higher risk for failure as well as central incisors. These results confirm that repair definitely increases the survival of anterior composite resin restorations. A second 12-year follow-up reported on the survival of amalgam and composite resin restorations with sealed marginal defects.²⁶⁵ The study included 34 participants with 51 composite resin and 86 amalgam restorations with minor localized margin defects comparing sealed with unsealed control restorations. After 12 years, there were no statistical differences between materials or sealing versus not sealing with respect to restoration longevity. Both sealed and unsealed groups were similar with regard to marginal adaptation, secondary caries, and tooth sensitivity. The authors' conclusion was that sealing of minor restoration defects would not affect overall longevity. This same group of authors reported on a 12-year follow-up of repaired amalgam and composite resin restorations.²⁶⁶ The study was of similar design with the exception that the 100 amalgam and 67 composite resin restorations were

randomly assigned to repair or replacement groups for comparison. In this case, all groups were again similar in margin adaptation, margin stain, tooth sensitivity, anatomic form, luster, and restoration survival. The authors' conclusion was that repair was a favored option over replacement because it was less invasive, less costly, and resulted in similar outcomes as complete restoration replacement. Taken together, these results support the option of repair when clinical indications are severe enough to warrant possible replacement of a restoration, but the straightforward sealing of minor margin defects do not appear to extend restoration survival.

OCCLUSION AND TEMPOROMANDIBULAR DISORDERS

Imaging

Talmaceanu et al²⁶⁷ described TMJ pathology as complex and includes temporomandibular disorders (TMDs), infections, tumors, traumatic lesions, and developmental anomalies. TMD is defined by the American Academy of Orofacial Pain (AAOP) as a complex designation covering several clinical problems involving masticatory muscles, joints, and associated structures. The AAOP categorizes TMD in 2 groups: muscular and articular. The most common clinical signs of TMD are pain, limited oral opening, and joint sounds (clicking and crepitus). The 2014 Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) clearly defines different TMJ internal derangements. According to RDC/TMD, 2 different degrees of disc displacement exist: disc displacement with reduction and disc displacement without reduction. The Piper disc classification is also useful in understanding internal derangements and includes (1) normal; (2) damaged ligaments or cartilage; (3a) partial disc subluxation, with reduction; (3b) partial disc subluxation, nonreducing; (4a) complete disc dislocation, with reduction; (4b) complete disc dislocation, nonreducing; (5a) no disc, bone to bone, adapting; (5b) no disc, bone to bone, adapted.

Although clinical examination is the most important means for diagnosis of TMJ pathology, imaging techniques are needed because of the complex anatomy and pathology. It is common to make an image of the joint when there is locking, pain, and articular sounds. The clinician should properly decide which patients would need special imaging techniques depending on the clinical examination and individual selection criteria. One important thing to consider when imaging the TMJ is the interpretation of the joint function, which can be accomplished by comparing the condyle in the closed and opened mouth position. Several imaging techniques are available for TMJ visualization.

Panoramic radiography shows the jaws and the associated structures being a helpful tool for the clinician in identifying any periodontal or odontogenic causes for

orofacial pain. Panoramic radiography does not appear in the list of imaging techniques provided by RDC/TMD. Only the lateral part of the condyle can be assessed with this technique, being limited due to the superimposition of the zygomatic arch and the base of the skull. Panoramic radiography can help evaluate degenerative bone changes (only in late stages; it is inadequate for the early detection of osseous modifications), asymmetries of the condyles, hyperplasia, hypoplasia, trauma, and tumors. Panoramic radiography does not reveal the functional status of the joint and has a relatively low specificity and sensitivity when compared with CT.

Plain radiography consists of transcranial projections of the TM joints. The use of flat plane films for TMJ pathology is not sufficient because this joint requires 3D imaging views. CT has been reported to be more suitable in identifying TMJ changes than conventional radiography.

Computed tomography (CT) was first used for TMJ evaluation in 1980 and is considered the best method for assessing osseous pathologic conditions of TMJ. Signs of degenerative changes in the joint, including surface erosions, osteophytes, remodeling, subcortical sclerosis, and articular surface flattening can be evaluated using CT. Some studies have reported that radiographic changes in the joint are not always related to pain. Therefore, some patients with osseous abnormalities may experience pain, while others may be pain free. Changes in the shape and location of the loading zone can also be seen on a CT. CT is the main radiological investigation for tumors, growth development anomalies, and fractures. CT examination of the TMJ should focus on the degree of intact cortex, size and shape of the condyles, position of condyles within their respective fossa, adequacy of joint spaces, and the loading zone in centric relation. Regarding the visualization of the soft tissues of TMJ (disc, synovial membrane, ligaments, lateral pterygoid muscle), CT is not used as a primary diagnostic method. The disc could be visualized on CT scans only with injection of contrast media in the joint (arthrography). Arthrography is a dynamic investigation but has not been widely used because of its invasiveness, pain, and allergic reactions to the contrast media. TMJ disc pathology and lateral pterygoid muscle pathology are better assessed with MRI. On CT scans, the position and shape of the mandibular condyle in the glenoid fossa are well seen.

The main disadvantage of CT, compared with other radiological methods, is the high cost and the radiation exposure. Introduced in TMJ evaluation in 1990s, cone beam CT (CBCT) is widely available now and provides high-resolution multiplanar reconstruction of the TMJ. The main advantage of CBCT, compared with CT, is lower radiation dose to the patient. Spatial resolution of CBCT is higher than that of conventional CT. Studies

developed by Hintze et al²⁶⁸ found no significant differences between conventional tomography and CBCT in the detection of morphological TMJ changes. CBCT performs better than conventional radiography and is as good as conventional CT, allowing early bony changes of TMJ to be observed. Previous literature detailed contributions of CBCT in the field of TMJ evaluation, including calculation of volume and surface area of the condyle; improved qualitative analyses of condylar surfaces and detection of condyle shape; improved accuracy of linear measurements of the condyle; clarification of condylar and joint space symmetry; and clarification of condylar position within the fossa. Although CT provides important information regarding the osseous components of the TMJ, it has several limitations, including artefacts related to patient movement during examination (particularly prevalent with children). In addition, a decrease in radiation dose with CBCT may affect the image quality.

MRI is currently considered the reference method for imaging the soft tissue structures of the TMJ (articular disc, synovial membrane, lateral pterygoid muscle) and has been pointed out as the best imaging modality in diagnosing disc displacements. MRI could also detect the early signs of TMJ dysfunction, such as thickening of anterior or posterior band, rupture of retrodiscal tissue, changes in the shape of the disc, and joint effusion. Images can be obtained in all planes (sagittal, axial, coronal). In most scanning sequences, T1-weighted, T2-weighted, and proton-density (PD) images are obtained. The PD images serve to visualize the disc-condyle relationship while T2-weighted images are used in diagnosing inflammation in the joint. The slice thickness is important for image quality. The most frequently used section thickness is 3 mm. Reducing slice thickness improves the quality of the images but requires longer scanning time. An axial localizing image is used to direct the long axis of the condyle in the closed-mouth position. Sagittal images are obtained perpendicular to the long axis of the condyle, and coronal images are obtained parallel to the long axis.

In the closed-mouth position, teeth should be in contact, whereas in the open-mouth position, the jaw should be at the widest comfortable opening. This way, misinterpreted disc positions could be avoided. Being a synovial joint, synovitis is a common situation, and it is characterized by swelling due to hypertrophy of the synovia and overproduction of synovial fluid. Synovitis can be clearly visualized on MRI images. Synovial inflammation could lead to joint effusion, defined as an increase in the volume of intraarticular fluid. Some disadvantages of the MRI investigation include the cost incurred and time; restricted use in patients with claustrophobia; the possibility of missing the portion of condyle having a pseudo cyst; and missing different bone conditions and

soft tissue calcifications with inflammatory diseases or tumors. In these situations, CT is the preferable imaging modality.

Aanenson¹¹⁶ discussed the radiation dose and risk involved with CBCT scanning in dentistry. CBCT imaging is relatively new to the dental clinical setting as an in-office technique used to diagnose and develop treatment plans. The technology uses a cone-shaped X-ray beam with the detector and the X-ray source located directly opposite one another rotating around the patient's head, resulting in a series of 2-dimensional images that are converted into a 3-dimensional reconstruction of the maxillofacial region.

In radiation safety, the phrase "as low as reasonably achievable" (ALARA) is used to describe how radiation releases to the environment or exposure to humans should be moderated. In diagnostic terms, "as low as diagnostically achievable" is an appropriate phrase. Users of CBCT technology in the dental office have a responsibility to balance diagnostic needs with dose and risk. It is critical to think about why the scan is required and what is necessary to visualize and then to consider how best to do that with as low a dose as possible. It is important to have an awareness of dose and potential risk from CBCT and to convey that information to the patient. Figures 4 and 5 presented in this report of Aanenson¹¹⁶ provide comparisons for dental professionals to share with patients which would allow them to understand the dose they would be receiving from CBCT in comparison with other routine sources of dose and how a risk of 1 in 1 000 000, which is the approximate risk of cancer from CBCT, compares with the risk from other sources. Communication of risk to the public tends to be most effective when people are managed from their frame of reference and provided a meaningful metric.

Matsubara et al²⁶⁹ explored the assessment of MRI finding and clinical symptoms in patients with temporomandibular joint disorders. Temporomandibular joint disorders (TMDs) present with characteristic clinical signs and symptoms, including temporomandibular joint (TMJ) and facial pain, joint noise, and irregular jaw movement. MRI is widely used to evaluate TMJ characteristics, such as disc configuration, disc position, condylar morphology, bone marrow signal pattern, and the presence of joint effusion. Complicated associations among various MRI findings of the TMJ have been reported. Deformity of disc configuration is associated with internal derangement of the TM and condylar degenerative changes. Internal derangement is associated with condylar degenerative change and joint effusion. However, these associations have involved only 2 or 3 MRI findings. A comprehensive study that includes more MRI findings and more detailed classification is necessary. An analysis of correlations among various changes in TMJ structures may reveal key abnormalities that are important for clinical treatment.

Relationships between the clinical signs and symptoms of TMD and MRI findings have also been reported. TMJ pain, the most common clinical symptom, correlates with internal derangement, bone marrow abnormality, condylar degenerative change, and joint effusion. Bone marrow edema has been associated with increased pain in TMDs. However, few reports have described the relationships between joint noise or irregular jaw movements and MRI findings. An evaluation of the relationships between TMD symptoms and MRI findings with detailed classifications may reveal which symptoms warrant MRI examination, thus reducing unnecessary radiographic examinations before MRI. The aim of this study²⁶⁹ was to comprehensively assess the correlations among various MRI findings, including disc configuration, disc position, condylar morphology, bone marrow signal pattern, and joint effusion, and the relationships between symptoms of TMD and MRI findings in a relatively large number of patients.

Correlations among MRI findings in the TMJ were comprehensively analyzed in a large number of patients in this study.²⁶⁹ Biconcave disc configuration correlated strongly with normal disc position, as previously reported. Positive correlations were found between DDWOR and folded disc and between DDWR and flattened disc. Given the hypothesis that internal derangement precedes disk deformation, DDWOR and DDWR appear to be responsible for folded and flattened deformation, respectively.

DDWOR had a moderate positive correlation with osteophytes and folded disc and was negatively correlated with other normal MRI findings. In contrast, there were no significant correlations between DDWR and abnormalities of the condylar surface, bone marrow signal pattern, or joint effusion. Moreover, the risk of each TMD symptom was significantly higher in joints with DDWOR. Conversely, the odds ratio (OR) for TMJ pain and noise was not higher in joints with DDWR. Both DDWR and DDWOR have been reported to increase the risks of condylar degenerative change. The different findings for DDWR in this study are interesting. It appears that when the disc intervenes between the temporal fossa and the condylar surface in the open-mouth position, the damage during jaw function is minimized. Retaining DDWR status seems to be beneficial in maintaining a normal condylar surface, bone marrow, and joint effusion. These findings suggest that treatment strategy for DDWOR to reduce strain and/or injury to the TMJ may effectively reduce the clinical symptoms of TMDs.

Folded disc correlated with abnormalities of disc position, condylar morphology, and bone marrow signal pattern. Osteophytes correlated with folded disc, DDWOR, and bone marrow edema with and without sclerosis. High-grade joint effusions, which reflect the

inflammatory reaction in the articular cavity, correlated with folded disc and DDWOR. Based on these observations, DDWOR, folded disc, and osteophytes appear to be the key MRI abnormalities in patients with TMDs. However, there was no significant correlation between condylar degeneration and joint effusion. This finding suggests that condylar degeneration is not related to inflammatory conditions in the articular cavity.²⁶⁹

Patients with TMJ pain had higher ORs for DDWOR, bone marrow edema, and high-grade joint effusion. These findings suggest that abnormalities in the articular cavity and condylar bone marrow cause TMJ pain. Moreover, in contrast with previous studies, osteophytes and combination-type condylar degeneration were associated with a decreased risk of TMJ pain. Changes were described in the soft tissues during the chronic progression of condylar degeneration, with soft-tissue proliferation allowing the contours to adapt morphologically to various mechanical stresses. In the late stages of condylar degeneration, osteophytes and combination-type degeneration seem to reduce TMJ pain because of the compensatory changes in the surrounding soft tissues.

Hammer and Kanaan²⁷⁰ discussed imaging of the pediatric TM joint. Imaging is an important component in the evaluation of temporomandibular joint (TMJ) symptoms. Sometimes, children do not exhibit TMJ symptoms. This lack of symptoms causes the clinical history and examination to be less reliable indicators of disease status. Identifying pathologic conditions of the TMJ is particularly important during development of the mandible. The mandibular condyle is in close proximity to the joint. Therefore, inflammation and synovitis could alter growth, resulting in worsening mechanical abnormalities over time. Imaging is also critical for monitoring response to therapy over time.

Pathologic imaging findings can include juvenile idiopathic arthritis, which is a set of inflammatory arthropathies that affect children which is distinct from adult rheumatoid arthritis. The TMJ is commonly involved, reportedly, in 39% to 75% of patients. Some studies have found variable involvement of the TMJ in the subtypes of JIA, namely, increased risk with polyarticular and early-onset arthritis and lower risk in B27-positive patients. However, other studies have found a more uniform risk among subtypes. Early findings of arthritis can be found on MRI before symptoms occur. The most common findings are mandibular condyle erosions, synovial hyperenhancement, articular surface flattening, and abnormal jaw motion. Disc changes are also common.

Abnormal morphology of the mandibular condyle can result in abnormal development of the TMJ joint over time. Condylar deficiency traverses the spectrum from minimal hypoplasia to complete absence (aplasia).

Hypoplasia can result from bone remodeling and erosive changes in the setting of inflammatory or infectious arthropathy. Complete aplasia resulting from arthropathy or secondary to another process is uncommon. Congenital aplasia can occur in multiple syndromes such as hemifacial microsomia, Treacher-Collins syndrome, auricular-condylar syndrome, and others. Complete agenesis is associated with other temporal bone and ear developmental anomalies.

Internal derangement of the TMJ refers to abnormal position and morphology of the disc with respect to the joint space. This is a condition most common in 20- to 40-year-olds but can also occur with children. It often presents with pain, clicking, and difficulty opening the mouth. In one longitudinal study of symptomatic and asymptomatic patients, disc displacement was found in 89% and 31%, respectively. As previously mentioned, the normal position of the disc is between the mandibular condyle and the temporal fossa with the mouth closed and between the condyle and articular eminence with the mouth open. The first stage of abnormality results in the anterior displacement of the disc in the closed position (posterior band more than 10 to 30 degrees anterior to the vertical orientation of the condyle), with recapturing or reduction of the disc to a normal position occurring when the mouth is open. Later-stage derangement occurs when the disc is displaced without recapture. A "stuck disc" occurs when there is no movement of the disc with mouth opening, possibly from adhesions. Although the disc can subluxate or dislocate in nearly any plane, posterior dislocation rarely occurs.

Morphologic degenerative changes to the disc itself occur along a spectrum. Initially, an abnormal disc may appear irregular or rounded and lobular in morphology. Abnormal flattening and thinning of the disc can occur in conjunction with the development of intrasubstance abnormal intermediate signal. A complete tear or near-complete loss of the disc is the result in advanced cases. This loss is often found in cases of osteoarthritis.

Other evidence of derangement includes a reactive joint effusion and abnormality of the retrodiscal space. There can be edema (hyperintense signal on T2-W sequences) within this space or a discrete tear of the superior or inferior retrodiscal layers of the bilaminar zone. Some have reported thickening or muscle atrophy of the lateral pterygoid muscle attachment, which could be a cause or effect of the derangement.

Condylar fractures occur in 25% to 50% of mandible fractures. These can involve the condylar head or neck (intracapsular or extracapsular, respectively). Traumatic arthrosis can result in exaggerated degenerative changes. Ankylosis of the TMJ is a rare posttraumatic outcome with loss of the joint space and osseous proliferation. CT can be helpful to determine if osseous bridging is present,

which can help with the difficult operative planning process.

Growth and development

Bender et al²⁷¹ reviewed the development of the pediatric TMJ. The mandible is small at birth, and the arch is more obtuse as opposed to the adult arch that is more angular. The TMJ is also loose at birth with a relatively flat mandibular fossa. The fibrous connective tissue transforms into fibrocartilage over time; the mandibular fossa, driven by surrounding muscle and the loading pressure forces, deepens along a straight vector. This deepening does not typically cause displacement of the mandible, but infrequently, the mandible moves posteriorly, causing the chin to be recessed. There are 2 periods of increased growth, between 5 and 10 years of age and between 10 and 15 years of age. The secondary condylar cartilage is considered a major growth site of the TMJ and is also the center of greatest growth in the craniofacial skeleton.

At the time of birth, most of the condylar cartilage is replaced by bone via endochondral ossification, but the remaining superior portion persists to adulthood. Both the thickness and vascularity of the condylar cartilage decrease with age. The condylar cartilage allows the condyle to maintain its relationship with the temporal bone, whereas the mandible extends downward and forward during development. It has the capacity for multidirectional growth, thus, allowing multiple trajectories of growth both superiorly and posteriorly. The ramus grows in a posterior and lateral direction alongside the laterally expanding cranial base. The coronoid grows superiorly and buccally. The condyles grow posteriorly, superiorly, and laterally. At birth, the angle of the mandible is obtuse, the ramus is small in comparison with the body, and the coronoid process is relatively large. Within the first 3 years of life, there is rapid lateral growth via symphyseal ossification and growth of the condyles in both the posterior and superior directions, allowing for an increase in height of the ramus. The articular eminence (AE) has a mild slope at birth, with its final form being influenced by forces generated by the muscles of mastication and teeth. By 3 years of age, these forces influence AE development to approximately half of its adult form. Adult form is achieved almost entirely by 12 years of age. After 3 years of age, there is extensive bony remodeling along all mandibular surfaces. Developmental mechanisms are not completely understood but may be directed by primary growth centers within the mandible and reactive to surrounding mechanical forces. Local biomechanical forces may influence both morphology and stimulated bony deposition. The general pattern of remodeling involves bony apposition along the condyle, coronoid, alveolar process, posterior ramus border, and buccal/labial mandibular

surfaces. Bony resorption tends to occur along the anterior ramus border and on the lingual surface of the mandible. The posterior ramus undergoes appositional growth that results in further relative lengthening of the body of the mandible.

The TMJ plays a role in the aerodigestive tract and affects the oral cavity and oropharynx. Thus, when determining proper care and management of TMJ malformations, multiple functional and structural factors must be considered. These factors may influence patient health via airway obstruction, masticatory dysfunction, sleep apnea, speech impediment, hearing loss, and loss of lower facial contour.

It is important to understand the complex interplay between these functions, especially in syndromic patients who present with TMJ malformations, such as in hemifacial microsomia. In nonsyndromic patients who have isolated TMJ pathology, it is important to acknowledge the interface with oral cavity functions including mastication and speech.

Costea et al²⁷² studied the position of the roots of the maxillary posterior teeth in relation to the sinus floor in different facial biotypes and found a relationship between facial biotype and the proximity of the roots of the maxillary posterior teeth to the maxillary sinus. Earlier studies on the relationship between maxillary posterior teeth and the maxillary sinus floor did not consider facial biotype. The most unfavorable root score from the dental perspective was found most frequently in the normodivergent group, indicating that the roots were generally projected into the maxillary sinus. However, the second molar roots in the hyperdivergent group were closer to the sinus floor than those in the hypodivergent group. The second molars were significantly closer to the sinus floor in the hyperdivergent group than those in the hypodivergent group. Furthermore, in the hyperdivergent group, the second molar score increased with age, meaning that the second molar roots tended to be closer to the sinus floor. This is an important observation from an orthodontic perspective; the treatment strategy for this facial biotype implies molar intrusion, meaning further displacement of the molars into the sinus.

Facial biotype is related to the growth of the mandible, and its rotation will affect the direction and amount of growth at the level of the nasomaxillary complex. The growth of the maxilla is a combination of passive forward and vertical displacement and active growth in response to soft tissue stimuli. The maxilla follows the mandibular growth pattern and responds by periosteal vertical apposition at the level of the dentoalveolar process. In hyperdivergent patients, because of the short mandibular ramus and consequently short posterior facial height, the maxillary plane rotates, inducing a compensatory dentoalveolar mechanism in an anteroposterior direction. In addition, the hyperdivergent

facial biotype has less dense buccal cortical bone than do the other facial biotypes. This may allow for expansion of the maxillary sinus and development toward the mandibular border. Thus, because of the lack of posterior dentoalveolar compensation, molar roots will project into the maxillary sinus. In contrast, in hypodivergent patients, the mandibular ramus growth will allow appropriate vertical dentoalveolar development and enough bone for the maxillary teeth. The muscular forces and greater osseous density in hypodivergent patients can be mechanisms involved in the development of the maxillary sinus and the relationship between roots of the posterior maxillary teeth and the sinus floor.

Kim et al²⁷³ measured and compared condylar bone densities in adolescent patients with varying skeletal patterns. In orthodontics, the ability to predict mandibular growth and the change of growth during and after treatment could be highly beneficial. This knowledge could be especially critical when evaluating patients with an undesirable growth pattern. Various parameters focusing on skeletal morphology have been used to predict mandibular growth with varying success. Bone density could be used to predict growth patterns because skeletal growth is influenced by bone metabolism. Many studies have examined the relationship between jawbone density and facial morphology, although the focus was bone density of the alveolar region in adults. The mandibular condyle is related to mandibular growth, so investigating condylar bone density as a factor to potentially predict mandibular growth pattern in adolescents could be advantageous. In this study, condylar bone density was associated with the skeletal pattern: the cortical, cancellous, and total bone densities were higher in the hyperdivergent and class II groups than in the hypodivergent and class III groups.

The cortical bone density of the condyle increased with age.²⁷³ A statistically significant difference in cortical bone density was seen between the early and other age groups (middle and late). Similar observations have been described where the critical period for bone mass increase in healthy boys was between the ages of 13 and 15 years and in sexual development stage G4. In this study, participants were classified according to age, and the early and middle age groups were divided at 14 years. It might be a transition age of growth and a significant turning point regarding the mandibular growth because a significant change was markedly shown in the cortical bone density between the early and middle age groups. This would be an important factor in predicting growth pattern. In this study, age was classified into 3 stages according to World Health Organization Technical Report Series, but more studies might be needed to differentiate the stage of growth according to sex.

The conclusions of the study were that (1) condylar bone density increased as the facial height ratio

decreased and the ANB angle increased; (2) ANB angle was a significant factor in predicting bone density; (3) the class II group showed a significantly different distribution from the class I and class III groups in a cross tabulation of facial height ratio and ANB angle; (4) significant differences were shown between the class II and class III groups in the cancellous and total bone densities; and (5) cortical bone density increased as age increased. These findings may be useful in predicting the vertical and horizontal skeletal growth patterns of growing adolescents for better orthodontic treatment results and stability.

Nejaim et al²⁷⁴ evaluated the pharyngeal space and its correlation with the mandible and hyoid bone in patients with different skeletal classes and facial types. The pharyngeal space is a region that allows passage of the inspired air from the nasal cavity to the glottis and the expired air from glottis to the nasal cavity. It is formed by the union of 3 anatomic areas: nasopharynx, oropharynx, and hypopharynx. In this study, only the volume corresponding to the union between the oropharynx and the hypopharynx was evaluated because these regions are related via muscles and ligaments to the hyoid bone and the mandible.

Some authors have stated that variations in the pharyngeal space may be associated with conditions such as functional anterior shifting head posture, skeletal classes, and facial types. This study can improve understanding about the morphology and relationship of structures in the head and neck regions, assisting in orthodontic diagnosis and treatment planning.

Linear and angular measurements have been performed in the mandible, hyoid bone, and pharyngeal space to classify different degrees of obstructive sleep apnea in previous studies. These have found that the smaller the measurement, the more severe the obstructive sleep apnea. In this study,²⁷⁴ the distance of greatest constriction in the pharyngeal space was measured. The results showed that these measurements were smaller in class II mesofacial and dolichofacial patients.

It was concluded that there are significant correlations between the volume of pharyngeal space and the mandible and hyoid bone measurements, suggesting that the stomatognathic system should be evaluated in an integral and nonindividualized manner. Furthermore, it was possible to develop a linear regression model with precision, resulting in a useful formula for estimating the volume of the pharyngeal space.

Structural changes in the TMJ

Ahn et al²⁷⁵ explored the relationship between TM joint disk displacement and condyle volume. MRI data were used to define normal disk position (NR), disk displacement with reduction (DDR), or disk displacement without reduction (DDNR). Previous studies have shown

that patients with DD have decreased condylar height and distally inclined condyles, and this condition becomes more severe as DD progresses. This means that patients with TMJ DD may have both qualitatively and quantitatively different condyles compared with those with NR. Although qualitative evaluation of the condyles with respect to DD has been extensively investigated, knowledge about quantitative changes, specifically the relationships between condylar volume and DD, is limited. Both CT and MRI were used to investigate differences in condylar volumes according to disc status.

CT has been increasingly used as an imaging modality in dentistry, including for the assessment of the TMJ. Both multidetector computed tomography (MDCT) and cone beam computed tomography (CBCT) are accurate in detecting osseous changes, with comparable intra-observer reliabilities. In this study, all 3 volumetric measurements were significantly influenced by TMJ DD. Total condylar volumes and trabecular volumes were significantly reduced in patients with DD (NR>DDR>DDNR), whereas cortical volumes were significantly different only when DD progressed to DDNR (NR/DDR>DDNR). These findings indicate that total condylar volume and its components are significantly associated with DD status, and condyles with DDNR show the smallest condylar volumes with the smallest cortical and trabecular volumes. These results are supported by previous studies reporting that osseous change of the mandibular condyle is significantly influenced by DD and that altered condylar morphologies become more severe as DD progresses.

The decreased total condylar volume can be explained by condylar resorption associated with DD. Previous studies have demonstrated that resorption of the condyle was highly prevalent in TMJs with DD, specifically advanced DD, because DD is commonly accompanied by osteoarthritis. During the course of osteoarthritis, progressive osseous erosion and remodeling occur repeatedly. The repetitive procedure between osseous remodeling and degenerative changes tend to decrease the condylar size, which may explain why condylar volume decreases as DD progresses. Osseous destruction by degenerative DD has been proposed, according to the direct mechanical trauma model, the hypoxia reperfusion model, and the neurogenic inflammation model. Each model predicts that highly reactive molecular species are generated in response to mechanical stimulation. As DD progresses, mechanical stimulation increases because the displaced disk cannot exert its proper protective function during functional jaw movement. Increased mechanical stimulation generates highly reactive molecular species that trigger the molecular cascades associated with catabolism of articular tissues in affected condyles.

In this study,²⁷⁵ cortical bone volume did not change exactly as did total condylar volume. Cortical bone

volume significantly decreased only when DD progressed to DDNR. This may be attributed to the detection limits of CT. Osteoarthritis associated with TMJ DD represents a destructive process by which the articular surfaces of the condyle are altered. The progressive degeneration results in loss of the subchondral cortical layer, bone erosion, and subsequent radiographic manifestation. Although radiographic changes are evident in the later stage of osseous destruction, the initial loss of the subchondral cortical layer is difficult to detect on CT images. This might explain why cortical volumes were not significantly different between NR and DDR in this study. Only when TMJ DD progressed to the later stage (DDNR) did the loss of the cortical bone become evident on CT images, with significantly reduced cortical volumes (NR/DDR>DDNR). The decreased cortical volume in condyles with DDNR may be attributed partly to decreased total condyle size because condyles with DDNR have the smallest size, and cortical bone may occupy a small part in condyles with DDNR compared with those with NR or DDR.

Many studies have reported that one of the common signs of TMJ DD is facial deformity caused by loss of posterior mandibular vertical dimension, decreased condylar height and condylar process, and a steep mandibular plane, resulting in a retrognathic mandible with hyperdivergent skeletal patterns. The results of the present study²⁷⁵ indicate that these specific dentofacial characteristics may be explained by decreased condylar volumes associated with TMJ DD.

Occlusion

Kajii et al²⁷⁶ authored an article evaluating how osseous changes of the mandibular condyle affect backward-rotation of the mandibular ramus in angle class II orthodontic patients with idiopathic condylar resorption (ICR) of the temporomandibular joint. Osteoarthritis or osteoarthrosis (OA) of the temporomandibular joint (TMJ), also known as degenerative joint disease of the TMJ, is characterized by resorbed deterioration and simultaneous remodeling of the articular cartilage and subchondral bone. Radiologically, OA 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 by OA. Host factors, such as age, hormones, and systemic disease may contribute to resorbed deterioration and dysfunctional remodeling of the TMJ, even when biomechanical stresses are within normal physiological ranges. Alternatively, excessive mechanical stress may provoke resorbed deterioration and dysfunctional remodeling in the absence of predisposing host factors. In ICR, it is postulated that the articular disc is displaced anteriorly, and hyperplastic synovial tissue surrounds the condyle releasing chemical

substrates that penetrate the condylar head, resulting in condylar resorption.

In patients with osseous changes of the condyle, unstable occlusion could produce compressive deflection of the condyle during interdigitation of the teeth with masticatory muscular force, and compressive resorption of the condyle may result. The muscles attached to the mandibular ramus might then retract the ramus upward and forward. The digastric and mylohyoid muscles of patients with short mandibular ramus height could retract the mandibular body backward and downward. In consequence, angle class II patients with osseous changes of the condyle might show shorter ramus height and subsequent backward (clockwise) rotation of the mandible.

Angle class II orthodontic patients with ICR and disc displacement without reduction of the TMJ showed a significantly smaller condylar ratio, shorter mandibular ramus height, and more backward (clockwise) rotation of the ramus than angle class II patients without ICR. With regard to the morphology, angle class II patients with ICR of the TMJ also showed a significantly more retruded mandible than angle class II patients without ICR.

Angle class II patients with ICR of the TMJ showed significantly less labially inclined maxillary incisors than angle class II patients without ICR, although angle class II patients both with ICR and without ICR had labially inclined maxillary incisors. Angle class II patients with ICR also showed significantly less horizontal overlap than angle class II patients without ICR. In addition, angle class II patients with ICR had a significantly steeper (clockwise rotated) functional occlusal plane. These novel maxillofacial characteristics of angle class II patients with ICR were shown in the present study.

Increased horizontal overlap in angle class II patients with ICR was significantly associated with greater class II intermaxillary relationships (more posterior position of the mandible relative to the maxilla) and a smaller condylar ratio. Greater class II intermaxillary relationships were also significantly associated with increased horizontal overlap in angle class II patients without ICR. These results could show that the maxillofacial phenotype of angle class II patients with ICR may originate in osseous changes of the condyle.

The backward-rotated mandibular ramus in angle class II patients with ICR was significantly associated with a larger gonial angle, steeper mandibular plane, and smaller condylar ratio. A smaller condylar ratio was not significantly associated with a backward-rotated mandibular ramus in angle class II patients without ICR. These results of multiple linear regression analyses of the present study could therefore show that osseous changes of the TMJ condyle may affect backward rotation of the mandibular ramus in angle class II orthodontic patients with ICR of the TMJ. From the clinical viewpoint,

the results of the present study suggest that orthodontists should pay attention to the potential for ICR of the TMJ when adolescent angle class II patients show less labially inclined maxillary incisors and a steeper occlusal plane, in addition to a backward-rotated mandible. When orthodontists diagnose adolescent angle class II patients with such morphology, they should examine the TMJ in detail and explain the potential for future ICR to such patients.

Angle class II orthodontic patients with ICR of the TMJ showed a significantly smaller condylar ratio, shorter mandibular ramus height, increased 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 showed shorter condylar height attributable to osseous changes of the TMJ condyle, and the shorter condylar height may affect the subsequent backward rotation of the mandibular ramus.

Roque-Torres et al²⁷⁷ described mandibular deviation to be one of the most common craniofacial deformities. Midline lateral displacement of the mandible or maxilla may have dental or skeletal causes, resulting in asymmetric growth or other changes that affect craniofacial growth. However, facial growth pattern, occlusal forces, dental occlusion changes, increases or decreases of muscle activity, functional pathologic changes, sex, and age are factors that affect morphology and position of the TMJ. Previous studies have evaluated TMJ morphology and position, especially the condyle-fossa relationship and condylar morphology related to different malocclusions. However, the influence of the type of malocclusion is still controversial, and little has been studied regarding midline lateral displacement of the mandible and maxilla, either dental or skeletal. The condyle-fossa relationship can be understood in different ways, depending on the type of image used for diagnosis, as well as the reference planes used in positioning the patient's head at the examination. With the introduction of CBCT in dentistry, tomographic examinations are increasingly requested; they have benefits for diagnosis of the craniofacial bony structures, especially the position and morphology of the TMJ. Unlike 2D images, 3D CBCT images do not have overlapped anatomic structures or magnification and image distortion problems. CBCT images are reliable and accurate representations of the patient's anatomy, spatial location, size, and shape, in addition to providing accurate information about the relationship with adjacent anatomic structures. In addition, several studies have confirmed the accuracy of measurements of the images generated by the CBCT compared with 2D images. The objective of this study was to evaluate lateral displacements of skeletal and dental midlines to the sagittal plane in relation to the position of the condyles in class II patients by using the 3D reference plane on CBCT images. Lateral displacement of skeletal and

dental midlines in relation to the condyle head position, by using the 3D reference plane, showed significant correlations with the anteroposterior difference between the geometric center of the right and left condylar processes of class II patients.

de Bragança et al²⁷⁸ investigated if ultra-low frequency transcutaneous electric nerve stimulation affects centric relation registration. When evaluating the condylar position, one should consider that the influence of the dental contacts on the muscle function, which would naturally lead the jaw toward CR position, might be interrupted because of the presence of deflective contacts. The proprioception of the periodontal ligament of the teeth involved in occlusal interferences accounts for inducing the central nervous system to avoid this position, which leads the mandible toward MIP position, regardless of the position of the condyle heads in the articular fossa. Therefore, the use of neuromuscular deprogramming tools that eliminate or reduce the influence of the dental contacts on mandibular positioning is widely reported in the literature and facilitates the proper manipulation and CR recording.

Because of the action of muscle relaxation, the literature recommended the use of ULF-TENS before the maxillomandibular record to find a more physiologic position for the patient. However, in this study, the use of ULF-TENS did not influence the total displacement or the direction of condyle displacement. Some disturbances in the lateral pterygoid muscle activity are related to the condylar position and intraarticular disorders, but there is no strong scientific evidence that supports this concept or explains the exact function of this muscle in the stomatognathic system.

The ULF-TENS application, before the CR record, did not change the total displacement or the condylar position. Therefore, there is no clinical relevance for using the ULF-TENS before the centric relation record with these studied techniques.

Hegab et al²⁷⁹ discussed the thickness of occlusal splints indicating that (1) splints ranging from 1 to 8 are related to different treatment results; (2) splints ranging from 12 mm to 15 mm in thickness may alleviate clenching; and (3) splints 4.4 mm to 8.2 mm in thickness may relax masticatory muscles more satisfactorily than 1-mm-thick splints. Thus, the vertical thickness of occlusal splints appears to be a key factor in treatment success.

The selection of the vertical thickness of occlusal splints in these reports was based on personal experience and the clinical results of different studies without evidence-based research. In the present study, the selection of the vertical thickness of the occlusal splint based on the condylar and disk movements observed during MRI acquisition could be considered an evidence-based method. The findings of this study suggest that an increase in the vertical thickness of the occlusal splint is associated with better clinical outcomes for patients with

internal derangement of the TMJ. These clinical results are supported by the MRI changes of the condyle-disk-fossa complex associated with an increase in the splint thickness from 2 mm to 6 mm.

This study demonstrated that an increase in splint thickness was associated with an increase in anteroposterior condylar movements, anteroposterior disk movements, and vertical condylar movements and led to improved clinical outcomes. Although the results of this study may suggest that the thicker splint is effective in patients with TMDs with DDNR, it is difficult to determine the best thickness of a splint. Based on MRI measurements and clinical outcomes in this study, the recommendation is a 4-mm vertical splint thickness for DDR and a 6-mm vertical splint thickness for DDNR cases and at least 1 year of treatment.

TMJ surgery

Zhou et al²⁸⁰ authored an article related to disk repositioning. Anterior disc displacement (ADD) is one of the most frequent TMJ disorders, which often results in clicking, joint pain, limited range of motion, and masticatory difficulties. Disc repositioning is a procedure to eliminate mechanical interference, relieve pain, and improve range of motion. This study evaluated the long-term stability of this technique by MRI.

There were 535 patients who underwent disc-repositioning surgery by 1 senior surgeon from 2010 through 2016. One hundred seven patients (149 joints) were included in the study. There were 11 men and 96 women, with a mean age of 29.04 years (range: 13-65 years). Twenty-five patients were younger than 18 years. The follow-up period was 12 to 84 months (mean: 23.40 months). Forty-three joints on the left side, 22 on the right side, and 42 on the right and left sides were operated on. T1 MRI scans showed that all 149 discs were repositioned; of these, 139 discs (93.29%) were in an overcorrected position and 10 discs (6.7%) were in a normal position. T2 MRI scans showed that 95.3% of discs (142 of 149) were still in a normal or overcorrected position, whereas 7 discs had relapsed with anterior displacement. Of the 7 relapsed discs, 2 were not overcorrected on T1 MRI scans. Five patients had relapse at 1 year, and 2 patients had relapse at 2 years after the operation. For the condylar bone, new bone formation was observed in 111 joints (74.50%); of these, 79 joints had new bone formed at the superior or posterior parts of the condyle, and 7 were at the anterior part of the condyle. Twenty-five joints of 18 young patients (age range: 13 to 26 years; mean age: 18.8 years) had new bone covering the entire condyle (anteriorly, superiorly, and posteriorly). No change was observed in 35 joints (23.49%). Bone resorption was observed in 3 joints (2.01%). New bone formation in relation to age was 90% in patients younger than 20 years, 73.68% in

those aged 21-40 years, and 43.48% in those older than 40 years.

Thus far, there is no direct evidence that disc repositioning can prevent bone resorption and stimulate bone regeneration. In this study, clear bone regeneration was found in 74.5% of joints (111 of 149) at MRI; especially young patients (<20 years) had apparent new bone formation in 90% of joints. This finding indicates that in a fast-growing stage, the condyle of adolescents might have vigorous growth ability after disc repositioning, which could decrease facial deformities. Therefore, the authors recommend that a reliable disc repositioning surgery should be taken into account in patients with anterior disc displacement (ADD) as early as possible, especially for teenagers, before the disc becomes severely deformed and shortened.

Zhu et al²⁸¹ discussed the effect of disc repositioning and postoperative functional splint for treatment of ADD in juvenile patients with class II malocclusion. TMJ ADD is a common malady that can lead to limited mouth opening, clicking, and joint pain. Dentofacial deformities such as malocclusion, mandibular retrognathia, and/or asymmetry can be induced when ADD occurs during the growth period. For the past decades, clinical researchers have reported that untreated ADD may be a critical factor that contributes to degenerative changes and even condylar resorption, which may increase the dentofacial deformity. Through quantitative analysis of magnetic resonance imaging (MRI), it has been found that displaced discs can decrease the height of the ipsilateral mandibular ramus because of condylar degeneration. Previous studies on patients with TMJ internal derangements have shown a high correlation between ADD and mandibular deformity. By evaluation of radiographs and MRI, previous research found that the more the disc is displaced and misshaped, the shorter the condylar height is and the more the mandible is deformed. Furthermore, animal studies have also shown that displaced discs load the condyle and inhibit its growth. Studies have also shown that conservative therapies including functional splints cannot stop condylar resorption. Whether disc repositioning could inhibit condylar resorption and stimulate bone regeneration has drawn increasing attention. The purpose of this study was to evaluate the effect of disc repositioning and postoperative functional splints in the treatment of ADD in juvenile patients with class II malocclusion.

Fourteen patients with 28 joints were included in the study. Among them, 13 were female and 1 was male. Their average age was 16.7 years (range: 12 to 20 years). Seven patients with 14 joints had MRIs made more than 6 months before disc repositioning. Between the pre-treatment MRI and the one performed just before surgery, 9 joints (64.3%) developed condylar bone resorption, and the other 5 joints (35.7%) had new bone

regeneration. Most of the change was located at the posterior border of the condyle (21.4%). MRI measurement showed condylar height had decreased an average of 0.81 ± 0.61 mm. MRI showed that all 28 joints had new bone regeneration located on the top and anterior-posterior borders of the condyle.

As a common disease in juvenile patients, TMJ ADD was strongly associated with mandibular retrognathia and asymmetry. Previous studies also revealed a higher incidence of ipsilateral jaw deviation in young unilateral ADD patients (72.12%) than in patients with normal joints (25.64%). Moreover, with time, condylar degeneration and jaw deformity became more severe. In this study, it was found that the natural course of ADD in juvenile patients with class II malocclusion could involve worsening of their malocclusion in a high percentage of patients (64.29%) because of continued condylar resorption. Although 35.71% of the untreated condyles had new bone formation, it was located mostly at the posterior border of the condyle (21.42%), not at the superior part, which will elongate the condyle. Hence, for those patients, whether disc repositioning could stimulate condylar growth and alleviate mandibular deformity is worthy of study. Previous studies have shown that functional splints, such as a Herbst, twin-block, or activator, could stimulate condylar growth and mandibular development in ADD with reduction by holding the mandible forward to adjust the disc condyle relationship. However, for ADD without reduction, functional splints may aggravate disc displacement and cause condylar resorption. In this study, the displaced TMJ disc was reduced. Then, a functional splint was used within 2 months after the operation to position the mandible forward. Results showed that all condyles in these patients had new bone formation located mostly at the superior and posterior parts of the condyle. The condylar height increased 1.74 ± 0.98 mm on average, which demonstrated that the mandible grew downward and forward.

The present study²⁸¹ also showed that disc repositioning could stimulate bone regeneration. Compared with no treatment and solely functional splint treatment, disc repositioning by surgery can increase condylar height. In this study, 92.3% of the condyles had new bone formation, which was located mostly at the superior-posterior part of the condyle. This can alleviate mandibular retrusion and decrease incisor horizontal overlap.

Orthodontic functional splints were used within 2 months after disc repositioning to adjust the mandibular position and create space for condylar growth. The authors believe that the earlier the splint is used, the better the results are, possibly because the regional acceleratory phenomenon (RAP) works in a limited time. The function of the splint is to bring the jaw gradually forward and

to hold the space created by disc repositioning. After confirming on MRI that new bone had formed and filled the joint space (usually 4 to 6 months), the functional splint can be removed and orthodontic treatment for the teeth can begin.

The peak velocity of mandibular growth appears at 12.5 years in girls and at 14.5 years in boys. In girls, approximately 98% of facial growth is usually completed by age 15 years and in boys by approximately age 17 or 18 years. Therefore, for skeletal class II malocclusion juvenile patients with bilateral ADD, positive treatment such as disc repositioning with postoperative functional splint therapy can promote condylar regeneration, which will alleviate jaw deformity and make the definitive orthodontic treatment easier.

Conservative treatment for ADD with class II malocclusion in juvenile patients may cause condyle resorption and aggravate the dentofacial deformity. Disc repositioning combined with postoperative functional splints can effectively promote condylar growth and help correct the dentofacial deformity.

SLEEP-RELATED BREATHING DISORDERS

A strong opinion among sleep researchers and physicians, evident throughout the literature this year, is the use of Apnea Hypopnea Index (AHI) as a clinical standard for the measurement of sleep disordered breathing severity. The discontent for this measurement was brought into heavy focus during the April 16, 2018, FDA workshop on "Study Design Considerations for Devices Including Digital Health Technologies for Sleep Disordered Breathing in Adults." The workshop began with the question, "What is the definition of an apnea?" As an attendee, my belief is that not one of the represented groups from the major academic sleep researcher laboratories could agree, even in general terms, on what constituted an apneic event. The term hypopnea was even more undecided. The group concluded that revising diagnostic criteria for obstructive sleep apnea (OSA) is necessary to include factors that encompass different clinical and pathophysiological phenotypes and pertinent comorbidities, such as nondipping nocturnal blood pressure.²⁸² Moreover, they call for revision to current severity thresholds to include factors such as the disparity in AHI between polysomnography (PSG) and sleep studies that do not measure sleep stage measurements, in addition to the poor correlation between AHI and daytime symptoms such as excessive sleepiness. They noted that patient management decisions should be tied to the underlying phenotype and consider outcomes beyond AHI.

The importance to dentistry is that many patients exhibit temporomandibular disorder (TMD) and have symptoms of poor sleep but register as "normal" (AHI<5) with objective sleep testing. The diagnosis of normal

typically eliminates all insurance benefits for mandibular advancement device (MAD) therapy for this group, which tends to be predominant in female. The result is daily suffering until the condition worsens to an AHI>5 and sometimes AHI>15, depending on coverage, before the patient is allowed to be treated. The American Thoracic Society Assembly on Sleep and Respiratory Neurobiology created a mini-symposium to address the issue of low-AHI symptomatic patients at the May 2018 Annual Meeting in San Diego, California.

The review for this year contains 1 article that addressed the need for multiple nights of study to gain a full perspective of the patient's sleep condition. It was also stated that Home Sleep Apnea Testing (HSAT) be used to analyze the patient's sleep habits. Alcohol and other sedatives can dramatically change the patient's sleep quality. A hospital in-laboratory polysomnography does not address negative habits practiced by the patient in the home environment. This is of special concern for dentistry because MADs are not mechanical, in comparison to continuous positive airway pressure, which can overcome the impact of substances. The nature of MADs' impact on the posterior airway space is more affected by habits and body position that negatively impact sleep quality.

An article was published this year concerning the removal of fluoride from the water in Juneau, Alaska.²⁸³ It may seem strange to address water fluoridation in the sleep section of this report, but a thematic poster presentation, "Global prevalence of obstructive sleep apnea in adults: estimation using currently available data," on May 21 (Monday) at the American Thoracic Society's Annual Meeting in San Diego, California, was eye-opening. It is estimated that 1 000 000 000 people worldwide are afflicted by obstructive sleep apnea (OSA). The number would be impossible to treat with CPAP, which means the MAD would be needed as a treatment option. The MAD depends on teeth in reasonable condition to support the dental appliance. A patient with the benefit of fluoride is more likely to have a suitable compliment of teeth as an older adult, thereby allowing for the use of a MAD. The situation amplifies when one considers the increase of the edentulous population. CPAP has difficulty with mask fit if the patient is edentulous. If the oral appliance is chosen because of a CPAP intolerance rate of approximately 50%, dental implants would possibly be necessary for OSA and might prove to be cost-prohibitive on a wide scale; a modified MAD-incorporating maxillary and mandibular complete dentures might be another solution, assuming that successful prostheses are in place. The use of fluoride is a benefit not only to the youth but also to the older adult as well. OSA is the comorbid condition for many of the major disease processes that afflict the US

population. The removal of fluoride from drinking water is terribly shortsighted.

Finally, a recent article that addresses hyperventilation syndrome in patients suffering from empty nose syndrome was published in 2017.²⁸⁴ However, nasal breathing after turbinate and septal surgery can cause seemingly unexplained complications with a MAD. It is recommended to include a question in the health intake questionnaire asking if this surgery has been performed by those providing MAD therapy for OSA patients.

Oral appliance therapy

One study set out to examine mandibular movement assessment as a method to evaluate efficacy of oral appliance therapy (OAT) in obstructive sleep apnea (OSA).²⁸⁵ The respiratory event index derived from vertical mandibular movements (MM-REI) is a possible marker of greater respiratory effort during sleep. They looked at the effectiveness of mandibular advancement splint (MAS) therapy using MM-REI and compared it with the apnea hypopnea index (AHI) and oxygen desaturation index (ODI). Fifty-six participants (median age: 47 years) with a diagnosis of OSA were treated with a custom Herbst-style MAS. They were evaluated at the end of the titration process when snoring was reported absent by the bed partner. A magnetometer was used to capture mandibular movements. MAS efficacy was evaluated as the percentage change from baseline, by using Bayesian multilevel models. All indices of OSA severity decreased compared with baseline after completion of titration: AHI (−48.9% to 71.1%); ODI (−49.5% to 77.2%); with obstructive hypopnea index and MM-REI showing the largest responses (−70.6% to −88.5% and 69.5% to 96.3%, respectively). MM-REI normalization as demonstrated by reductions in both mandibular movement event rate and duration accurately reflected efficacy of the device. They concluded that the reduction of vertical respiratory mandibular movements estimated by MM-REI and sleep respiratory effort duration accompanied the reduction in obstructive hypopneas, ODI, and AHI after snoring resolution in OSA patients treated with optimally adjusted MAS.

An observational cohort study in a Republic of Korea tertiary hospital setting sought to identify adequate criteria to determine the success or failure of mandibular advancement device (MAD) therapy for OSA based on new-onset hypertension (HTN) and long-term symptoms.²⁸⁶ Ninety-seven adults with a diagnosis of OSA who had been treated with MAD over almost 8 years were enrolled. Participants underwent objective testing before therapy and 3 months after device delivery. Success or failure was determined based on 7 different criteria. MAD compliance, witnessed apnea, snoring, Epworth Sleepiness Scale (ESS) score, and occurrence of new-onset HTN were surveyed via telephone follow-up

to determine the criteria that could elucidate success and failure of MAD therapy. Mean follow-up duration was 60.5 months, and mean AHI was 35.5/h. Two of 7 criteria could substantially differentiate the success and failure groups based on long-term symptoms: AHI<10/h with MAD and AHI<10/h and AHI reduction of >50% with MAD. Kaplan-Meier survival analysis demonstrated that success and failure groups were based on new-onset HTN ($P=.035$). The cutoff AHI for new-onset HTN based on receiver operating curve was 16.8/h (71.4% sensitivity and 75.0% specificity). This study suggested that AHI<10/h, AHI<10/h and AHI reduction of >50%, and AHI<15/h (all with MAD in place) may be useful in determining success from failure within the study population. They note that further studies are warranted to validate the findings presented.

A double-blinded, randomized controlled trial sought to determine the impact of MAD therapy on ambulatory nighttime and daytime blood pressure in women and men with daytime sleepiness and snoring and mild or moderate sleep apnea (AHI<30).²⁸⁷ Over a 4-month span, 96 untreated patients (31 women and 65 men; age 31 to 70 years) participated. The active group was fitted with adjustable MADs, and controls were given custom-made sham devices to be worn during sleep. Polysomnographic sleep measurements and ambulatory 24-hour blood pressure recordings were performed at baseline and at follow-up. In women with MAD, the mean nighttime systolic blood pressure was 10.8 mm Hg (95% confidence interval)=4.0-17.7 mm Hg; $P=.004$) lower than women in the sham arm, adjusted for baseline blood pressure, age, body mass index (BMI), and AHI. The mean nighttime adjusted diastolic blood pressure was 6.6 mm Hg (95% confidence interval=2.7-10.4 mm Hg; $P=.002$) lower in the MAD group. In men, there were no significant alterations in blood pressure at night or during the daytime between the intervention groups. The authors concluded that MAD for OSA reduces nocturnal blood pressure in women. Based on the sample size of 27 women, these results need to be interpreted cautiously until replicated.

A review revisited side effect avoidance and management during OAT therapy.²⁸⁸ It is noted that considering all potential side effects thoroughly before initiating individual treatment with MAD is important. Many side effects are self-limiting, easily remediated, or innocuous; other side effects are difficult or impossible to correct and may impact the patient. The author states that if alternative treatment is not acceptable, the carefully weighed risk of no therapy is what allows clinicians to justify these likely problems to coexist with OAT. It is critical for dental sleep medicine providers to stay updated with continuing education and prudent practice to operate ethically in the care of OSA patients with OAT.

A systematic review and meta-analysis was performed to evaluate continuous positive airway pressure

(CPAP) and MAD therapy in patients with OSA.²⁸⁹ Specific comparisons were made in quality-of-life (QOL) domains, including sleepiness and cognitive and functional outcomes in these patients. Randomized, placebo-controlled studies were selected from MEDLINE via PubMed, Web of Science, and Cochrane Library databases. The initial search revealed 240 studies, which were reduced to 12 relevant articles. CPAP patients exhibited no statistically significant difference in post-treatment QOL measured with the SF-36 mental health component ($P=.994$) or SF-36 physical functioning component ($P=.827$). There was no significant improvement in Functional Outcomes of Sleep Questionnaire ($P=.788$) or cognitive performance ($P=.395$) as compared with patients with OAT. The meta-analysis elucidated a significant improvement in posttreatment AHI for CPAP as compared with oral appliance group ($P<.001$) and unclear results for daytime sleepiness with average ESS ($P=.203$) but significant differences in change in ESS from baseline favorable to CPAP therapy ($P=.047$). Compliance was 1.1 hour lower per night with CPAP as compared with MAD ($P=.004$), which might explain why no significant differences are shown for QOL measures even with a greater AHI reduction with CPAP. This review and analysis did not generate novel information for the sleep medicine community.

Another study evaluated the clinical feasibility of a novel OAT device with an objective compliance recorder (OAT-CR) and reported the data.²⁹⁰ The authors claim their study to be the first study to report on a commercially available OAT-CR. It was a single-center pilot study using an intercept case format. Eight consecutive patients already diagnosed with OSA who were undergoing treatment with a standard MAD were enrolled in the study. Each participant received a new custom-made OAT-CR. The objectively recorded data were acquired at subsequent follow-up visits. The recording device was successful for 8 of 8 patients. The objectively recorded compliance rate was 87.9% \pm 20.4%; the average usage was 7.4 \pm 1.4 hours per night. The authors concluded that the new OAT-CR is an option for clinical situations where objective compliance tracking is required or preferred. Reported compliance and usage affirm data reported in previous studies.

A different project set out to assess the influence of mouth opening on the outcome of MAD therapy in participants with positional OSA (p-OSA).²⁹¹ Sleeping in the supine position can elevate the risk of sleep-disordered breathing (SDB). Individuals with p-OSA have a supine AHI that is at least 2 times greater than that in nonsupine positions. Secondary data of 230 patients treated for p-OSA with MAD (standard MAD group) or MAD plus vertical elastics to prevent mouth opening (MAD+elastics group) were compared in terms of treatment response. Therapy success was defined

as $\geq 75\%$ reduction in AHI from baseline. Secondary outcomes included change in AHI, supine AHI, and nonsupine AHI. Both groups demonstrated a substantial decrease in AHI with MAS in situ. MAD+elastics group experienced a greater decrease in AHI, supine AHI, and nonsupine AHI than the standard MAD group; treatment success rate was significantly increased in the MAD+elastics group (67.4% versus 36.2%; $P < .001$). The odds of successful treatment with the use of vertical elastics increased 3.8-fold after adjusting for confounding variables. They concluded that this pilot study suggests that vertical elastics that minimize mouth opening enhance MAD treatment outcomes in those with p-OSA. Further research is warranted to verify the role of vertical elastics with bimaxillary oral appliances to enhance the response to treatment in patients with p-OSA.

Obstructive sleep apnea is associated with chronic inflammation secondary to nocturnal hypoxemia. Neutrophil-to-lymphocyte ratio (NLR) is a measure of subclinical systemic inflammation. This study investigated alterations in NLR levels resulting from treatment of OSA with MADs.²⁹² Pretreatment and posttreatment complete blood counts (CBCs) were obtained. NLR was derived by dividing the number of neutrophils by the number of lymphocytes obtained from the CBCs. Individuals with preexisting conditions known to impact NLR were excluded from this study. Twenty-two participants met inclusion criteria and completed the study protocol; their NLR and ODI were compared before and after therapy with MAD. There was a significant difference in NLR before and after treatment ($P = .01$); the difference in 3% ODI and 4% ODI before and after treatment was also significant ($P = .014$ and $P = .007$, respectively). In a subgroup analysis exploring NLR in those treated optimally versus those treated suboptimally, a significant decrease was shown in the optimally treated group ($n = 10$, $P < .01$) as opposed to the suboptimally treated arm ($n = 12$, $P = .349$). It was concluded that NLR might be useful in demonstrating improvement in systemic inflammation in OSA patients undergoing MAD therapy, and NLR values are tied to the decrease in ODI.

Another literature review provided an updated look at OAT for the management of OSA.²⁹³ This review covered appliance classification and mechanism of action; indications for use; titration; prediction of treatment response; and a discussion of defining treatment success, efficacy versus effectiveness, and comparison with CPAP. Adherence to therapy and mean disease alleviation were examined. Combination therapy and side effects were also covered. This article is a current rehash of topics that have been previously covered extensively within the literature.

Researchers in Turkey examined the long-term (LT) adherence to MAD treatment and patients' experiences

related to the course of treatment.²⁹⁴ Sixty-nine patients participated in the study (52 men and 17 women; mean age: 54.4 ± 10.8 years). Mild (56%) and moderate (44%) OSA had been treated for at least 4 years previously with a MAD. Phone surveys were carried out to determine demographic characteristics as well as to ascertain self-reported adherence to therapy, subjective LT effectiveness, and individual experiences with their appliances. Data analysis consisted of descriptive statistics, Pearson chi-square test, and independent sample *t* test. Only 22 (32%) respondents reported regular appliance use. Most of the participants who were nonadherent discontinued appliance use in the first year (55%); the mean duration of device use was 33.5 months (median: 12 months). No significant differences were found in appliance type, disease severity, educational level, sex, marital status, income status, employment status, or place of residence between adherent and nonadherent individuals. Adherent participants were substantially younger than nonadherent patients (50.6 ± 11.9 versus 56.1 ± 9.9 years, $P < .05$). The most prevalent reasons reported for discontinuation included inability to adapt to the appliance (62%) and TMJ pain (38%); continued use was due to effectiveness (100%) and ease of use (64%). It was concluded that nonadherence to MAD was high, and measures should be taken to prevent side effects and increase utilization of OAT in OSA patients to strive for better treatment outcomes.

A study assessed whether CPAP pressures predicted OAT outcomes in patients that failed auto-CPAP therapy.²⁹⁵ According to the authors, research has demonstrated that therapeutic CPAP pressure is associated with OAT outcomes in patients with OSA. These studies included either CPAP-adherent patients using fixed pressures or partly CPAP nonadherent individuals using fixed pressures or auto-adjusting (a-PAP) devices. a-PAP is predominantly used in many countries, and only those who do not adhere to therapy need to switch to an oral appliance. Therefore, studies evaluating the connection between CPAP pressures and OAT outcome should focus on the patient's nonadherence to a-PAP. Eighty-seven patients with moderate-severe OSA were included. OAT responders and nonresponders were defined by 2 success criteria: (1) $AHI < 5$; (2) $5 \geq AHI < 10$ and $> 50\%$ AHI reduction. Logistic regression analyses were performed for CPAP pressures and baseline variables. ROC curve analyses were conducted to identify CPAP pressure cutoff values, alone and combined with other explanatory variables, predicting OAT outcomes. Maximum CPAP pressures ($CPAP_{max}$) were higher in nonresponders by both criteria and were, together with baseline AHI, associated with OAT outcomes in multivariate regression analyses. ROC curves identified an optimal $CPAP_{max}$ cutoff of 12 cm H_2O , relating to a positive predictive value (PPV) of 0.85 in predicting

nonresponse using criterion 1. A prediction model joining CPAP_{max}>12 and baseline AHI \geq 30 had a PPV of 1.0 for nonresponse by both criteria. The authors concluded that maximum CPAP pressure was a moderate predictor of OAT outcome, but combined with baseline AHI, the ability to identify OA nonresponders was high.

A different trial sought to determine whether drug-induced sleep endoscopy (DISE) would be useful in predicting OAT outcomes.²⁹⁶ A retrospective review of patients undergoing DISE over 2.5 years designated the DISE group; patients undergoing OAT based on recommendations from the DISE were included (n=20). Control participants were chosen from patients undergoing polysomnography (PSG) with an oral appliance in place but who had not received DISE (no DISE group, n=20). No differences between the 2 groups existed with respect to age, sex, pre-OAT BMI, post-OAT BMI, or pre-OAT PSG markers including AHI, oxygen desaturation nadir, or ESS score. Post-MAD AHI was significantly lower ($P=.04$), and more patients reached an AHI<5/h with OAT ($P=.04$) in the DISE group. They concluded that patients showing increased airway dimensions at the level of the velum and/or oropharynx with a jaw thrust may benefit the most from OAT, and using DISE to identify this subset of patients is helpful in optimizing outcomes with appliance therapy.

A retrospective, single-center cohort study also looked at DISE using different passive maneuvers to affect upper airway (UA) patency during examination as compared with literature on treatment outcomes of positional therapy (PT), OAT, and combined treatment for OSA patients.²⁹⁷ A consecutive series of 200 OSA patients participated (80.5% male; mean age: 50.1 \pm 11.7 years; BMI: 27.0 \pm 3.1; median AHI: 19.2/h). All underwent DISE with and without manually performed jaw thrust and lateral head rotation by using the VOTE classification. The results of the maneuvers were analyzed by using the sum VOTE score comparing nonpositional (NPP) and positional (PP) OSA patients. Forty-four percent of the participants were NPP; of the remaining 56%, 34% were diagnosed with supine isolated and 66% with supine predominant p-OSA. Manually performed jaw thrust demonstrated a reduction of sum VOTE score of 66.7% in all subgroups. Lateral head rotation showed a reduction of 33.3% in NPP and supine predominant PP and 50% in supine isolated PP. A combination of the 2 maneuvers led to a reduction of >75% in all patients. They note that this model leaves room for improvement; the effect of manually performed jaw thrust is greater and lateral head rotation alone is less than what was expected compared with recent literature on OAT, PT, and combined therapy.

Another retrospective study evaluated the predictors of dental changes associated with long-term (LT) treatment with oral appliances in Japanese patients with

OSA.²⁹⁸ Cephalometric analyses were carried out at initial and follow-up visits to assess dental and skeletal changes. Based on dental changes, predictors that may cause side effects were investigated. Sixty-four patients (mean age at start of treatment: 57.7 \pm 14.2 years, 44 men) participated. The average duration of therapy was 4.3 \pm 2.1 years. Over the total treatment duration, there was a significant decrease in horizontal overlap (HO) (1.5 \pm 1.3 mm) and vertical overlap (0.90 \pm 1.5 mm) and an increase in the mandibular incisor line to the mandibular plane (3.1 \pm 5.4 degrees). A larger decrease in HO of \geq 1 mm was associated with treatment duration, use frequency, and mandibular movement of the MADs. The number of teeth was also correlated with the amount of HO reduction. They concluded that the risk of dental side effects (such as a reduction in HO) should be considered in LT treatment of OSA with OAT. A small number of maxillary teeth, as well as appliance factors such as treatment duration, use frequency, and mandibular advancement, were correlated with an elevated rate of HO reduction.

Another study explored whether patients' maximum protrusion could be increased after wearing a MAD for 3 months, such that individuals with weak protrusion (who could at first be ineligible for effective treatment) could become candidates for the therapy.²⁹⁹ The treatment group consisted of 30 patients with PSG-diagnosed OSA; 30 healthy participants without OSA were matched controls. MAD was worn for 90 days while the control group received no treatment. Both groups underwent 2 assessments of mandibular borderline movements (protrusion, maximum opening, and left and right lateral movement) at baseline and 3 months with computerized mandibular scanning. Wearing the device did not cause greater changes in mandibular movements compared with controls; in the MAD group, maximum opening decreased, lateral movement increased, and maximum protrusion increased. Individuals with weak maximum protrusion at baseline demonstrated increased maximum protrusion. The authors note that further research is needed to assess changes in maximum protrusion in patients with minimal protrusion. MAD has the potential to be an effective treatment option for patients with a pretreatment maximum protrusion <5 mm.

An Australian group set out to determine if a qualitative classification system of awake, nasopharyngoscopic observations would reflect treatment response during MAD for OSA.³⁰⁰ Patients were recruited for therapy with a custom, 2-piece appliance (n=80, 53.8% male). A custom scoring sheet was used to record observations of the pharyngeal airway (velopharynx, oropharynx, hypopharynx) during supine nasopharyngoscopy in response to mandibular advancement and performance of the Müller maneuver. Qualitative scores for degree (<25%, 25% to 50%, 50% to 75%, >75%), collapse pattern

(concentric, anteroposterior, lateral), and diameter change (uniform, anteroposterior, lateral) were recorded. Treatment outcome was verified by PSG after a titration period of 14.6 ± 9.8 weeks. Treatment response was defined as treatment AHI < 5, treatment AHI < 10 plus > 50% AHI reduction, or > 50% AHI reduction. The most common nasopharyngoscopic finding with mandibular advancement was a small (< 50%) increase in velopharyngeal lateral diameter (37.5%). Most of the individuals (72.5%) were recorded as having > 75% velopharyngeal collapse during the Müller maneuver. Mandibular advancement decreased the observed level of pharyngeal collapse at all 3 levels of the pharynx ($P < .001$). None of the nasopharyngoscopic qualitative scores differed between responder and nonresponder groups. They concluded that qualitative assessment of awake nasopharyngoscopy appears useful for assessing the effect of mandibular advancement on UA collapsibility. However, it lacks the sensitivity to predict the OAT outcome.

Another study sought to examine the feasibility of the application of a remotely controlled mandibular positioner (RCMP) during DISE for the determination of effective target protrusive position (ETPP) for patients with OSA.³⁰¹ Ten patients in whom OSA was diagnosed (1:1 male to female; age: 54 ± 9.5 years; BMI: 26.9 ± 2.1 ; AHI: 28.4 ± 13.2 /h) were enrolled prospectively. Dental RCMP trays were fitted while the participants were awake; maximal protrusion and edge-to-edge positions were measured. Upper airway collapsibility was scored during DISE, including full-range mandibular RCMP titration within 45 minutes. ETPP was defined as the mandibular threshold protrusion yielding a stable UA in the absence of snoring, oxygen desaturation, and apneas. RCMP trays were fitted intraorally before sedation with maxillary and mandibular trays in edge-to-edge position; they were retentive, and no adverse issues arose. After sedation, progressive mandibular advancement was carried out, followed by reversed titration until ETPP was evident. One participant had ETPP fall outside the mandibular range of motion; 1 participant had the RCMP removed because of clenching. The authors concluded that it is feasible to use RCMP during DISE and to determine ETPP within 45 minutes. They note that comparative studies with PSG would be helpful to further validate the therapy outcome upon use of RCMP during DISE.

A systematic review provided a comprehensive review exploring the craniofacial side effects of OAT for snoring and OSA.³⁰² PubMed and Virtual Health Library databases were searched from their inception until October 2016. They selected RCTs whose primary aim was to measure objectively identified side effects on craniofacial complex from a custom-made OA for treating primary snoring or OSA. Participants were aged ≥ 20 years. Bias risk was evaluated in accordance with the

recommendations of The Cochrane Risk of Bias criteria. Sixty-two full-text articles were assessed for eligibility; following review, 6 met the inclusion criteria. All studies were rated as having a high risk of bias. The most uniformly reported side effects secondary to MAD therapy were mostly dental in nature and included a decrease in horizontal and vertical overlap. The risk of developing pain and function impairment of the temporomandibular complex appeared limited with long-term device use. They concluded that MAD for snoring and OSA results in changes in craniofacial morphology that are primarily dental in nature, especially with LT use. Based on the chronic nature of OSA and that OAT may be a lifelong treatment, careful follow-up should be considered to evaluate for craniofacial alterations. Appropriate informed consent before treatment commencement is necessary. Longer term studies of OAT impact with larger study numbers and homogenous populations are warranted.

Sleep bruxism and temporomandibular disorders

A review dealt with temporomandibular disorders (TMDs) and OAT for SDB.³⁰³ TMD is an umbrella term for pain in the face, head, and neck; cervical disorders are integral components of TMDs. Three-dimensional maxillomandibular relationships are important in the assessment and management of TMDs with appliance therapy. Sleep disorders and TMDs are intimately related. MADs may have side effects on TMDs. This review did not contribute important new information to the sleep medicine literature.

Another review examined research from the last 10 years concerning the use of oral appliances in the management of sleep bruxism (SB) in adults.³⁰⁴ Sixteen studies of 641 identified citations involving 398 individuals were included in the review. Seven were RCTs, 7 were uncontrolled before-after studies, and 2 were crossover trials. Analysis of the articles revealed a high degree of variability of study designs and results. The risk of bias was low to unclear for RCTs and high for crossover studies, while the before-after studies demonstrated several structural limitations. Nine studies used PSG/polygraphy/electromyography for SB diagnosis; others were based on history-taking and clinical examination. Most featured small sample sizes and lasted for a short term. Of those using objective SB evaluations, 8 showed positive results for almost every type of OA in decreasing SB activity, with a higher reduction for devices that are designed to provide a certain amount of mandibular advancement. Among the studies using a subjective SB evaluation, 1 demonstrated a significant decrease in SB activity, and 2 others showed a myorelaxant effect of OA in SB therapy. Although many positive studies support the efficiency of OA treatment for SB, accepted evidence is insufficient to support its role in the LT reduction of SB

activity. It is noted that further studies with larger sample sizes and longer treatment periods are needed to obtain more validation for clinical application.

A different trial explored the presence of a first-night effect (FNE) and the extent of internight variability in SB activity when a self-applicable electrode set is used in home PSG in a sample of participants with possible SB.³⁰⁵ Fourteen women and 2 men (mean 38.3 ±9.1 years) with self-reported SB underwent home PSG on 3 consecutive nights. The participants applied PSG sensors themselves, including self-applicable electrode sets used to record sleep and masseter muscle activity. Repeated-measures analysis of variance was used to compare SB and sleep variables among the nights. The researchers were surprised to discern statistically significant increases in the rhythmic masticatory muscle activity (RMMA) episode index ($P=.009$), burst index ($P=.016$), and bruxism time index ($P=.049$) over the course of 3 nights. More participants were diagnosed as bruxers on the second (6 bruxers, ≥ 2 episodes/h) and third night (7 bruxers) compared with the first night (2 bruxers). Most individuals (14/16) had their highest RMMA index on the second or third night. The mean coefficient of variation for RMMA episode index was 50.7%. No statistically significant differences were noted in other sleep variables. They concluded that an FNE might be present in SB activity, possibly lasting several nights in some participants. Also, FNE appears to be combined with high internight variability of SB activity without indications of internight changes in sleep macrostructure. To confirm the level of ongoing SB activity, several nights of PSG may be necessary, especially in those with low first-night SB activity.

A Brazilian group evaluated the prevalence of probable SB and its association with sleep features, orthodontic fixed appliance wearing, and extraoral and intraoral clinical signs and symptoms in a population of adolescents.³⁰⁶ Two hundred thirty-nine 12-year-olds enrolled in private and public schools in Brumadinho, southeast Brazil, and their parents were recruited to participate. Two hundred thirty-one (96.6%) agreed to participate. They answered a questionnaire containing information regarding adolescents' sleep features and history of SB. Extraoral and intraoral examination was performed to identify certain clinical signs (absence of lip competence; presence of mouth breathing; clicks in the TMJs; tooth wear) and symptoms (pain in the masseter muscle upon palpation) and ongoing orthodontic treatment with fixed appliances. Parental report and clinical examination were used to determine probable SB. Descriptive statistics and logistic regression were performed to identify association of probable SB with independent variables. Prevalence of probable SB was 16.9%. Children who snored during sleep (OR=3.14; 95% CI=1.47-6.70), adolescents who did not have clicks

in the TMJ (OR=3.37; 95% CI=1.11-10.15), and those who wore orthodontic appliances (OR=2.72; 95% CI=1.04-7.14) were more likely to be in the group with probable SB. The authors concluded that snoring, absence of clicks in the TMJs, and wearing fixed appliances were associated with probable SB among adolescents. This adds to the ongoing research on SB in adolescents and its associated factors.

A commentary accompanied the previous 2 studies on SB.³⁰⁷ The authors noted that SB is a repetitive motor activity associated with tooth clenching and/or grinding. Owing to its clinical presentation and symptomatology, the diagnosis and management of SB falls mostly under the purview of sleep physicians and sleep dentists. The definitions, diagnostic tools, and management options offered differ between the 2 fields, creating confusion and lack of clarity around SB, impeding collaboration between the groups of specialists. A medical-dental collaboration is required to achieve optimal management when sleep breathing conditions or neurological disorders are suspected in children, adolescents, or adults. Concerning the study of adolescent SB,³⁰⁸ they note that self-reports and clinical examination findings are of interest in assessing risk factors but cannot explain causation. Future studies in this area should address these questions: (1) What is the role of oropharyngeal and facial growth on SB risk? (2) Are the adolescents with SB and snoring at risk of having sleep breathing issues in adulthood? (3) Why is snoring considered the primary risk factor for the development of sleep breathing problems? Concerning the study of SB and FNE,³⁰⁵ they note that it is unclear how many nights are necessary to capture the presence of RMMA and to avoid the FNE. PSG recording of at least 3 nights can help to better capture the oral behavior in a more natural setting, especially in those with low-frequency RMMA. A "dummy" night with home testing montage, as they demonstrate, can help reduce the adaptation period and improve tolerance to the unusual face connections. They note that dentists can screen and monitor for RMMA during sleep by using a 1-channel, type 4 recording device, but if findings are associated with risk of sleep disorders such as apnea or other conditions, referral to a sleep medicine specialist is warranted.

Pathophysiology and medical implications

A review was performed to explore current knowledge to assess whether available data are sufficient to guide policy decisions concerning restrictions to noncommercial drivers with OSA.³⁰⁸ Excessive daytime sleepiness and impaired cognitive function due to OSA have been identified as important health-related risks in commercial motor vehicle operation, possibly conferring an elevated risk of road accidents. As a result, a variety of policies and restrictions have been imposed on commercial drivers.

The review found that there is a lack of uniformity among different consensus conferences and guidelines as to how to treat drivers with OSA. Guidelines are typically unclear, and few are evidence-based. There is a question as to what is the most valid measure of OSA severity (for example, AHI versus ODI). Traditionally, sleepiness has been invoked as a major risk factor for impaired driving. More recently, daytime fatigue has been recognized as distinct from sleepiness and can impact driving behavior. However, the precise effect of fatigue on motor vehicle operation, as well as its role in the formulation of guidelines, remains to be studied. The authors concluded that there are at least 2 major difficulties for the driving recommendation process: (1) there is no accurate metric quantifying severity of driving risk associated with OSA; and (2) significant individual differences exist among those with OSA, both experiential and behavioral. They offer implications from the review for future research direction and policy creation.

Computer simulation to develop a high-fidelity model has been proposed as a novel and cost-effective method to help guide therapeutic intervention in sleep apnea surgery. This study describes a computer model based on patient-specific anatomy in those with OSA wherein the percentage and sites of UA collapse are compared with findings with DISE.³⁰⁹ Three-dimensional finite element techniques were undertaken for model development in a pilot study of 4 individuals with OSA. Magnetic resonance imaging was used to capture images of patients' anatomy, and a software program was used to outline critical anatomical structures. A finite-element mesh was applied to the volume enclosed by each structure. Each model underwent computer simulation to determine the degree of displacement on various structures within the UA and then compared with DISE on each participant. Computer simulation predictions for percentage of airway collapse and site of maximal collapse show agreement with results visualized with DISE. The authors concluded that modeling the UA in patients with OSA is feasible and holds promise in helping patient-specific surgical treatment.

Another study compared the effects of sleep deprivation and fragmentation on upper airway dilator muscle responsiveness during wakefulness.³¹⁰ Poor UA dilator muscle function may contribute to OSA; sleep deprivation reduces dilator muscle responsiveness, but sleep fragmentation has not been assessed. Twenty-four healthy participants (10 women) participated in 2 consecutive overnight PSG sessions. The first was to adapt the recordings to normal sleep. The second was an experimental PSG where individuals were designated to groups of normal sleep, no sleep, or fragmented sleep. Inspiratory resistive loading assessment occurred the morning after each PSG. Four 10-cmH₂O and four 20-cmH₂O loads were presented in random order for 60

seconds while participants were awake and supine. Sleep (EEG, EOG, EMG), intramuscular genioglossus activity (EMG-GG), and ventilation were measured throughout the loading sessions. Five controls, 7 sleep deprivation individuals, and 7 sleep fragmentation participants provided information. Contrary to expectations, neither EMG-GG nor ventilation showed significant interaction effects (group×session×load) during resistive loading. There was a main effect of load, with peak EMG-GG (average % max ±standard error) significantly higher for the 20 cmH₂O load (4.1 ±0.6) than the 10 cmH₂O load (3.3 ±0.6) across both sessions and all groups. Similar findings were observed for peak inspiratory flow, duty cycle, and mask pressure. The authors concluded that UA function was not impacted by one night of no sleep or poor-quality sleep. This raises doubt as to whether fragmented sleep in OSA increases disorder severity via decreased UA dilator responses.

A different project investigated the effects of increased pharyngeal tissue mass on the acoustic features of snoring sounds.³¹¹ Snoring sounds are produced by the vibration of pharyngeal tissue due to UA narrowing. A microphone placed around the neck may record snore sounds passing through pharyngeal tissue surrounding the UA. Therefore, alterations in the pharyngeal tissue mass may change the acoustic properties of snoring sounds. Rostral fluid shift and resultant elevations in neck fluid volume (NFV) and neck circumference (NC) can increase pharyngeal tissue mass. Data were obtained from a previous study in which 20 nonobese men participated in a daytime PSG, and their NC and NFV were measured before and after sleep. A microphone over the neck recorded snore sounds during sleep. The spectral centroid of the snore sounds was estimated; then, the first 5 snoring segments were selected from the first and last 30 minutes of N2 sleep. A significant reduction in the snoring spectral centroid from the beginning to the end of sleep was revealed. The spectral centroid from the end of sleep in ranges <200 Hz was inversely correlated with increases in NFV and NC from before to after sleep. They concluded that snoring spectral centroid can be used at a noninvasive and convenient way to assess variations in the pharyngeal tissue mass.

Another study looked at associations between OSA and metabolic syndrome (MetS), including different components of MetS in adults, which are common chronic conditions associated with cardiovascular (CV) morbidity and mortality.³¹² Data were gathered from the 2007-2008 National Health and Nutrition Examination Survey, which included 5909 individuals aged ≥20 years (2898 men, 3011 women), who had undergone a complete medical examination and had self-reported 3 OSA symptoms. The primary outcome was possible OSA (pOSA) and MetS components. Participants in the pOSA group had significantly more MetS components ($P<.001$).

In the group aged ≥ 60 years, there was a stronger relationship between pOSA and MetS components. After further adjustments, the odds ratios for pOSA among those with 2, 4, and 5 MetS components were 3.11, 3.19, and 4.89, respectively ($P < .05$). It was concluded that the risk of pOSA is higher in association with increased MetS factors, particularly among the elderly. Leading a healthy lifestyle may help reduce OSA risk in elderly patients with MetS.

An observational study sought to determine whether gout is associated with a higher risk of OSA in older adults.³¹³ The 5% United States Medicare beneficiary sample from 2006 to 2012 was used to assess gout and new diagnosis of OSA in adults aged ≥ 65 years, adjusting for demographics, medical comorbidity (Charlson-Romano index), HTN, hyperlipidemia and coronary artery disease (CAD), and medication use for CV diseases or gout (allopurinol, febuxostat). Calculating 10 448 472 person-years of follow-up in a cohort of 1.74 million adults aged ≥ 65 years, the crude incidence rates of OSA were 14.3/1000 person-years in those with gout and 3.9/1000 person-years in people without gout. Multivariable-adjusted analyses demonstrated that gout was associated with elevated risk of a new diagnosis of OSA during the follow-up; hazard ratio was 2.07 (95% CI=2.00, 2.15). In sensitivity analyses that substituted continuous Charlson-Romano score with a categorical variable or individual Charlson-Romano comorbidities plus HTN, hyperlipidemia, and CAD, the main finding was verified; hazard ratios were 2.11 (95% CI=2.03, 2.18) and 1.79 (95% CI=1.73, 1.85). The authors concluded that the independent association of gout with a twofold greater risk of OSA in older adults indicates that common mechanisms may be shared by the 2 conditions. Further research is warranted to further explore these mechanisms.

A retrospective chart review set out to characterize the incidence of lingual tonsil hypertrophy (LTH) in adults with and without OSA and examine any correlation between them.³¹⁴ A single-center database was searched from September 2016 to April 2017; 93 patient charts were studied in total. Lingual tonsil grade (LTG) determined by awake endoscopy was collected as well as other examination findings such as Friedman tongue position, palatine tonsil size, and neck circumference (NC). STOP-BANG scores and PSG data were gathered to characterize OSA. Incidence of clinically meaningful LTH (defined at LTG 3 and LTG 4) was compared between OSA and non-OSA participants. No significant differences were found between patients with and without OSA in the incidence of clinically meaningful LTH (OSA, 13.5%; non-OSA, 14.6%; $P = .872$). Those with and without OSA were compared by grade: LTG 1, 13.5% (OSA) versus 35.6% (non-OSA); LTG 2, 73.1% (OSA) versus 48.8% (non-OSA); LTG 3, 13.5% (OSA) versus

14.6% (non-OSA). There were no significant correlations between OSA status and LTG ($P = .190$ and $P = .069$). They note that incidence of LTH is uncommon, even among those with OSA, and does not greatly differ between patients with or without OSA. NC appears to be a better clinical indicator than lingual tonsils for likelihood of OSA.

Another project explored whether the instability of parasympathetic nerve (PN) function is associated with sleep fragmentation accompanying OSA and can this instability be improved by CPAP therapy.³¹⁵ Fifty-three OSA and 50 non-OSA individuals were examined by full PSG, and pulse rate variability (PRV) was recorded simultaneously using photoplethysmograph and evaluated by instantaneous time-frequency analysis by using the complex demodulation method. PN and sympathetic nerve (SN) activity were assessed by mean high-frequency (HF) amplitude and ratio of low-frequency (LF) and FH amplitude (LF/HF ratio), respectively. The shift in central frequency (CF) of the main HF peak over time was also monitored continuously. The relative times over which the same main HF peak was sustained for ≥ 20 seconds and 5 minutes in total recording time (% HF_{20s} and % HF_{5min}) were considered as markers of PN stability. Twenty-two of 53 patients with OSA also were evaluated under CPAP treatment. A significant increase in mean LF/HF ratio and decrease in HF amplitude were observed in severe OSA. Moreover, both % HF_{20s} and % HF_{5min} were significantly decreased not only in mild-to-moderate OSA but also in severe OSA, and % HF_{20s} was the strongest independent determinant for arousal index. CPAP treatment significantly decreased the LH/HF ratio and elevated both % HF_{20s} and % HF_{5min}. The results suggest that the stability of PN function is impaired by arousal due to repeated apnea and hypopnea in OSA and that CPAP therapy improves SN activity and PN dysfunction.

OSA during REM sleep is a common disorder; data on whether OSA occurring predominantly during REM sleep is associated with adverse health outcomes are lacking. This study explored the association between OSA during REM sleep and a composite CV endpoint in a community sample with and without prevalent CVD.³¹⁶ Full-montage home-PSG was conducted as part of the Sleep Heart Health Study. The cohort was followed up for a mean of 9.5 years, during which time CV events were assessed. Only individuals with a non-REM AHI < 5 were included ($N = 3265$). A composite CV endpoint (CCVE) was determined as the occurrence of nonfatal or fatal events, including myocardial infarction, coronary artery revascularization, congestive heart failure, and stroke. Proportional hazards regression was used to derive the adjusted hazards ratios for the CCVE. Using a REM AHI $< 5/h$ as the reference group ($n = 1758$), the adjusted hazards ratios for the CCVE in those with severe

REM OSA ($\geq 30/h$, $n=180$) was 1.35 (95% CI=0.98-1.85). Stratified analyses demonstrated that the association was most evident in those with prevalent CVD and severe OSA during REM sleep with an adjusted hazards ratio of 2.56 (95% CI=1.46-4.47). They concluded that severe OSA that occurs primarily during REM sleep is associated with higher incidence of a composite CV endpoint but only in those with prevalent CVD.

A different trial sought to determine whether cardiac rehabilitation may benefit patients who had myocardial infarction (MI) in terms of OSA and associated autonomic nervous system (ANS) activity.³¹⁷ Regular physical exercise improves OSA in the general population, but this has not been evaluated in post-MI patients. Consecutive individuals in an ambulatory cardiac rehabilitation program were included in the cohort. AHI-calculated electrocardiogram (ECG)-derived respiration (AHI_{EDR}) was acquired through nocturnal Holter ECG recordings. According to AHI_{EDR}, patients were classified as normal, mild, moderate, or severe OSA (<5, 5-14, 15-29, and ≥ 30 , respectively). Physiological performance (peak VO_2) was determined via cardiopulmonary exercise testing. ANS activity was evaluated through spontaneous baroreflex sensibility as well as heart rate variability (HRV) analysis. One hundred five patients with coronary artery disease (CAD) and OSA were included (95 men, 55 ± 12.4 years); 100 had at least 1 CV risk factor (98%), and 52 individuals (50%) had an ANS dysfunction. Notably, 68 of these patients with OSA (65%) were free of classical diurnal symptoms typically accompanying OSA. In response to cardiac rehabilitation, AHI_{EDR} decreased significantly (-9.3 ± 9.5 , $P < .001$) only in patients with severe OSA, and the decrease was even greater when peak VO_2 and baroreflex sensibility improved beyond 20% compared with baseline values (-11.6 ± 9.1 , $P < .001$). The authors concluded that severe OSA in patients with CAD is significantly improved after 2 months of cardiopulmonary rehabilitation. Reviving ANS activity via physical activity might be a target for complementary therapy of OSA in patients with CAD.

A systematic review was performed to explore the relationship between uvula size and SDB (snoring and OSA), as data are lacking for objective interpretation.³¹⁸ The international literature was searched for research describing the measurable characteristics of the uvula (size, length, width) and any association with snoring and OSA. PubMed, Scopus, Google Scholar, Embase, and the Cochrane Library were each searched from inception through November 15, 2016. After screening 1037 titles and abstracts, 54 articles were downloaded and fully reviewed. Sixteen articles consisting of 2604 participants met inclusion and exclusion criteria. Articles included data and information for normative data for uvula size in controls, snoring and uvula size, OSA and uvula size, and overall uvula function. The review

demonstrated variability in findings; however, in general, uvula length >15 mm was considered elongated, and uvula width >10 mm was considered wide. The studies in the review reveal a relationship between uvula size, snoring, and OSA. Moreover, larger uvulas appear associated with more severe snoring and OSA. Further research is warranted to discern the direct correlation between uvula size and its relationship specifically to snoring and OSA.

A literature review provided a current overview of the relation and mechanism of kidney injury in OSA.³¹⁹ The presence of OSA leads to formation of structural, ultrastructural, functional, and proteomics changes of the kidney. These alternations are based on pathological processes, such as elevated production of free radicals, disruption of mediated nitric oxide vasodilation reactions, activation of the sympathetic ANS, the renin-angiotensin-aldosterone system, dysfunction of endothelium, the development of renal venous HTN, and stimulation of atrial natriuretic peptide production. All this in turn leads to an elevation in intraglomerular pressure, the occurrence of glomerular hyperfiltration, nocturnal polyuria, renal functional changes, proteinuria, and renal tubular dysfunction. Kidney injury in patients with OSA can also be secondary to pathological conditions associated with OSA such as cor pulmonale, erythrocytosis, diabetes mellitus, MetS, HTN, coronary heart diseases, and atherosclerosis, which can lead to the development of kidney damage in isolated conditions and can exacerbate its course co-occurring with OSA. There is a bidirectional relationship between kidney diseases and OSA through a number of potential pathological mechanisms, which suggests the possibility of both diseases to be a possible risk factor for each other. Furthermore, kidney diseases may lead to OSA through a multitude of mechanisms, including chemoreflex responsiveness, pharyngeal narrowing due to fluid overload, and accumulation of uremic toxins.

A cross-sectional analysis investigated the association between OSA and plasma lipid concentrations in patients enrolled in the European Sleep Apnea Database (ESADA) cohort.³²⁰ The analysis involved 8592 participants without physician-diagnosed hyperlipidemia or reported intake of a lipid-lowering drug (age: 50.1 ± 12.7 years; 69.1% male; BMI: 30.8 ± 6.6 kg/m²; mean AHI: $25.7 \pm 25.9/h$). The independent relationship between measures of OSA (AHI, ODI, mean and lowest oxygen saturation) and lipid profile (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and fasting triglycerides [TGs]) was determined via general linear model analysis. A dose-response relationship was found between TC and ODI (mean \pm SE [mg/dL]: 180.33 ± 2.46 , 184.59 ± 2.42 , 185.44 ± 2.42 , and 185.73 ± 2.44 ; $P < .001$ across ODI quartiles I-IV). TG and LDL concentrations were better

predicted by AHI than by ODI. HDL-C was significantly reduced in the highest AHI quartile (mean \pm SE [mg/dL]: 48.8 \pm 1.49 versus 46.50 \pm 1.48; $P=$.002, AHI quartile I versus IV). Morbid obesity was associated with lower TC and higher HDL-C values. Lipid status was influenced by geographical location, with the top TC concentration noted in Northern Europe. They concluded that OSA severity was independently associated with cholesterol and TG concentrations.

ORAL MEDICINE AND ORAL AND MAXILLOFACIAL SURGERY

As in previous years, the objective of the oral medicine (OM) and oral and maxillofacial surgery (OMFS) section of this review is to identify and provide topical, pre-selected information from the field with relevance to restorative dentists. Advances in pharmacology, new developments on diagnosis and therapy of oral mucosal diseases and skeletal changes, and disorders with influence on occlusion and the temporomandibular joints (TMJs) are considered as the main interfaces between OM/OMFS and prosthodontics. The literature review of 2018 will discuss current problems of antibiotic prescription patterns in dentistry and their impact on antimicrobial resistance development. Furthermore, new discoveries in the etiology, diagnosis, and therapy of burning mouth syndrome and the underlying reasons and clinical appearance of condylar changes either of idiopathic nature or after orthognathic surgery will be presented.

Epidemiological studies aiming to improve the understanding of antibiotic prescription patterns in medicine and dentistry have been carried out recently.³²¹⁻³²⁴ The studies revealed that dentistry and its specialties are accountable for about 10% of all antibiotic prescriptions worldwide, which widely exceeds the percentage of several medical specialties.³²⁵⁻³²⁷ Although antibiotic prescriptions are decreasing in general because of the implementation of clinical recommendations giving clear indications for the use of antibiotic prophylaxis and therapy, those rates have increased in dentistry.³²⁵ Antibiotics are indispensable drugs, the benefit of which is undeniable when used in correct indications. However, there is doubt that all antibiotic prescriptions, especially in dentistry, are inevitable.^{322,325,326} Unnecessary and excessive antibiotic use is both hazardous to patients and uneconomical.^{326,327} Increased and prolonged antibiotic prescriptions will enhance the rates of unwanted side effects and antimicrobial resistance.^{327,328}

The ongoing evolution of multiresistant bacterial strains has become a serious challenge in medicine. While the problem of methicillin-resistant *Staphylococcus aureus* (MRSA) has been widely recognized, many dentists are still unaware that the most serious threats are

presently posed by multiresistant gram-negative (MRGN) bacterial strains (for example, *Pseudomonas spp.*, *Acinetobacter spp.*), extended spectrum beta-lactamase-producing bacteria (for example, ESBL *E. coli* strains), and multiresistant *Enterococcus spp.*^{328,329} Infections with multiresistant bacteria (MRB) are associated with increased mortality and severe economic burden.³²⁶ Only few innovations in antimicrobial therapy can be expected in the future.³²⁶ Therefore, the main focus to fight this challenge is currently on the containment of further antimicrobial resistance development, which can be achieved by antibiotic stewardship (the deliberate use of antibiotics in suitable doses and duration in correct indications).³²⁷

The main reason for antibiotic resistance development is the disproportionate use of broad-spectrum antimicrobial agents.³²⁶⁻³²⁸ As stated previously, this seems to be everyday practice in dentistry.^{322,323,325} Uncertainty about appropriate indications for antibiotic treatment, unnecessary antibiotic prophylaxis, patient expectations, and legal issues are mentioned as the underlying reasons of this trend.^{322,323,327} Furthermore, there is evidence that antibiotics in dentistry are falsely used to enhance the efficacy of analgesics or to alleviate acute symptoms which could be relieved by immediate dental treatment.^{322,323}

The most widely prescribed antibiotics in dentistry are broad-spectrum penicillins (for example, amoxicillin with or without beta-lactamase inhibitor) and clindamycin.^{322,323,325} These antibiotics exert considerable selection pressure on bacteria and thus facilitate the differentiation of resistant strains.^{326,327} Antibiotic resistance can evolve by spontaneous mutation of the bacterial DNA or by transfer of resistance genes between bacteria by different mechanisms (direct or bacteriophage-mediated).³²⁷ Unfortunately, resistance genes cannot only be exchanged between bacteria within specific strains but also between different species.³²⁷ A single bacterium may gain resistance against several antimicrobial agents and become multiresistant. Presently, the majority of intraoral bacteria implicated in infections still show sufficient susceptibility to established antibiotic therapy regimens.³³⁰ However, resistant strains are emerging and are causing complicated and potentially lethal clinical scenarios.³³¹ Considerable resistance rates are reported for clindamycin already.^{330,331}

The solution to this problem lies within an altered antibiotic prescription policy. First, small-spectrum antibiotics such as basic phenoxymethylpenicillin should become the first choice for empirical antibiotic therapy if necessary (clindamycin in allergic patients).^{326,327} Phenoxymethylpenicillin shows acceptable efficacy against the majority of intraoral bacteria.^{326,327} Macrolides or fluoroquinolones are to be considered as second-line antibiotics, and their routine prescription should not be

continued due to limited efficacy or risks of unwanted side effects. In cases of treatment failure, use of broad-spectrum antibiotics (amoxicillin without/with clavulanic acid) may be indicated. At the same time, referral to a specialist and targeted antibiotic therapy after bacterial culture and resistance analysis should be considered. Then, all available clinical guidelines for antibiotic prophylaxis should be reviewed and followed closely.³³²⁻³³⁴ Finally, dentists should pay attention to appropriate dosing and refrain from extended antibiotic prescription.³²⁷

These recommendations are not meant to prevent dentists from prescribing antibiotics in general but to limit their use to clearly defined scenarios. One example of false reduction of antibiotic usage is mentioned by Dayer and Thornhill.³³⁵ The authors examined the development of antibiotic prescription rates for patients at risk for infectious endocarditis (IE) after the implementation of the new guidelines for antibiotic endocarditis prophylaxis (AEP) issued by the American Heart Association in 2007.³³² The authors found an overall reduction of IE and reduced prescription rates of AEP, which corroborates the benefit of the new guidelines. This beneficial impression changed when the subgroups were analyzed individually. It is worrisome that an increase of IE and a decrease of AEP prescriptions were found in the high-risk patient group, which was defined as all the patients who need EP according to the guidelines³³² (heart valve replacement, patients after heart transplantation, patients who have experienced IE, and patients with congenital heart disease with residual vitium). This implies that AEP was falsely omitted in this group putting vulnerable patients at unnecessary risk to obtain IE. The authors concluded that limited knowledge of the correct AEP indications mainly by dentists might be the reason for this development.³³⁵

Diagnosis and treatment of diseases of the oral mucosa are a challenge for many dentists. Distinct clinical features are missing in many situations, and tissue biopsy may be the final possibility to find the correct diagnosis. The clinical scenario becomes difficult if the biopsy comes back negative and the patient still complains about discomfort of the oral mucosa. These disorders constitute a severe burden for the patients' quality of life. Furthermore, restorative dentists are usually reluctant to intervene in an already disrupted stomatognathic system, which might delay necessary dental treatment and further increase the affected patients' strain.

Many of these enigmatic oral mucosal disorders are finally labeled as burning mouth syndrome (BMS). Significant progress has been made in the investigation of the etiology and treatment of BMS recently. Although BMS is an exclusion diagnosis, distinct neuronal and biochemical changes can be perceived in affected patients.^{336,337} These changes comprise anatomical and

histological differences in the prefrontal cortex, the postcentral gyrus, the basal ganglia, and the hippocampus.³³⁶ Altered expressions of neurotransmitters and ion channels implicated nociception can be found in the oral mucosal tissues of patients with BMS. Systemically, decreased adrenalin and increased cortisol levels have been associated with the presence of BMS which may imply a malfunction within the hypothalamic-pituitary system.³³⁶ Patients with BMS frequently suffer from concurrent psychopathology, such as depression and anxiety, and neurological disorders, such as neuropathy or neuralgia, and exhibit a distorted circadian rhythm with sleep deprivation.^{336,338,339} Most patients with BMS are female.^{336,338,340,341} Promising advances have been made in the field of BMS management. Topical and systemic therapeutic options are available. The benzodiazepine clonazepam has been proven effective in the treatment of BMS both topically and systemically.^{336,340,341} The benefit of symptom reduction has to be weighed against the unwanted side effects of clonazepam, namely sedative effects and addiction. Furthermore, well-designed studies have shown that the substances alpha lipoic acid, gabapentin, and antidepressants (amitriptyline and paroxetine), as well as herbal therapies (Catuma) and the endogenous analgesic palmitoylethanolamide (PEA) can be used for BMS symptom relief.^{336,339-341} It is important to tailor a holistic treatment approach including psychotherapy and cognitive behavioral therapy to cure BMS.³³⁶

Dentists and prosthodontists play a key role in the therapeutic algorithm of temporomandibular joint disorders (TMDs). There is a wide array of etiologic factors for TMDs, including malocclusion, muscular malfunction, bruxism, inflammatory changes of the intraarticular structures, and arthrosis.³⁴² Imaging findings within the temporomandibular joint (TMJ) may or may not be present.³⁴³ Rarely, signs of condylar resorption can be found either unilaterally or bilaterally.³⁴⁴ Condylar resorption might not be clinically apparent. However, if symptoms evolve, condylar resorption usually presents as malocclusion, progressive anterior open occlusion, reduced posterior facial height, and TMDs.³⁴⁴⁻³⁴⁶ Condylar resorption, which mostly affects female patients, is a rare event and can be idiopathic or develop as a consequence of orthognathic surgery.^{345,347,348} Condylar resorption may appear in up to 5% of the patients who underwent orthognathic surgery.^{345,347-349} Excessive load on the condyles and/or misguided condylar remodeling after orthognathic surgery have been discussed as etiologic factors.^{347,348} Most cases of condylar resorption occur as a sequel of the surgical correction of class II occlusion which involves counterclockwise mandibular rotation and anterior repositioning.³⁴⁷ These surgical jaw movements are known to cause increased muscular tension and changes in muscular

activity.³⁴⁹ As a result, the force distribution within the TMJ structures changes, which might induce enhanced remodeling and resorption.³⁴⁹ However, patients with condylar resorption have been reported after mandibular setback surgery as well.³⁴⁸ As this movement of the mandible should relax muscle tension and reduce the load on the TMJs, the mentioned etiologic theory may not be universally applicable. Hormonal imbalance and avascular necrosis are also discussed as supplementary etiologic parameters. The exact underlying mechanisms implicated in condylar resorption have yet to be elucidated.

Several conservative and invasive therapeutic approaches have been suggested to decelerate, impede, or reverse condylar resorption. The onset of condylar resorption can occur as early as 3 months post-operatively, and the disorder should be suspected when patient report TMD symptoms.³⁴⁷ When condylar resorption is detected, the patients need to be monitored both clinically and radiologically for at least 24 months to assess the dynamics of the process.^{344,347} The main aim of all condylar resorption treatment algorithms is to reduce load on the condyle. Primarily, this can be achieved by occlusal devices, the efficacy of which has been demonstrated in recent studies.^{344,347} If clinical symptoms are absent, no further treatment is required even if condylar resorption progresses in radiological imaging as a self-limiting course of the disease is possible.³⁴⁷ An array of surgical options is available if clinical symptoms arise or worsen.³⁴⁴ General dentists and prosthodontists should be aware of the different etiologic mechanisms of condylar resorption and keep the differential diagnosis in mind when exploring the history of patients with TMDs.

DENTAL CARIES AND CARIOLOGY

In 2018, a significant volume of professional literature was published on dental caries contributing to our understanding of the disease, its treatment, and more effective prevention. Although randomized controlled trials and systemic reviews are important clinical tools, the present report begins with a look at recently published general reviews that may help guide readers to a more complete appreciation of the disease.

“Are the *Streptococci mutans* still considered relevant to understanding the microbial etiology of dental caries?” This question was the title of a report out of the University of Iowa that elegantly summarized current philosophies driving modern research in dental caries.³⁵⁰ As long ago as 1924 when Clarke³⁵¹ proposed the dominant role of *S. mutans* in the etiology of caries, dental research focused on the coincidence of tooth demineralization in the presence of *S. mutans*. For this reason, some modern approaches to caries prevention, such as the use of

selectively targeted antimicrobial peptides (STAMPs)³⁵² or replacement therapy,³⁵³ strategically target the eradication of *S. mutans* as a means of preventing initiation of decay. However, available biomolecular evidence indicates a variety of oral microorganisms with the genetic capability to substitute for *S. mutans* in biofilm formation and caries initiation.³⁵⁴ Even fungi, such as *Candida albicans*, may considerably enhance the cariogenic virulence of dental biofilms.^{355,356}

Returning to the original question, authors³⁵⁰ indicated that answers might range from, “Yes, *S. mutans* remains the most important oral cariogenic species,” to “No, in the absence of *S. mutans*, different acidogenic species can play the same role.” While *S. mutans* may still be considered a key factor in dental caries, other *S. mutans*-like organism are capable of synthesizing intracellular and extracellular polysaccharides from sucrose. Intracellular polysaccharides represent a carbohydrate reserve that may be used to produce acid, despite the absence of dietary sugars, while extracellular polysaccharides make key contributions to the plaque matrix.³⁵⁷

Readers are encouraged to carefully review the open-access report by Banas and Drake³⁵⁰ to better appreciate current research directions and to critically evaluate modern literature on the topic. Table 2 in this article by Banas and Drake³⁵⁰ is particularly helpful in summarizing obstacles to determining the microbial etiology of caries. Initially, a multifactorial etiology of caries was stressed, and that caries does not develop in the absence of bacteria. However, the presence of biofilm, even when rich in acidogenic bacteria, is not sufficient per se to initiate caries. Many factors impact caries risk, including saliva flow and composition, diet and nutrition, parental education, socioeconomic, age at transmission and acquisition of cariogenic species, oral hygiene, fluoride exposure, tooth anatomy, and enamel composition.³⁵⁸⁻³⁶⁸ The tridimensional crystal structure of dental enamel is nonhomogeneous, differs between individuals, differs from tooth to tooth, and differs from site to site on the same tooth, thus influencing acid sensitivity. Furthermore, host genetics plays a determinant role. Some polymorphisms, such as those found in lactoferrin, a natural antibacterial protein³⁶⁹ (note: recent research found no association between gene polymorphism and caries in primary teeth³⁷⁰), or in the production of salivary mucins that cover and protect the mucosa and tooth surface,³⁷¹ may influence caries susceptibility. If enamel differs in sensitivity to acid, then it may be possible that the microbial challenge required to initiate and propagate caries is not equivalent at all sites. Because *S. mutans* is not associated with all decay sites and *S. mutans* is often found on sound enamel, questions arise regarding *S. mutans* as the sole, or even primary, etiology of caries. The authors indicated that, “... with the above considerations in mind, these anomalies may be explained by

instances where substrate (localized tooth enamel) sensitivity plays an essential role in shaping caries risk. When teeth, or sites within teeth such as non-fully formed fissures are abnormally sensitive to acid challenge, the situation is analogous to an immunocompromised host who is at risk of disease from opportunistic pathogens within the normally mutualistic microflora. The key to understanding disease acquisition in these instances is found more in recognizing the contribution of host susceptibility than focusing solely on the microbial challenge.”

A second worthwhile review, published in *Biomedicine & Pharmacotherapy*, discussed the role of the oral microbiome as an important aspect of the human microbiome for the modulation of oral health.³⁷² The authors indicated that humans are supraorganisms composed of both their own cells and microbial cells. This leading statement indicates the importance of microbiota in human life. The number of microorganisms living in or on the human body is 10 times greater than the number of cells in the body. Authors suggest that, by cell count, we are only one-10th human! This incredible volume of commensals contributes positively to host health by fighting pathogens, preserving homeostasis, and regulating immune processes. For this reason, the National Institute of Health of the United States initiated the Human Microbiome Project (HMP) to comprehensively characterize the human microbiome and define associations between microbiome alterations and human health and disease. This report focused exclusively on the human oral microbiome. For interested readers, the report is available at www.homd.org. Therein is a list of all oral microorganisms with feature descriptions and available genomic information. The article focuses initially on composition of the oral microbiome, including bacteria, fungi, archaea, and viruses. Then, it covers the location of the oral microbiota, including saliva, soft tissues, and dentition. Additionally, associations between oral microbiota and disease are addressed. These associations include not only caries and periodontal disease, but also recurrent aphthous stomatitis, oral tumors, and known associations between oral microbiota and systemic diseases such as diabetes, cardiovascular diseases, and tumor of distant organs. Finally, this report addresses modulation of the oral microbiota through mechanical debridement, antibiotics, probiotics, prebiotics, and other modulation methods, including avirulent bacteria, phages, and nanoparticles for selective drug delivery. For complete coverage of the role of the oral microbiome in health and disease, the reader is encouraged to review this report³⁷² as it is logistically impossible to summarize it here.

A third review published by Philip et al³⁷³ is in agreement with reports discussed previously regarding ecological approaches to dental caries prevention. The

authors emphasized that caries is a biofilm-mediated, multifactorial disease occurring when acidogenic and/or aciduric bacteria, generally part of the normal oral flora, surmount over other species disrupting homeostatic balance of the dental biofilm and initiating the disease process. Therefore, preventive measures should not only target aggressive acid-producing microorganisms but should also work to preserve a healthy, microbially diverse, resident microbiome.

Typically, the control and prevention of any disease encountered in medicine is based on etiological elements involved. However, control and prevention of dental caries remains largely based on the daily mechanical debridement of biofilm and dietary modifications that limit exposure to fermentable sugars. There is a significant need for an ecological approach to caries prevention that targets selectively killing of acidogenic bacteria, promotion of healthy microorganisms, or both simultaneously. The next several paragraphs are about a review reported by Philip et al³⁷³ to discuss probiotics, prebiotics, antimicrobial peptides, sugar polyols, quorum sensing targets, and natural products, with the intent to better understand dental caries management and microbial homeostasis within the biofilm.^{357,374}

Probiotics

As previously discussed, the human microbiome is critical to health and disease. In fact, the World Health Organization has indicated that by 2050, more human deaths will be related to antibiotic-resistant bacterial infection than the current trend of death from cancer. Today, probiotics are considered extremely important and safe tools for maintenance of a healthy balance within the microbiome. Likewise, probiotic applications in caries control and prevention has become the object of much scientific investigation.

Probiotics are defined as living microorganisms, safe for human consumption, that provide health benefits when ingested in sufficient quantities. The use of probiotics in oral health care has increased in recent years. Mounting evidence suggests that consumption of probiotic strains, originally used to improve gut health, also bring benefits to the oral cavity because probiotic bacteria also colonize the oral cavity. It is important to appreciate the extensive ecological variation within the mouth secondary to probiotic ingestion, as well as the long-term effects of probiotic use on oral health and disease. Oral probiotic therapy should be considered an alternative approach for deterring oral biofilm development and reducing the cascade of harmful immune-inflammatory reactions.³⁷⁵

The mechanisms by which probiotics reestablish ecological balance within oral biofilms are not completely understood. However, probiotic bacteria are believed to have both systemic and direct local effects. Local effect

include competitive inhibition of cariogenic microorganisms, selective coaggregation of *S. mutans* (a process by which genetically distinct bacteria become attached to one another conditioning the development of the biofilm), and bacteriocin-producing probiotics targeting *S. mutans*. The true efficacy of probiotics for dental caries is controversial. The main problem in using probiotics for caries prevention is that commonly available *Lactobacillus* and *Bifidobacterium* probiotic bacteria are acidogenic and aciduric and could contribute to the caries process if colonized in the oral cavity. Indeed, most oral probiotics studies use *S. mutans* count as the objective outcome assessment, rather than caries rate.

In a triple-blind, placebo-controlled, randomized trial, Villavicencio et al³⁷⁶ evaluated the effect of milk supplemented with probiotic bacteria, compared with standard milk, on levels of *S. mutans* and *Lactobacillus* spp., in 3- to 4-year-old children after 9 months of intervention. Participants included 363 preschoolers attending 5 child-development centers in Cali, Colombia. Participants were randomly divided into 2 groups. Children in the intervention group drank 200 mL of milk with *Lactobacillus rhamnosus* and *Bifidobacterium longum*, while children in the control group drank 200 mL of standard milk. Data reflected the number of colony forming units (CFUs) of *S. mutans* and *Lactobacillus* spp. present in saliva. Secondary data indicated dental caries rated by the International Caries Detection and Assessment System (ICDAS), dental plaque, pH, and salivary buffer capacity. After 9 months, no significant differences were identified for *S. mutans* CFU/mL ($P=.173$), prevalence of dental caries ($P=.767$), salivary pH, or dental plaque. Statistically significant differences between groups were found for *Lactobacillus* spp. CFU/mL ($P=.002$) and salivary buffering capacity ($P<.001$). The authors suggested that 9 months of regular consumption of milk containing probiotics appears to reduce *Lactobacillus* spp. CFU/mL and increase salivary buffering capacity. This clinical finding is relevant because *Lactobacilli* are critical to increasing acidity once the caries process is initiated, and the buffering effect of saliva is one of the last barriers against caries in the ongoing process.³⁷⁷

A second randomized trial investigated the use of probiotic lozenges containing *L. reuteri*, one of the most investigated probiotic anticaries agents.³⁷⁸ Healthy 3- to 6-year-old ($N=178$) children were randomly divided into 2 groups. The control group received placebo lozenges twice daily for 28 days, while the experimental group received *L. reuteri* probiotic lozenges. Bacterial counts (*S. mutans* and *Lactobacillus*), dental plaque accumulation, and salivary buffer capacity were compared. After 28 days, the experimental group realized a statistically significant drop in *S. mutans* and *Lactobacilli* count ($P<.001$ and $P=.020$, respectively). Both groups had less plaque accumulation than at baseline. Salivary buffer capacity

was not statistically different between groups ($P=.577$). Compliance was 90%, with no adverse events. The authors concluded, in accordance with the previous studies, that the consumption of probiotic lozenges containing *L. reuteri* reduces caries-associated bacterial counts significantly, and, therefore, probiotics consumption may be beneficial to caries prevention.

Similar results were reported by Bafna et al³⁷⁹ measuring *S. mutans* in saliva after consumption of yogurt containing *L. acidophilus* La5 and *Bifidobacterium lactis* Bb12. However, this study enrolled a high-risk caries population. Seventy participants were randomly divided into 2 groups. The experimental group received yogurt with probiotics, once daily after meal for 2 weeks. The same product without probiotics was given to the control group. No other products that could affect *S. mutans* count (xylitol, fluoride, or other probiotics) were used. Effects of probiotics were assessed without controlling participants' routine oral hygiene and nutritional habits. A significant difference in *S. mutans* count was observed in the experimental group during the 2-week period, suggesting that the probiotic bacteria *L. acidophilus* La5 and *Bifidobacterium lactis* Bb12 were effective in reducing the *S. mutans* counts in saliva.

All previously mentioned studies found beneficial effects of probiotics on the *S. mutans* count in saliva. However, *S. mutans* count does not necessarily mean that caries will not develop, especially if bacteria that replace *S. mutans* are capable of producing acid. This can vary dramatically given the stages of biofilm formation and caries progression at which *S. mutans* is eliminated. If caries formation has already initiated, removing the *S. mutans* and introducing other acidogenic microorganisms may affect *S. mutans* bacterial count, but not necessarily caries rate. Additionally, analyzing saliva will not necessarily render data on *S. mutans* biofilm count. In the first study mentioned previously,³⁷⁶ there was a reduction in *Lactobacilli* spp. and an increase in the buffering capacity of saliva, but no evaluation of caries rate was reported.

Pahumunto et al³⁸⁰ evaluated the effect of *Lactobacillus paracasei* SD1 added to milk in 124 children aged 1.5 to 5 years and reported a reduction, after 3 months, of both salivary *S. mutans* count and development of new caries. Additionally, the strain investigated (SD1) was indicated safe for use in young children, suggesting that *L. paracasei* SD1 may be a good alternative caries-prevention tool in young children. Although the evaluation time was limited and the patient population was extremely diverse in number of teeth present (due to age range), results were encouraging.

For reasons previously discussed, 2 new probiotics strains isolated from supragingival plaque of healthy individuals have been investigated, one in 2016 (*Streptococcus* A12)³⁸¹ and one in 2017 (*Streptococcus dentisani*).³⁸²

Both demonstrate a double probiotic capacity by inhibiting the proliferation of *S. mutans* and by regulating the biofilm pH through arginolytic actions. These 2 types of bacteria are commensals and not acidogenic. Their effect appears more promising than gut-associated *Lactobacillus* and *Bifidobacterium* probiotic species.

Scientifically rigorous research on *Streptococcus* A12, exploring its microbiologic, molecular, and genomic basis, was published by Huang et al.³⁸¹ A12 was highly arginolytic and capable of inhibiting growth and intercellular signaling in *S. mutans* in a way that may promote stability of health-associated biofilm communities. A12 not only expressed the ADS (arginine deaminase system) pathway at high levels under a variety of conditions but also effectively inhibited growth and 2 intercellular signaling pathways in *S. mutans*. A12 produced abundant quantities of hydrogen peroxide via pyruvate oxidase enzyme, which was sufficient to prevent growth of *S. mutans*. It also produced a protease similar to chitinase (Sgc) of *Streptococcus gordonii* that blocked the competence-stimulating peptide (CSP)-ComDE signaling system, which is essential for bacteriocin production by *S. mutans*. The complete genome sequence of A12 was determined, and phylogenomic analyses compared A12 to streptococcal reference genomes. A12 was most similar to *Streptococcus australis* and *Streptococcus parasanguinis* but sufficiently different that it may represent a new species. A12-like organisms may play crucial roles in promotion of stable, health-associated, oral biofilm communities by moderating plaque pH and interfering with growth and virulence of caries pathogens.

A noteworthy article by Thurnheer and Belibasakis,³⁸³ using the University of Zurich Biofilm model, compared the effect of different microorganisms inside the biofilm by looking at what happens within the biofilm when the microorganisms in question are present and when they are absent. Results suggested that *S. oralis* might regulate growth of *A. oris* and suppress overgrowth of *S. mutans* in a biofilm environment. These data support the role of *S. oralis* as a commensal essential in maintaining homeostasis inside the biofilm, primarily by antagonizing *S. mutans* and therefore preventing a caries-promoting dysbiotic state. It is important that future ecological approaches to caries prevention or treatment strategies ensure stability of *S. oralis* in the oral microbiome and in biofilms. This role of *S. oralis* is in full agreement with that suggested by Liu et al³⁸⁴ who demonstrated production of hydrogen peroxide by *S. oralis*, which was toxic to *S. mutans*, even in the presence of sucrose.

Finally, Fang et al³⁸⁵ isolated the BBE-Y52 strain of *Lactobacillus brevis* that, in rigorous research, exhibited antimicrobial activity against *S. mutans* by releasing compounds such as hydrogen peroxide and low quantities of lactic acid. Being a weak acid producer makes

L. brevis BBE-Y52 more suitable for further research than traditional gut-derived *Lactobacilli*. Additional studies have demonstrated that this strain is also capable of adhering to oral epithelial cells and promoting the production of interleukins in peripheral blood mononuclear cells. This suggests that *L. brevis* BBE-Y52 could alleviate inflammation and might confer benefits to host health by modulating the immune system. Future research will reveal the full probiotic spectrum of *L. brevis* BBE-Y52.

Prebiotics

Prebiotics are compounds that, when added to resident microflora, stimulate the growth of beneficial microorganisms, positively shifting the biofilm toward a healthier composition. A common prebiotic example is arginine that, when metabolized, creates alkalizing effects counteracting the acidic environment produced by cariogenic bacteria. For this reason, arginine has been used in the development of commercial oral health-care products.³⁸⁶

A review of 8 articles on the efficacy of arginine, when combined with fluoride dentifrices, concluded that 1.5% arginine combined with fluoride toothpaste has superior anticaries efficacy to toothpaste containing fluoride alone.³⁸⁷ Similarly, an in vitro study in high-risk specimens indicated that daily use of 2% arginine in NaF toothpaste provided synergistic anticaries activity by demonstrating a significant remineralization effect.³⁸⁸ Conversely, an in vivo study followed up 12 participants wearing acrylic resin appliances with embedded bovine enamel disks. Brushing with fluoride toothpaste was compared with brushing with arginine-enhanced fluoride toothpaste. The results suggested that arginine-enhanced fluoride dentifrice and regular fluoride toothpaste have similar anticaries effects.³⁸⁹

Specifically targeted antimicrobial peptides (STAMPs)

STAMPs are small peptides composed of amino acids consisting of 2 parts, a targeting domain capable of selective membrane binding to specific microorganisms and a killing domain responsible for cell lysis. In 2006, Eckert et al³⁹⁰ reported on the first STAMP (C16G2), which was provided to patients in gel form for delivery in dental trays. The FDA has recognized C16G2 as a new investigational drug for dental caries prevention. The drug has now successfully completed clinical phase II trials.

Several other peptides were discussed in 2018. Wang et al³⁹² and Jiang et al³⁹¹ investigated a selective peptide called GH12, relative to virulence factors of *S. mutans* and to the functional mechanisms at enzymatic and transcriptional levels. Effects of GH12 on acidogenicity of *S. mutans* were evaluated by pH drop, lactic acid measurement, and lactate dehydrogenase (LDH) assay. The effect on aciduricity was tested by survival rate at pH 5.0 and F1F0-ATPase assay. Then, the influence on EPS

synthesis was studied by quantitative measurement, morphology observation, vertical distribution analyses, and biomass calculation. Finally, quantitative real-time PCR was performed to obtain the expression profile of related genes. The results demonstrated that 1/2 MIC (4 mg/L) concentration of GH12 inhibited acid production, EPS synthesis, and biofilm formation. Enzymatic activity of LDH and F1F0-ATPase was inhibited, and *ldh*, *gtfBCD*, *vicR*, *liaR*, and *comDE* genes were significantly downregulated. The authors concluded that GH12 effectively inhibited *S. mutans* virulence factors by decreasing the activity of related enzymes, down-regulating virulence genes, and inactivating specific regulatory systems. With promising antibacterial and antibiofilm properties, the use of GH12 might have a role in preventing and controlling caries and other dental infections.

The same research group in China published a second remarkable report investigating the peptide GH12 coupled with a second peptide, TVH19, that has notable remineralization capabilities.³⁹² Several peptides were produced, and their remineralization potential was tested by evaluating the shape and organization of crystals after immersion in CaCl₂ (3.3 mM) with Na₂HPO₄ (1.6 mM, pH=7.4) at 37 °C for 24 hours. The authors concluded that a method to obtain the first bifunctional anticaries peptide, TVH19, was developed, and its convincing antibacterial and remineralizing capability in vitro was confirmed. A method for designing bifunctional anticaries agents is feasible. The authors are now in the process of investigating the effect of TVH19 on the oral microbiome using a method that more closely mimics oral niches, such as multispecies biofilms, acquired pellicle, saliva, continuous flow, pH, and temperature. In addition to fusion, mixing 2 peptides together may be an alternative way to control dental caries.

Similarly Huo et al³⁹³ analyzed the effect of 11 different STAMPs, based of 5 diverse targeting domains, to identify the best performer for use in further research and future clinical applications. The STAMPs were tested against 3 strains of *S. mutans* and 2 other *Streptococci* (*gordonii* and *sanguis*), not only in the planktonic stage but also in a biofilm environment. The major finding was that STAMPs had selective antibacterial activity against *S. mutans* grown in liquid or biofilm states but did not affect other oral *Streptococci* tested. Of the peptides used, C11H and C12H obtained the greatest effects and were selected for further investigation. C11H repressed the expression of nucleic acid metabolism-related enzymes, which represents one mechanism for inhibiting *S. mutans*. The authors concluded STAMPs could be used to improve antimicrobial therapies in the treatment of dental caries.

STAMPs probably represent the most advanced system for prevention of dental caries. Only time will tell if

the efficacy of this approach is adequate to stop the most diffuse disease on the planet. Philosophically, STAMPs are based on the concept that *S. mutans* is still the “main actor in this play.” Therefore, once clinical trials are completed, we will have the necessary information to answer questions regarding its effective etiological role in dental caries.

Sugar polyols

Well-known experiments by Stephan³⁹⁴ in 1940 demonstrated that the pH drop seen in dental plaque was related to intake of starches and sugars, as represented in a pH graph. Stephan indicated that the simpler the sugars, the greater the pH drop and the longer the delay in returning to a neutral pH. Since this pioneering work, the role of sugar and starches has been widely investigated. If we return to our initial etiological question on dental caries, we could conclude, paradoxically, that in light of current knowledge, dental caries has a single specific cause and that being free sugars because in their absence, there is no caries! Sugars induce acid formation, which ultimately causes lesions. This understanding of caries formation supports preventive efforts directed at dietary modification in the high-risk population.³⁹⁵ For this reason, polyols (sugar alcohols that are low-digestion carbohydrates and naturally found in fruits, vegetables, and some fungi) have been proposed as healthy alternative to sucrose. Owing to slow and incomplete gut absorption, polyols have low nutritional value, when compared with sugars, and are helpful in reducing caloric intake. According to the European Union, 7 polyols are defined as nutritive food additives: sorbitol (E420), mannitol (E421), isomaltose (E953), maltitol (E965), lactitol (E966), xylitol (E967), and erythritol (E968). In vitro and in vivo data suggest that these nonfermentable sugars have a potential anticaries effect through a number of different mechanisms. Xylitol, an often-studied sweetener, is capable of inhibiting *S. mutans* growth by disrupting cellular energy production processes. Although not all *S. mutans* strains are inhibited by xylitol, even resistant bacteria have been found to be less virulent.³⁹⁵ While complete agreement and consensus on efficacy do not exist, the general trend regarding xylitol is currently in favor of its use.

A double-blind randomized controlled trial reported by Kayalvizhi et al³⁹⁶ evaluated the effectiveness of xylitol and placebo wipes on *S. mutans* count in 19- to 35-month-old children. Forty-four children were randomly selected and divided into 2 groups: a control group who used placebo wipes and an experimental group who used xylitol wipes. Interventions were applied twice daily for 2 weeks. *S. mutans* levels in saliva were recorded before and after each intervention. Clinically significant reduction in *S. mutans* counts was seen in the xylitol wipes group. The authors concluded that the use of xylitol

wipes can aid in reducing cariogenic bacteria, especially *S. mutans*, and be considered an adjunct oral hygiene tool for childhood caries prevention.

Aluckal and Ankola³⁹⁷ in another randomized controlled trial that included sixty 12- to 15-year-old students reported that xylitol chewing gum used twice daily for 5 minutes over the course of 30 days can effectively reduce salivary *S. mutans* counts. Xylitol gum has shown a maximum benefit against salivary *S. mutans* when compared with polyol gum and controls.

Xylitol has also been used to potentiate the anticaries effect of other products. Jafari et al³⁹⁸ compared different fluoride varnishes containing xylitol and casein phosphopeptide amorphous calcium phosphate and found varnish containing both products to be the most effective.

Quorum sensing targets

When few bacteria are present in the biofilm, it would seem pointless for them to produce a gene product, such as an enzyme or virulence protein, because protein concentration would be too low to be effective. Quorum sensing is a regulatory process that ensures sufficient cell density before a specific gene product is made.³⁹⁹ This process allows bacteria to proliferate to a specific level before beginning production of a particular gene product. Therefore, quorum sensing is a means of bacterial communication within a biofilm. Quorum sensing is also the mechanism by which dormant bacterial genes in a planktonic stage become active within the biofilm. For this reason, another approach to maintaining the ecological equilibrium of plaque is to interfere with this type of cell-to-cell communication.

Muras et al⁴⁰⁰ investigated the efficacy of *Tenacibaculum sp.* 20J, a bacterium of marine origin, for interfering with the quorum-sensing signal AI-2, which could prevent biofilm formation in *S. mutans*. Three strains of bacteria were tested, *S. mutans* ATCC25175, *S. oralis* DSM20627, and *S. dentisani* 7747. The AI-2 inhibitory activity was verified by using the biosensors *Vibrio harveyi* BB170 and JMH597. *S. mutans* ATCC25175 biofilm formation was observed by using impedance real-time measurements with the xCELLigence system (ACEA Biosciences), confocal laser microscopy, and the crystal violet quantification method. The results demonstrated that addition of cell extract from *Tenacibaculum sp.* 20J reduced *S. mutans* biofilm formation by 40% to 50% compared with controls without significantly affecting growth. Therefore, with this method, bacteria were not killed. Rather, bacteria were inhibited (a decrease of almost 40% was also observed for *S. oralis* and *S. dentisani* biofilms), did not form biofilm, and thus were rendered harmless. The authors concluded that the ability of *Tenacibaculum sp.* 20J to interfere with AI-2 and inhibit biofilm formation in *S. mutans* was demonstrated. The inhibition of quorum-sensing processes may constitute a

suitable strategy for inhibiting dental plaque formation, although additional experiments using mixed biofilm models should be pursued.

Additional research on this subject was published by Araujo Alves et al⁴⁰¹ who described identification of 2 independent regulatory systems controlling the transcription of a surface-associated protein (cnm) that mediates binding to extracellular matrices, intracellular invasion, and virulence. A better understanding of the mechanisms controlling expression of virulence factors such as cnm may facilitate the development of new strategies to treat bacterial infections.

Natural products

Natural products are metabolites or phytochemicals derived from herbs, plants, fruits, or spices. They are a rich source of structurally assorted molecules with an extensive variety of biological behaviors and might be suitable alternative anticaries products that respect the ecology of microbiome by interfering only with the “bad guys.” They have widely varied mechanisms of action, ranging from the inhibition of cell growth, reduced acid production, inhibition of glucan synthesis, or alteration of cell adhesion properties. An interesting article that addressed natural products was presented by Philip et al.⁴⁰² Researchers used extracts from dark-colored berries (cranberries, blueberries, and strawberries) and a combination of 3-berry extracts (orphenol) on 24-hour-old *S. mutans* biofilms. Different concentrations were tested. Resultant biofilms were assessed for metabolic activity, acidogenicity, biovolumes, structural organization, and bacterial viability. Biofilms treated with the cranberry and orphenol extracts demonstrated the greatest reductions in metabolic activity, acid production, and bacterial/exopolysaccharide (EPS) biovolumes, while their structural architecture appeared less compact than control-treated biofilms. Cranberry extract was found to be the most effective extract in disrupting *S. mutans* virulence properties without significantly affecting bacterial viability. This suggests a potential ecological role for cranberry phenols as nonbactericidal agents capable of modulating pathogenicity of cariogenic biofilms.

Ferreira et al⁴⁰³ studied the antibacterial capability of 3 essential oils on *S. mutans*, *S. salivaris*, and *S. oralis* following an in vitro protocol. When testing antibacterial agents against *S. mutans*, *S. salivaris* and *S. oralis* are often included because of their genetic similarity. If a product is effective against *S. mutans*, but not against the other 2 bacteria, the antibacterial activity under investigation is deemed highly selective. Products tested in the present investigation were thymol, linalool, and citronellol. The minimal inhibitory concentration (MIC) and the 2 immediately higher concentrations, as well as positive controls, were subcultured on Müller Hinton agar plates. After 24 hours of incubation at 37 °C, minimal

bactericidal concentrations were related to growth of the control group, which was chosen as the lowest drug concentration that prevented visible growth in subculture. All tested phytochemicals exhibited antibacterial activity, thus representing natural products with potential application in caries preventions.

Heteropyxis natalensis, commonly known as Lavender Tree, is found especially in South Africa. Extracts of this plant have been widely used as an oral rinse by the indigenous population to address toothache and oral soft tissue inflammation. Henley-Smith et al⁴⁰⁴ tested the effect of this extract on several oral pathogens, including *Actinomyces israelii*, *Prevotella intermedia*, *S. mutans*, *Lactobacillus paracasei*, *Candida albicans*, and a strain of drug-resistant *Candida albicans*. In addition to cell growth inhibition, the authors also tested effects on acid production. The results revealed reduction in the acid production for each bacterium after exposure to *Heteropyxis natalensis* extract. Concomitantly, pH levels possibly indicated a reduced potential for enamel demineralization. This, in turn, may help to prevent dental caries formation. Additionally, periodontal disease may also be positively affected as periodontal pathogens were inhibited.

Natural products are largely an unexplored source of effective, nontoxic antibiofilm molecules that could be used in combination with fluoride as alternatives to conventional microbicides such as chlorhexidine or triclosan. Although fluoride remains the most used, effective, and economical protective agent against dental caries, at least on a large scale, fluoride alone does not offer complete protection against tooth decay. Furthermore, current theories emphasize the importance of maintaining a healthy and stable oral plaque biofilm for long-term disease control. One possible adjunct is reduction or elimination of refined sugars from the diet. Unfortunately, behavioral dietary changes are difficult to achieve and even more challenging to sustain. Adopting ecological preventive measures is the key to long-term dental caries control indicating a paradigm shift to a biological model for disease management. Therefore, the efficacy of ecological preventive measures must be assessed in a population that consumes a conventional diet containing a high level of sugars before any reliable clinical recommendations can be made. Furthermore, we completely agree with Philip et al³⁷³ when they conclude their review by saying "... rather than surrogate end points like lower MS levels or reduced acid production, the critically important outcome for all new caries-preventive measures will be whether they can ensure a significant reduction in individual caries experience."

Silver diamine fluoride

Since its recent introduction in the United States, silver diamine fluoride (SDF) has been the object of much

research and a significant volume of publications. SDF is highly effective, which was again well supported by 2018 reports. A noteworthy publication by Duangthip et al⁴⁰⁵ focused not on the success of SDF, but on the product's safety. This randomized clinical trial was designed to compare adverse effects and parental satisfaction following the different application regimes of SDF treatment in preschool children. Eight hundred eighty-eight preschool children with active dentin caries received 12% SDF applied once per year (group 1); 12% SDF applied every 6 months (group 2); 38% SDF applied annually (groups 3); or 38% SDF applied semiannually (group 4). Information on adverse effects (tooth and gum pain, swelling, gum bleaching or soft tissue staining, and systemic toxicity) was collected through parent questionnaires, within 1 week after every SDF or placebo application. Information of parental satisfaction with their child's dental appearance was collected at the beginning of the study and 30 months later. A total of 799 children (90%) completed the study. No acute systemic illness or major adverse effect was reported. No differences in minor adverse effects among experimental groups were found ($P>.05$). As expected, blackening of carious lesions was common among all groups and increased with increasing application and concentration frequencies. Based on parental reporting, SDF does not appear related to acute systemic illness, and pain, gum swelling, and gum bleaching were not significant adverse consequences. The authors concluded that application of SDF, according to protocols investigated for caries arrest, is safe for preschool children.

Blackening of tooth structure is a consequence of SDF. However, application of potassium iodide (KI) has been suggested to counteract this effect. Using an in vitro method, Patel et al⁴⁰⁶ demonstrated the efficacy of KI, by applying it immediately after the application of SDF.

A systematic review²²⁹ found SDF effective for root caries prevention and arrest in older adults. Root caries prevented fraction and arrest rate for SDF were significantly higher than those for placebo. No severe adverse side effects were observed. The authors concluded that reports of SDF trials support its effectiveness in root caries prevention and arrest, remineralization of deep occlusal lesions, and treatment of hypersensitive dentin.

Similarly, Oliveira et al²²⁸ used a systematic review to evaluate the effectiveness of SDF in preventing and arresting caries associated with exposed root surfaces of adults. The authors found 2356 unique records and included 3 trials in which the investigators had randomly assigned 895 older adults. Primary results were weighted mean differences in decayed or filled root surfaces and mean differences in arrested carious lesions comparing SDF with control groups. The studies included in the review had a low risk of bias in most domains. SDF applications had a significantly better preventive effect than

placebo and had similar capacity to prevent new root surface carious lesions when compared with chlorhexidine or sodium fluoride varnish. It was concluded that yearly application of 38% SDF to exposed root surfaces of older adults is a straightforward, inexpensive, and effective means of preventing caries initiation and progression.

Finally, a technique article described the use of SDF to arrest and prevent new caries with the goal of maintaining fixed and removable prostheses and supporting teeth in a cost-effective manner.⁴⁰⁷ When caries is present at crown margins and economy makes crown removal and replacement impossible, the authors suggested SDF application, with or without mechanical caries debridement, followed by sealing of the lesion with glass ionomer cement. This approach may be applicable when no acceptable clinical alternative is available and maintaining existing restorations is desirable.

Sealing, infiltration of caries, and partial caries removal

In line with the technique article discussed previously, but using a more rigorous scientific approach, Dias et al⁴⁰⁸ reported that sealing carious dentin might be effective because it does not increase the child's dental anxiety, reduces chair time, and demonstrates clinical success with no radiographic difference when compared with partial caries removal followed by restoration. Peters et al⁴⁰⁹ treated 42 high-caries-risk individuals, having 2 active proximal carious lesions. One lesion was infiltrated with resin (experimental group) while the second lesion received mock infiltration (control group). Thirty-two lesion pairs (76%) were evaluated after 2 years. Lesion depth was similar between groups. Comparative pairwise assessment showed significantly more caries progression in controls versus infiltrated lesions. Cumulative prevented fraction after 2 years was 97% for infiltrated lesions versus 74% for control lesions. Therefore, the authors concluded that 2 years after follow-up, resin infiltration demonstrated higher efficacy with 24% more stabilized lesions. Resin infiltration provided effective microinvasive and inhibited short-term lesion progression. Long-term follow-up is needed to strengthen evidence for efficacy of resin-infiltration as an adjunct to standard care.

Abdelaziz et al⁴¹⁰ investigated several self-etching adhesives for resin infiltration into natural noncavitated proximal lesions. Additionally, they sought to verify effects of dehydration protocol on infiltration of self-etching adhesives. For this *in vitro* experiment, 29 extracted posterior teeth with natural proximal lesions (ICDAS 1-2) were sectioned through the lesion offering 2 specimens of each lesion. Three groups of 8 lesions were abraded with metallic strips and etched for 2 minutes

with 37% phosphoric acid. All sample teeth were stained with rhodamine isothiocyanate, dried with compressed air and ethanol, and the caries lesions were infiltrated with Scotchbond Universal (3M ESPE), Clearfil SE Protect (Kuraray Dental), or OneCoat 7 Universal (Coltène) for 3 minutes. A thin layer of flowable composite resin was then applied (Tetric N-Flow; Ivoclar Vivadent AG). One group was dried by using compressed air alone to be able to compare the influence of dehydration on infiltration. After light polymerization, dyes were bleached by immersion in hydrogen peroxide, and the remaining lesion pores were stained with sodium fluorescein solution. The specimens were then cut in thin slices for confocal microscopy and computer image analysis. ANOVA and Duncan post hoc tests revealed no significant differences between the 3 adhesives or between air-drying and drying with compressed air and ethanol. The authors concluded that conservatively treating initial caries with metallic strips and 37% orthophosphoric acid might effectively facilitate infiltration of adhesives into noncavitated lesions.

Freitas et al⁴¹¹ also looked at *in vitro* infiltration and arrived at an interesting conclusion. In this study, a resin infiltrant was used for treatment of active white spot lesions because of its ability to penetrate enamel pores and prevent lesion progression. The authors indicated that there is limited information regarding mechanical effects of resin infiltration on artificial enamel lesions and resistance to demineralization. This point is relevant because many *in vitro* studies involve artificially created carious lesions. Here, artificial lesions were produced in bovine enamel by using 3 different protocols and subjected to resin infiltration. The results demonstrated that the infiltrant was able to partially recover surface hardness and prevent further surface hardness loss in enamel previously demineralized. However, this effect depends on the type of lesion created *in vitro*. Additionally, this effect is limited to surface enamel only. The authors estimate that these effects are likely similar to *in vivo* outcomes. Thus, although resin infiltrates the lesion to a certain degree, success of the procedure likely results from superficial sealing.

A split-mouth randomized clinical trial was accomplished to determine the effectiveness of sealants in preventing carious lesions within a 2-year follow-up.²³⁴ Two resin-based sealants were evaluated (with and without fluoride) for retention and caries risk factors related to outcomes. The study incorporated 663 tooth pairs in 400 children aged 5 to 15 years in a high-risk caries population presenting permanent caries-free molars or molars affected by ICDAS 1 or 2 lesions. At the 2-year follow-up, 483 tooth pairs were evaluated. Sealed molars had 83% less risk of developing grade 3 to 6 caries (ICDAS scale) than molars without sealant. The authors concluded that sealants prevent new ICDAS 3 to

6 lesions or prevent progression of noncavitated carious lesions in high-caries-risk children. The efficacy of the sealant was similar regardless of whether it contained fluoride or not.

However, Estay et al²⁶⁵ reported that sealing minor marginal defects associated with composite resin or amalgam restorations did not increase restoration longevity. Therefore, this intervention should be considered over-treatment for patients with low-to-medium risk for developing dental caries. Similarly, it was reported that infiltration of noncavitated proximal lesions had no additional effect if patients were properly instructed to focus on caries control.⁴¹²

Although few studies indicate that nonintervention is the preferred strategy, conscientious clinicians are encouraged to use best practices and informed clinical judgment in all situations as a wide variety of minimally invasive procedures are currently available. An excellent guideline to help direct clinical judgment in this regard was published by Giacaman et al.⁴¹³

Additional papers

A Japanese group published a noteworthy report in World Neurosurgery.⁴¹⁴ Although rare, there are strains of *S. mutans* (cnm-positive) that are identified in cardiovascular specimens, likely due to the collagen-binding activity of these strains. Their presence has been linked to inhibition of platelet aggregation and damage to arterial walls. Therefore, these strains of *S. mutans* might be considered risk factors for cardioembolic infarction, intracerebral hemorrhage, and intracranial aneurysm rupture, yet another example of how bacterial infection can significantly affect human life. Further studies and efficient means of strain identification must be developed.

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