Annual review of selected scientific literature: Report of the committee on scientific investigation of the American Academy of Restorative Dentistry

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The information in this review is extremely valuable in light of the reoccurring call for dentists to practice evidence-based dentistry and the explosion in both the number of journals and the articles related to the profession of dentistry. It is a monumental task for practitioners to locate studies pertinent to current clinical issues, but it is an even greater problem to evaluate the validity of the scientific methods used in any study and the relative validity of the conclusions that are reached.

One issue that is addressed in this report is the increasing number of systematic reviews published each year. These systemic reviews are ranked at or near the top of the hierarchy of scientific evidence. However, systemic reviews can only answer key questions and provide clinical guidance when the quality of the clinical trials included in the reviews has sufficient scientific validity. Sadly, the authors of many systemic reviews admit that the quality of the reviewed trials is low, that confounding variables have not been controlled, and that there is a high likelihood of bias and a host of other problems with the included trials. Thus, the conclusions reached in many systemic reviews may not be valid and can actually provide clinicians with misinformation.

The analysis of scientific literature published in 2016 is divided into 8 sections: (1) prosthodontics, (2) periodontics, (3) dental materials, (4) occlusion and temporomandibular disorders, (5) sleep-disordered breathing, (6) implant dentistry, (7) oral medicine and oral and maxillofacial surgery, and (8) dental caries.

PROSTHODONTICS

The section on prosthodontics is divided into 8 subtopics to facilitate convenient review: (1) general prosthodontic

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considerations, (2) conventional removable complete prosthodontics, (3) conventional removable partial prosthodontics, (4) conventional fixed prosthodontics, (5) general implant prosthodontic considerations, (6) implant-removable prosthodontics, (7) implant-fixed prosthodontics, and (8) prosthodontic materials. In addition to selected reports, a sizable number of excellent reviews, systematic reviews, and clinical descriptive materials were also published on topics of prosthodontic interest. Although commenting in detail on this additional material is impossible, it is listed here for those interested in practice guidelines, anatomy and physiology, bruxism, conventional removable complete prosthodontics, conventional fixed prosthodontics, diagnostics, digital dentistry, digital dentistry, evidence-based dentistry, general topics in implant dentistry, general topics in prosthodontics, geriatric dentistry, implant-fixed prosthodontics, implant-removable prosthodontics, implant site development, implant surgery, implant treatment planning considerations, maintenance, maxillofacial prosthetics, occlusion, pathology and disease, pharmacology, radiology, restorative success-survival, tooth structure loss and restoration, and xerostomia.

General prosthodontic considerations

Accurate transfer of condylar guidance controls from the patient to an articulator is important prior to laboratory fabrication of indirect occlusal restorations. Named after Sir Norman Godfrey Bennett of the United Kingdom, the Bennett angle is formed between the sagittal plane and the average path of the advancing mediotrusive condyle as viewed in the horizontal plane during lateral mandibular movements. Errors in transferring this angle to the articulator may adversely impact ridge and groove positions and directions, as well as cusp height and cusp tip locations in resultant restorations. With this in mind, Cimic et al investigated the effect of the angle occlusal classifications of Bennett angle values recorded in vivo.

Participants included 98 young adults (average 26.0 years of age) characterized as having no previous orthodontic treatment, no signs or symptoms of TM dysfunction, complete (except for third molars) and healthy dentitions, no reverse articulation or open occlusal relationships, and no previous extensive dental restorations. Participants were divided into 4 study groups based on bilaterally similar angle classification, as follows: class I (n=58), class II/division 1 (n=10), class II/division 2 (n=14), and class III (n=16). All recordings were obtained using an ultrasound mandibular recording device (Arcus Digma II; Kavo) with 6 degrees of freedom, using a paraocclusal clutch rigidly fixed to the mandible. Upon mandibular movement, device software calculated condylar spatial positions, mid-sagittal incisal point, and occlusal determinants. Three protrusive, 3 left laterotrusive, and 3 right laterotrusive movements were recorded for each participant. All movements were unguided. Software calculated the Bennett angle for each participant’s left and right mandibular fossae, and data were statistically analyzed.

With respect to the Bennett angle, no significant differences among angle occlusal classifications were observed. The average Bennett angle for all participants was 7.7 degrees. This finding corresponds well with classic data reported by Lundeen, indicating an average Bennett angle of 7.5 degrees.

Results of this in vivo investigation indicated that angle occlusal classification did not significantly impact Bennett angle values. The authors encourage clinicians to consider this information when programming average values into an articulator during indirect restoration fabrication.

Appropriate sensory feedback from periodontal mechanoreceptors optimizes the masticatory process. Alteration (using tooth-supported fixed partial dentures) or elimination (using implant-supported fixed partial dentures) of this critical neural feedback may adversely influence the masticatory mechanism. Grigoriadis et al conducted a study designed to elucidate motor activity during the first mastication cycle and to evaluate the role of periodontal mechanoreceptor input in these patient groups.

Sex- and age-matched experimental groups consisted of 11 individuals with metal-ceramic tooth-supported fixed, complete prostheses (TSP) in both jaws, 10 participants with metal-resin implant-supported fixed complete prostheses (ISP) in both jaws, and 10 controls with natural dentition consisting of at least 24 occluding teeth and no history of periodontal disease. A magnetic sensor jaw tracking device recorded mandibular movements during the mastication of 1 hazelnut per experimental trial placed initially on the dorsum of the tongue. Bilateral external masseter electromyographs (EMGs) and nut cracking sounds during mastication were recorded. Data obtained during the first chewing cycle (that is, beginning of jaw opening to initial fracture of the hazelnut) of each trial were analyzed.

The vertical and lateral extents of mandibular movement and duration of jaw opening did not differ significantly among groups. However, 82% of the TSP group and 70% of the ISP group exhibited slippage of the hazelnut (that is, unintended loss from between occlusal surfaces) during initial jaw closure, compared with 30% of the controls. The TSP and ISP groups also exhibited more irregular and narrower patterns of jaw motion.
During the first mastication cycle, individuals with TSPs or ISPs in both jaws demonstrated less accurate control of mandibular movement than those with natural dentition. Authors theorize that effective mastication requires 3D awareness of the teeth and optimal mandibular coordination in order to establish efficient tooth-food-tooth relationships and contacts. Awareness of these optimal functional relationships may require appropriate input from the periodontal mechanoceptors. When this information is lost or lacking because of TSPs or ISPs in both jaws, a critical systematic reference for efficient mastication may be lost, requiring alternative strategies involving irregular mandibular movements, as seen in this investigation.

The causes of noncarious cervical lesions (NCCLs) are complex, controversial, and poorly understood, likely involving erosion, abrasion, and/or tooth flexure secondary to occlusal loading. In order to investigate the relationship between NCCLs and various potential causal factors, Sawlani et al.188 conducted a 5-year prospective clinical trial. The NCCLs (n=83) in 29 participants (15 men, 14 women; average 60.3 years of age) were evaluated for sclerosis, cold sensitivity, and shape. Polyvinyl siloxane impressions were made, and casts were developed to record conditions at baseline, 1, 2, and 5 years. The casts were scanned (noncontact profilometry), and 1-, 2-, and 5-year scans were superimposed on baseline scans to identify NCCL volumetric change. Computerized occlusal analysis (T-Scan; Tekscan Inc) and pressure-indicating film (Fujifilm Prescale: Sensor Products Inc) were used to record relative and absolute occlusal loading of affected teeth at the 5-year recall. A questionnaire was used to assess diet, medical condition, tooth brushing, and adverse oral habits. Mounted casts facilitated assessment of occlusion, wear facets, and eccentric guidance. Lesion progression from 1 to 5 years was statistically correlated with absolute and relative occlusal forces. Statistical comparison of lesion progression with diet, medical condition, tooth brushing, adverse oral habits, wear facets, and eccentric guidance was completed.

The NCCLs investigated were present primarily in premolars (32.2%) and then in canines and molars (23.7% each). The rate of lesion progression over 5 years was 1.50 ±0.92 mm³/year and significantly correlated with absolute mean occlusal stress (P=.011) and relative mean occlusal force in maximal intercuspal position (P=.032). No significant relationship was seen between NCCL progression and any other factors (such as, protractive forces, laterotensive forces, mediobusive forces, acidic diet, deficient or acidic saliva, tooth brushing technique or rigor, adverse oral habits, presence of occlusal facets, or group function lateral guidance). The authors concluded that heavy occlusal forces, as characterized here, appeared to play a significant role in the multifactorial causes of NCCL progression.

### Conventional removable complete prosthodontics

Conventional complete maxillary dentures undoubtedly remain a viable and preferred therapeutic option for many patients who cannot afford or tolerate implant-based treatment alternatives. Although many reports focus on restoration of the edentulous mandible, attention to treatment of the edentulous maxilla with conventional complete dentures is relatively lacking. With this in mind, current studies reporting patient satisfaction as a primary outcome of conventional maxillary complete denture therapy were systematically reviewed by Thalji et al.189 The investigation addressed patient satisfaction and related objective clinical measurements, including mastication, prosthesis retention, and occlusion.

Existing reports were searched in publications up to March 2014. In order to establish clinical guidelines based on available information, prospective comparative studies, cohort prospective studies, and retrospective studies of more than 10 participants were included. The initial, multiple database electronic search identified 4530 articles. Application of exclusion criteria yielded 31 articles focusing on patient-based outcomes and satisfaction data associated with conventional maxillary complete dentures, maxillary implant overdentures, and implant-supported fixed complete dentures. The selected articles reported 5485 patients, including 2685 conventional maxillary complete denture wearers (men and women, mean 59.7 to 73.6 year of age).

Results indicated that providing new conventional maxillary complete dentures to patients with edentulism resulted in improved self-reported satisfaction and oral health-related quality of life. However, the reviewed material inadequately reported variables that might have influenced this result (such as, edentulous ridge relationships and conditions, impressions, records, tooth form, and tooth arrangement). Thus, because if this inadequate reporting on these important clinical variables, not enough information was provided to determine which aspects of therapy were important to provide an optimum outcome with maxillary complete dentures.

The results indicated that a broad range of evidence supports the use of conventional complete dentures for management of maxillary edentulism. The authors indicated that patient expectations for optimal esthetic and phonetic outcomes are high and can be met by conventional complete maxillary dentures. Dissatisfied patients may then be evaluated for fixed or removable dental implant therapies.

In order to achieve optimal support, stability, and retention for a maxillary conventional complete denture, intimate adaptation of the denture base to the denture foundation is necessary. Given the need for accurate

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adaptation and various denture base fabrication processes currently available, Goodacre et al\textsuperscript{190} carried out an in vitro study comparing compression molding, injection molding, fluid resin, and CAD-CAM methods to determine which produces the most accurate and reproducible denture base adaptation.

Forty identical duplicate gypsum casts (edentulous maxilla) were laser scanned prior to initiating denture fabrication procedures. A single master denture was developed and used to create a silicone mold for subsequent production of 30 standardized wax test dentures, 10 for each compression molding, injection molding, and fluid resin methods. The CAD-CAM test specimens were developed from scans of 10 casts. The resultant 40 complete denture test specimens were hydrated for 24 hours, and intaglio surfaces were laser scanned. Each denture scan file was superimposed on its corresponding cast scan file, using surface-matching best-fit software. Measurements were made at 60 identical locations on all specimens and casts. Discrepancy in fitting was evaluated at 5 locations (denture border apex, 6 mm from denture border, crest of ridge, palate, and posterior palatal seal). Data analysis identified accuracy, reproducibility, and differences between processing techniques.

Considering all measurements, results indicated that the CAD-CAM process yielded the most accurate and reproducible denture base adaptation compared with those of compression molding, injection molding, and fluid resin techniques. Specifically, the CAD-CAM technique yielded the most accurate adaptation at the denture border apex, 6 mm from the denture border, and palate and was most reproducible at the denture border apex, palate, and posterior palatal seal. Compression molding was most accurate at the crest of the ridge and posterior palatal seal areas but was clearly the least reproducible technique. The fluid resin technique was most reproducible at 6 mm from the denture border and crest of the ridge.

Within the limitation of this in vitro investigation, the authors concluded that, overall, the CAD-CAM process resulted in the most accurate and reproducible denture adaptation. Unfortunately, clinical correlation of these findings is difficult because of variables in the in vivo compressibility of the denture foundation. Therefore, in vivo investigation remains necessary to arrive at practical clinical conclusions.

Depending on the definitive impression technique chosen, the delivery of targeted pressure to the denture foundation during impression making is generally considered important to conventional complete denture fit and function. The goal of a selective pressure impression is to intentionally direct region-specific tissue displacement to the denture foundation (that is, primary stress-bearing areas) during impression making. In order to investigate procedure feasibility, Iwasaki et al\textsuperscript{191} designed an in vitro investigation to compare the pressure dynamics along the maxillary denture foundation resulting from different impression materials and different amounts of custom impression tray relief.

An experimental edentulous maxillary model was developed by embedding 6-mm-diameter pressure sensors at 8 locations, as follows: incisive papilla (×1 sensor), anterior mid-palatal suture (×2 sensors), postpalatal seal area (×3 sensors), and first molar areas (×2 sensors). The model surface was then covered with a 2- to 3-mm layer of silicone representing mucosa. Three different custom impression tray designs were used: no relief, relief provided (1 or 2 layers of wax) along the anterior ridge crest, and anterior mid-palatal suture areas. The study examined 2 types of polyvinyl siloxane, a polyether material, and an irreversible hydrocolloid impression material. Impressions were manipulated according to the manufacturer’s instructions. A loading frame designed to apply a consistent centralized seating force on the trays was used. Impressions from each material-tray combination were made and measured 5 times. Pressure sensor output was recorded at a sampling speed of 10 Hz. Values for each impression material were compared at 10 seconds and 20 seconds after the start of measurement. Values for each tray were compared after 20 seconds.

Results indicated that a tray with no relief produced the greatest impression pressure at the incisive papilla regardless of the impression material used. Compared with 1 layer of wax relief, the use of 2 layers resulted in more uniform pressure in the relief area. Finally, the use of relief seemed to direct impression pressure to the first molar regions and the posterior palatal seal area.

The authors concluded that, within the limitations of this in vitro protocol, making selective pressure definitive impressions of the edentulous maxilla may be possible if the pressure dynamics resulting from custom tray fabrication and impression material selection are considered. Care must be taken when extending these laboratory-based conclusions to clinical applications. Further in vivo research in this area is needed.

Conventional removable partial prosthodontics

With the obvious influence of socioeconomic factors on the selection of modern dental treatment, the provision of high-quality conventional, RPDs will remain a popular treatment option well into the future. Unfortunately, concerns related to RPD performance, including mucosal pain associated with the denture foundation, are common. Mucosal pain experienced by RPD wearers may have multiple causes. Kumagai et al\textsuperscript{192} conducted a clinic-based cross-sectional study to ascertain these potential factors and to identify their relative importance.
A total of 333 patients (111 men, 222 women; mean 71.4 years of age) wearing 500 RPDs (54 maxillary, 112 mandibular, 167 both jaws) were consecutively recruited from the prosthodontics clinic in a dental hospital. Participants rated pain intensity and pain frequency associated with denture-bearing mucosa. An examiner recorded age, sex, medical history, medications, smoking habits, diurnal bruxism, oral dryness, residual ridge contour/size, denture-bearing mucosa conditions, pressure-pain threshold, pattern of partial edentulism, number of abutments, and anxiety level.

Pain intensity was rated as present to severe for 34% of the RPDs wearers, and pain was experienced after denture delivery in 43% of them. Bivariate analyses revealed jaw side, number of missing teeth, Kennedy classification, denture type, number of abutment teeth, residual ridge contour/size, mucosal condition/damage, bone prominence, pressure-pain threshold, diurnal bruxism, oral dryness, and anxiety level were significantly associated with pain intensity and frequency ($P<.05$). Logistic regression revealed age, number of missing teeth, mucosal condition/damage, bone prominence, pressure-pain threshold, diurnal bruxism, oral dryness, and anxiety level were significantly associated with pain intensity ($P<.05$). In addition to these predictors, denture type and residual ridge contour/size were significant independent predictors of pain intensity ($P<.05$).

The authors concluded that, within limitations of the study, multiple factors appeared to be significantly associated with and independent predictors of denture-bearing mucosal pain in patients with RPDs. A somewhat unexpected finding was that denture-bearing mucosa condition/damage, pain sensitivity, and behavioral factors were more critical to the pain experience for RPD wearers than the pattern of partial edentulism and number of abutments.

The design of an RPD (such as, extension-base versus tooth-borne) and condition of abutments may significantly influence the survival of residual teeth. However, limited information is available analyzing the relationship between the type of edentulous spaces and tooth loss in RPD wearers. Therefore, Mizuno et al. reported a retrospective cohort study to investigate the matter.

In 102 consecutively treated patients with partial edentulism (50 men, 52 women; mean 63.2 years of age at baseline) provided RPDs at a university-based dental clinic were analyzed to identify predictors of tooth loss. All patients received continuous follow-up care for at least 5 years. Seventy-three extension-base (31 bilateral, 42 unilateral) and 38 tooth-borne (3 anterior, 35 posterior) RPDs were available for study. Clinical records were analyzed at baseline (before RPD placement) to obtain age, sex, carious teeth, attachment loss, endodontically treated teeth, natural tooth occlusal contacts, number of RPD rests, missing teeth, and edentulous spaces.

Throughout the follow-up period, data for tooth loss as it occurred were collected.

More than one-third of the participants lost at least 1 tooth during the follow-up period. Overall, tooth loss was significantly associated with endodontic treatment ($P<.05$), although not all extracted teeth had received root canal therapy. For tooth-borne RPDs, tooth loss was significantly associated with attachment loss and maxillary restoration. For extension-base RPDs, tooth loss was significantly associated with endodontic treatment and age. Removable partial denture design (extension-base versus tooth-borne) was not a predictor of tooth loss.

The authors concluded that the presence of endodontically treated teeth at RPD placement was a significant predictor of future tooth loss. Surprisingly, the design of the RPD (extension-base versus tooth-borne) and presence of caries at baseline appeared to have no significant influence on tooth loss over the 5-year follow-up period in this cohort. Care should be taken when prescribing RPDs for patients with existing endodontically treated teeth.

Although several reports have compared conventional complete dentures, implant overdentures, and implant-supported fixed complete dentures with respect to a number of important outcomes, few studies have compared RPDs with ISFPDs. To address this shortfall, Nogawa et al. compared masticatory performance, occlusal force, and OHIP scores in mandibular Kennedy class I and II patients wearing conventional RPDs and ISFPDs.

Patients meeting strict inclusion/exclusion criteria and treated at 1 university-based clinic were recruited (44 patients, 19 ISFPDs, 25 RPDs; mean 62 years of age). Masticatory performance was evaluated using glucose-containing gummy jelly as the test food. Occlusal force was measured with a 97-μm pressure-sensitive sheet (Dental Prescale 50H type R; glucose-containing jelly), and scanned data were subjected to computer analysis. Oral health-related quality of life was evaluated using the OHIP metric. Masticatory performance, occlusal force, and OHIP scores for ISFPD and RPD groups were statistically evaluated, and relationships among the variables were analyzed.

The results indicated no significant differences between the 2 groups with regard to masticatory performance and occlusal force. The OHIP scores were significantly lower in the ISFPD group than in the RPD group. The OHIP score was not significantly correlated with masticatory performance but was correlated with occlusal force and prosthesis type. Younger age, wearing RPDs, and lower occlusal force were significantly associated with a higher OHIP summary score.

The authors concluded that oral function (as measured by masticatory performance and occlusal force) did not significantly differ for Kennedy class I and II
patients restored with mandibular RPDs and ISFPDs. However, ISFPD appeared to be superior to RPDs with regard to OHRQoL in this population. In addition, there appeared to be a weak relationship between the OHIP score and occlusal force in these patients. The authors noted that the OHIP instrument contains questions about physical pain, functional limitations, and psychological/social outcomes and suggested that the more favorable subjective patient assessments of ISFPDs were more likely influenced by factors such as comfort and less influenced by objective functional measures such as masticatory performance and occlusal force.

Conventional fixed prosthodontics
Although ceramic restorations are routinely considered esthetically superior to metal-ceramic alternatives for anterior crowns, debate exists over the appropriate use of ceramic crowns for the restoration of posterior teeth. Direct comparison of anterior and posterior ceramic crowns is limited. Therefore, Kassardjian et al195 systematically reviewed differences in survival for complete coverage ceramic materials used in adults to restore anterior or posterior vital teeth (not involved with fixed partial dentures) and opposed by teeth.

The reference search included the use of multiple databases and manual searches of articles published between 1980 and 2014. Inclusion criteria targeted ceramic complete coverage crowns in human adults older than 17 years of age, prospective and retrospective studies, opposed by teeth, and periodontal pocket depth of <5 mm. Implant crowns and nonvital teeth were excluded. The initial search produced 3937 articles, which were narrowed to 14 papers (9 prospective and 5 retrospective studies) upon application of selection criteria. Given study heterogeneity and the lack of sufficient directly comparable data, studies were assessed at the binary level (success versus failure; failure being any reported problem). The ceramic materials encountered included slip cast alumina, leucite-reinforced glass ceramic, pure alumina, lithium disilicate, and zirconia. Pooled data yielded 1112 anterior crowns with 73 failures (6.5%) and 1821 posterior crowns with 166 failures (9.1%), with a follow-up time between 36 and 223 months. Relative risk meta-analysis indicated that anterior ceramic crowns were 50% less likely to fail than posterior ceramic crowns (P=.001). Interestingly, 2 studies reported follow-up data of ≥7 years, indicating a pooled anterior crown failure at 18.6% and posterior crown failure at 38.8%. The authors concluded that, based on the current data, clinicians need to be cautious about using ceramic crowns to restore posterior teeth.

With the rise in popularity of and intrigue surrounding digital impression making, questions related to accuracy and reliability must be addressed. There appears to be a general lack of consistency in the current research with respect to these important clinical parameters. To address this issue, Tsrigiannis et al196 systematically compared outcomes of available studies investigating the marginal fit of single tooth-supported ceramic crowns fabricated from digital with conventional impression methods and combined available data in a meta-analysis.

The initial search for available reports yielded 63 articles on the topic. Application of inclusion/exclusion criteria resulted in 12 articles for consideration in the final analysis. For statistical purposes, mean marginal fit values from each study were extracted and categorized according to impression method in order to calculate mean (95% CI) values and to compare digital and conventional methods separately with respect to in vitro and in vivo data.

For in vitro conventional impression studies, the mean marginal discrepancy was 58.9 μm, whereas the mean marginal discrepancy associated with digital impressions was 63.3 μm. For in vivo studies, mean marginal discrepancies of 79.2 μm and 56.1 μm were calculated for conventional and digital impressions, respectively.

The authors concluded that no significant differences were observed in marginal discrepancy for tooth-supported single-unit ceramic restorations fabricated using digital or conventional impressions. Overall mean marginal discrepancy remained below the 120-μm threshold commonly cited as clinically acceptable. The authors commented that the digital workflow not only exceeds standards of clinical acceptability but also performs equally well compared with conventional impression methods.

With the increasing popularity of zirconia tooth-supported crowns and the desire to apply thin, conservative preparation restorations, the development of predictable adhesive luting methods is desirable. However, zirconia’s resistance to conventional etching materials/processes and the remarkable differences in zirconia materials currently on the market complicate matters. In order to better understand and apply the best methods, Tzanakakis et al197 systematically reviewed studies in order to analyze and classify the methods and materials proposed to improve adhesion to zirconia surfaces.

A preliminary search uncovered mainly in vitro reports and a small number of systematic reviews and randomized controlled trials involving zirconia restorations. A total of 134 publications (from 1998 to 2014) were initially reviewed. Twenty-three of the most relevant experimental articles were selected for this study.

The results indicated that reports addressed different adhesive techniques and different testing methods. As a result of this heterogeneity, studies were difficult to compare as parameters varied widely in each of the research
protocols. General concepts reviewed included airborne-particle abrasion, rotary grinding, other roughening techniques (such as, low-fusing porcelain micropearls, selective infiltration etching), chemical erosion, laser erosion, chemical bonding (silane couple, 10-methacryloyloxydecyl dihydrogen phosphate [MDP] adhesive monomer, plasma oxyfluoride), tribochemical silica coating, pyrolytic silicon deposition, plasma spray hexamethyldisiloxane, zirconia/metal primers, and combination approaches.

Despite problems with study heterogeneity, the authors provided several closing observations. Because of consistently positive results, airborne-particle abrasion has become a reference pretreatment method in contemporary research. Tribochemical silica coating effectively enhances bonding capacity, particularly when silanes are applied. The role of adhesive monomers and silanes in zirconia adhesion is important and necessary for chemical bonding. Surface contamination and aging have significantly negative effects on adhesion to zirconia. Many factors influence the zirconia bonding process, including surface treatment, adhesive medium, and aging conditions. To date, most information on this topic has been generated by in vitro investigation. Laboratory studies have limits and should be confirmed by well-designed clinical trials.

**General implant prosthetic considerations**

Bruxism is generally considered a risk factor to continuously successful dental implant function and survival. To investigate the impact of bruxism, Chrcanovic et al\(^{198}\) reviewed a retrospective study designed to investigate the association between awake and sleep bruxism and the risk of dental implant failure and to describe and compare bruxers with nonbruxers.

The study initially examined 2670 patients who received 10,096 implants at a specialist clinic between 1980 and 2014. Implant- and patient-related data were collected, including general/behavioral health history, implant surface characteristics, implant length and diameter, antibiotic use, bone grafting, jaw and location, patient sex and age, days to failure, and follow-up duration. Bone quality and quantity were classified at the time of surgery (Lekholm and Zarb classification). Bone quality ranged from type 1 (large homogeneous cortical, high-density trabecular bone) to type 4 (thin, cortical, low-density trabecular bone). Bone quantity ranged from type A (highest volume) to type E (lowest volume). Multilevel mixed effects parametric survival analysis was used to test the association between bruxism and risk of implant failure (defined as loss of the implant).

There were 3549 implants in 994 patients, with sufficient information on all variables. From this group, 179 implants were registered failures (46 at abutment connection and 86 during the first year). Implant failure rates were 13.0% (24 of 185) for bruxers and 4.6% (155 of 3364) for nonbruxers (\(P<.001\)). The statistical model revealed bruxism to be a statistically significant risk factor for implant failure (hazard ratio [HR], 3.396; 95% CI, 1.314–8.777; \(P=.012\)).

The authors concluded that bruxism may be associated with an increased risk of dental implant failure. The authors speculated that this may be related to the absence of proprioceptors associated with implant restorations and the lack of proprioceptive feedback control of jaw-closing muscles during heavy occlusal function. The statistical model also implicated the following factors in the increased risk of implant failure, as follows: implant length (shorter in relation to longer), implant width (narrow in relation to wide), implant surface (turned in relation roughened), bone quantity (D in relation to A), bone quality (4 in relation to 1), smoking (smokers in relation to nonsmokers), and proton pump inhibitors (patient taking proton pump inhibitors in relation to nonmedicated patients).

The perceived value assigned to currently available implant-abutment connection geometries has greatly populated the research database, yet rigorous clinical investigation of internal versus external connection in identical implants is lacking. Esposito et al\(^{199}\) reported a multicenter randomized controlled trial (RCT; parallel group design, blinded outcome assessments) intended to evaluate the advantages and disadvantages of identical implants with internal or external connections.

This trial included 120 patients affected by tooth loss (edentulism, partial edentulism, or single tooth loss), requiring a single-implant-supported prosthesis. Patients were randomly allocated to receive external connection (EC) implants or relatively identical internal connection (IC) implants (EZ Plus; MegaGen Implant). Slight differences in implant/component design necessitated IC implants be platform switched, whereas EC were not. Patients were followed for 5 years after initial loading. Outcome measures were prosthesis/implant failure, any complication, marginal bone level changes, and clinician preference.

Sixty patients received 96 EC implants, and 60 patients received 107 IC implants. All patients were followed for 5 years after loading. One EC prosthesis and 2 IC prostheses failed. One EC implant and 3 IC implants in 2 patients failed. Ten complications occurred in 10 EC patients, whereas 9 complications occurred in 9 IC patients. No significant differences were found in prosthesis/implant failures or complications associated with connection type. Five years after loading, there were no significant differences in marginal bone levels for connection groups, and both groups lost bone from implant placement in a statistically significant way: 1.13 mm for the EC implants and 1.21 mm for the IC implants. Two operators had no preferences, and 2
preferred the handling of IC abutments during clinical connection procedures.

The authors concluded that, within the limitations imposed by subtle implant design variation, 5-year post-loading evaluation did not reveal any significant differences between internal and external implant connection performance. It therefore seems reasonable that clinicians choose whichever connection geometry they prefer based on factors other than clinical performance.

The 2016 publications produced a second report that substantiates the findings of Esposito et al.199 Vigolo et al200 reported on a retrospective evaluation of 5-year clinical results on single implants in order to ascertain whether different clinical outcomes were associated with EC or IC implants.

All single-implant EC or IC restorations placed in 27 private dental practices from 2003 to 2007 were evaluated. Initial statistical assessment was performed to detail the sample population at baseline and then to compare clinical outcomes of IC with EC configurations.

The study included 1159 patients (481 men, 667 women, mean 46 years of age) and 2010 implants (821 in men, 1097 in women; 75 dropped out because of lack of data). Of the remaining implants, 1431 (74%) were followed for ≥5 years, and 332 implants (17%) were followed for ≥8 years. Patients generally demonstrated canine-incisal laterotrusive guidance (46%), did not report bruxism (76%), displayed moderate dental wear (52%), received regular dental prophylaxis (82%), and did not smoke (77%). Abutments used were titanium (66%), gold (19%), zirconium (14%), metal-zirconia (1%), and alumina (>1%). Restorations were cemented (73%), screw-retained (27%), and most often incorporated supragingival margins (63%).

The results indicated that implant survival was 98.9%. Differences between the survival of EC and IC configurations were not significant with respect to the negative event studied, that is, fracture of implant, retention screw, abutment, or connection (log-rank test, P>0.05). No significant differences were found between EC and IC configurations with respect to restoration fracture, implant screw loosening, and peri-implant disease.

The authors concluded that, within the limitations of this study, there appeared to be no difference in clinical outcomes for single restorations fabricated for IC or EC implants.

Although the biological role of peri-implant keratinized tissue (KT) remains controversial, it is generally believed to facilitate plaque control and provide a circumferential sealing effect prerequisite to long-term implant success. In order to shed light on the biological function of peri-implant KT, Roccuzzo et al201 conducted a prospective 2-arm long-term blinded cohort study comparing the presence and absence of KT under soft-tissue conditions around the posterior mandibular implants of healthy or moderately periodontally compromised patients. The aim was to better understand the significance peri-implant KT for long-term tissue health and stability.

The study consecutively enrolled 128 participants (52 men, 76 women, mean 52.4 years of age, 21 smokers) who required treatment involving the placement of 1 implant in the posterior mandible to support a single crown or a fixed partial denture. The implant could have been in either a molar or premolar position but no natural dentition could be present distal to the implant site. Bone augmentation of the implant site and distal canti-levers were not permitted. Only 1 implant per patient could be included in the study. Implant placement was either within KT or alveolar mucosa (AM). Baseline radiographs were made at prosthesis placement.

During follow-up, if AM patient demonstrated insufficient plaque control because of soreness during oral hygiene procedures, they were given the option of receiving a free gingival graft (FGG) around the implant. At 10 years, clinical and radiographic measures (that is, probing depth and bleeding, soft tissue recession, radiographic crestal bone height, plaque score, smoking habit, and soreness/discomfort) were recorded by a calibrated, blinded operator. The number of sites requiring antibiotic and/or surgical interventions during the 10 years was also registered.

Results indicated that 98 participants (38 men, 60 women) completed the 10-year study; 63 in the KT group, 24 in the AM group, and 11 in the AM with subsequent FGG group. The absence of KT was associated with higher plaque accumulation, greater soft-tissue recession, and increased need for additional antibiotic and/or surgical interventions to manage complications. Nearly half the AM participants reported pain or discomfort associated with hygiene procedures, and one-third received additional FGG that successfully reduced discomfort and facilitated optimal plaque control.

It was concluded that implants not surrounded by KT were more prone to plaque accumulation and recession, even in patients exercising sufficient oral hygiene and receiving adequate therapeutic support. In carefully selected patients, particularly in the edentulous posterior mandible, where ridge resorption leads to reduced vestibular depth and lack of KT, authors suggested peri-implant soft tissue grafting can facilitate proper oral hygiene procedures. Continuous monitoring of peri-implant tissue conditions is necessary to prevent biological complications.

**Implant removable prosthodontics**

Strategic placement of dental implants beneath an RPD can offer an esthetic advantage as conventional metal clasps are eliminated from view. Additionally, the placement of implants in the posterior edentulous areas
in patients with Kennedy class I and II conditions can supplement prosthesis support and stability, mechanically converting a tooth-tissue borne restoration to a more favorable tooth-implant supported restoration. With this biomechanical advantage in mind, Jensen et al.202 studied the benefits of implant support for patients requiring mandibular bilateral distal-extension RPDs to determine whether the most favorable implant position is in the premolar (PM) or molar (M) region.

The study enrolled 30 participants (15 men, 15 women, mean 60.9 years of age) with Kennedy class I residual mandibular tooth distributions and edentulous maxillae restored with conventional complete dentures. Each patient received a PM and M implant, bilaterally, Locator abutments (Zest Anchors), and a new metal-based RPD with conventional clasps. Initially, the RPD contained Locator attachment metal housings without attachments; thus the implants proving neither prosthesis support nor retention. At 3 months, patients randomly received either PM or M attachments. At 6 months, the investigation crossed over, such that new attachments were placed in unoccupied housings, and previously used attachments were removed. Outcome measurements included OHRQoL (OHIP-NL49), patient-reported general health status, general contentment, and daily duration of prosthesis wear. Data were collected prior to treatment and at 3, 6, and 9 months after receiving the prosthesis. Finally, patients reported their preference for PM or for M attachment location.

Patient-reported general health status was not influenced by prosthesis design. OHRQoL and mean prosthesis wearing time were significantly more favorable for implant-supported RPDs, regardless of attachment position. Per day, implant-supported RPDs were worn 2 to 3 hours more than the conventional RPD. Patient expectations (that is, general contentment) were satisfactorily met, and VAS for implant-supported RPDs with PM or M attachments were similar. At the conclusion of the trial, 56.7% of the patients preferred the M attachments, 30% preferred PM attachments, and 13.3% indicated no preference.

The authors concluded that the mandibular implant support investigated here favorably influenced oral health related, patient-based outcome measures. Most patients preferred attachments located in the molar region to facilitate the support and retention of the RPD. Careful planning may optimize the RPD experience for these patients.

Maxillary implant overdenture (mxIOD) therapy has significantly improved over the years, permitting unique and specific advantages compared with implant-supported fixed complete denture treatment (such as, reduced initial cost, improved hygiene access, esthetic support of facial contours, concealment of prosthesis-ridge junction during animation, accommodation of adverse ridge relationships, improved phonetics, and ease of repair). In order to qualify therapeutic expectations and offer treatment considerations, Sadowsky and Zitzmann203 systematically reviewed available studies evaluating patient-related outcomes associated with the restoration of the edentulous maxilla using implant overdentures.

The review concentrated on publications reporting patient-based outcomes and implant and/or prosthetic success. Following the application of inclusion/exclusion criteria to initial article identification, 20 study cohorts between 1993 and 2014 were identified, including 2 randomized controlled clinical trials, 13 prospective case series including 2 crossover trials, and 5 retrospective studies. Cumulatively, 530 patients received mxIODs supported on average by 4 to 6 implants (range, 1-10 implants). Prosthesis retention was predominantly provided by bar systems, although individual attachments and double crowns were also reported.

The authors concluded by stating well-designed RCTs with larger sample cohorts and longer follow-ups are required to better elucidate expected mxIOD outcomes. Despite the obvious heterogeneity of the included articles (that is, variable sample size, follow-up, implant design/number, retentive mechanics, prosthesis design, and data collection), authors were able to identify clinically noteworthy outcome trends as follows:

- mxIODs offered a stable, removable, maxillary edentulous prosthesis that provided increased patient satisfaction and oral health-related quality of life;
- Higher failure rates were experienced with machined implants;
- Generally, 4 to 6 implants were used in successful cohort studies;
- With ≤4 implants, unsplinted designs had higher implant/prosthesis failure rates than splinted designs;
- Generally, both splinted and individual attachment systems were advocated. Maintenance may be higher for individual attachments. Increased soft tissue inflammation was reported beneath bars;
- Palateless design offered better patient satisfaction.

This article reflects conclusions drawn from the Academy of Osseointegration’s “Summit on Clinical Practice Guidelines for the Edentulous Maxilla,” held in August 2014. Based on reported findings, Sadowsky and Zitzmann203 offered the following clinical guidelines:

- When considering the design of an mxIOD, the treatment team and patient must consider the need for long-term regular maintenance;
• Diagnostic identification of systemic, local (such as, vertical restorative space), and patient-based factors is critical for selecting the most appropriate treatment;
• MdIODs should be maintainable, retrievable, repairable, and replaceable;
• Placing a minimum of 4 implants with wide anteroposterior distribution is recommended for optimal support. Consider more implants when risk factors are present. Implants <10 mm in length should be used cautiously, but moderately rough implants may provide successful solutions regardless of implant length.

For patients with mandibular edentulism and facing the selection of a prosthodontic restorative plan, a choice must often be made between a conventional complete denture (mdCD) and an implant overdenture (mdIOD). The absence of sufficient prosthesis support, retention, and stability provided by mdCDs can be disconcerting to patients, if not functionally debilitating. Limited, high-quality information is available addressing the overwhelming advantage of one treatment option over the other, especially in terms of patient-centered outcome measures. Therefore, Sivar-ramakrishnan and Sridharan204 systematically reviewed available reports on patient satisfaction with mdIODs and mdCDs (opposing maxillary complete dentures) as measured using the OHIP questionnaire and applied meta-analytic techniques to assess any statistical significance in results.

A structured search of publications, involving major electronic databases and hand searching, was conducted and produced 88 articles. Full text review and application of inclusion/exclusion criteria narrowed the pool of acceptable articles to 5 eligible studies. Included were a total of 441 patients wearing 228 mdIODs and 213 mdCDs. The results of all OHIP questionnaires were pooled and analyzed to determine primary (that is, total OHIP score) and secondary (that is, functional limitations, physical pain/disability, psychological discomfort/disability, social disability, and handicap) outcomes.

Results indicated that statistically significant differences in total OHIP scores favored the mdIOD group over the mdCD group. With regard to secondary outcomes, except for physical pain, all other outcomes also favored the mdIOD group.

From the meta-analysis, it appeared that mdIODs performed better than mdCDs in improving overall quality of life and its various domains for patients with edentulism. The authors expressed concern regarding the limited volume of published reports on this important topic, highlighting the need for large robust RCTs with low risk of bias in both selection and outcome measurement before arriving at definitive conclusions.

**Implant-fixed prosthodontics**

Several factors may influence the long-term success of implant-supported restorations. From a mechanical perspective, the implant-abutment connection design and its relative horizontal interface geometry have been implicated as a possible factor in short- and long-term complication rates influencing soft and hard tissue health. To assess this issue in greater detail, Anshiesta et al205 evaluated survival/failure modes of 3-unit ISFPDs with external hexagon-platform matched or switched geometry compared with internal connection platform-matched or switched geometry. Authors hypothesized that no differences in survival/failure modes would be identified considering the “splinted” nature of ISFPDs in this in vitro protocol.

Eighty-four standardized 3-unit ISFPDs (molar pontic) were cemented on abutments fastened to 2 implants mounted in resin blocks. The implants possessed either external or internal hexagonal connection geometry. Four experimental groups (21 specimens each) were established: external hexagon-platform matched (EM), external hexagon-platform switched (ES), internal hexagon-platform matched (IM), and internal hexagon-platform switched (IS). Prostheses were subjected to step-stress accelerated life testing in water. Weibull curves and survival probability over 100 000 cycles at 400 N (2-sided 90% CI) were calculated.

Beta values of 0.22, 0.48, 0.50, and 1.25 for groups EM, ES, IM, and IS, respectively, indicated the limited role of fatigue in damage accumulation, except for group IS. Survival decreased for both platform switched groups (ES: 74% and IS: 59%) compared with platform matched counterparts (EM, 95%; IM, 98%). Characteristic strength was higher only for EM compared with ES, with no difference between internal connections. Failures chiefly involved the abutment screw.

The authors concluded that, from a load-to-failure perspective, platform switching decreased the probability of survival for ISFPDs incorporating both external and internal connections. The authors caution that 1 of the cited advantages of platform switching (that is, minimized peri-implant bone loss after insertion) is currently well supported but was not an element in the present mechanical loading in vitro protocol. Multiple factors must be considered when selecting implant components in the design of optimal prostheses.

It is important to review studies detailing long-term data on restoration survival, particularly those incorporating more than 30 years of follow-up. Jemt206 reported on the long-term clinical survival of single-crown implants consecutively placed in 1 clinic over 31 years, focusing on the survival of implants still in function.

This retrospective observational study addressed all patients consecutively treated with single-crown implants from 1982 to 2013 in a single clinic. Included
were turned implants (followed up to 31 years, 1982 to 2004) and moderately rough surface implants (followed up to 14 years, 2001 to 2013). In total, 9124 patients received 41,897 implants over the retrospective period. Of these, 2417 patients (26% of the global patient database) were provided 3211 implants in 2662 surgeries and were included in the study. Of these, 573 patients were followed for at least 10 years, 231 for at least 15 years, 83 for at least 20 years, and 29 for at least 25 years. For all patients, data for implant failure at last examination were collected. Thereafter, cumulative survival rates (CSR) were calculated.

Patient follow-up compliance was higher for those patients treated in the early period of inclusion (1982-1988). Of the total 3211 implants, 67 implants failed (83.6% during the first year, none after 10 years). Differences in survival rates were observed during early treatment (that is, osseointegration phase), but no or only small changes in survival rates were observed after the first year of function (that is, maintenance phase). Overall, 25-year implant CSR was 97.1%. The turned surface implant CSR was 95.8% (15 years) in the mandible and 95.1% (25 years) in the maxilla. The moderately rough surface implant CSR was 97.2% (11 years) in the mandible and 98.5% (11 years) in the maxilla.

Within the limitations of the present study design (that is, numbers of included/lost patients and complexity of long-term routine population data), the authors concluded that single-implant treatment was predictable over the long term, with subtly lower failure rate for moderately rough implants placed in the maxilla. This difference between turned and moderately rough implant failure seemed to be established during the early phase of osseointegration.

A second long-term investigation of the performance of single-implant restorations was published. Hjalmarsson et al. systematically reviewed implant and implant-supported single crown survival over a period of at least 10 years.

Publications between 2011 and 2014 were searched to identify data pertaining to implant and single-implant crown survival. Nine publications (421 patients, 527 implants, 522 single crowns) were identified. A total of 367 patients (87%) followed for at least 10 years, accounting for 502 implants (95.3%) remaining in function, and supporting 432 original and 33 refabricated single-implant crowns were finally analyzed. Based on patient-level and implant-level data, implant survival reached 93.8% and 95.0%, respectively. The corresponding survival rate for original crown restorations was 89.5%.

The authors considered single-implant therapy to have been predictable treatment over the 10-year follow-up period, with no changes in implant failure rate between 5 and 10 years. The authors warn that replacing crowns must be considered during the follow-up as part of regular maintenance and expressed concern that, compared with the number of patients treated worldwide, the volume of available data describing 10-year follow-up outcomes is unfortunately lacking.

The loss of interproximal contact between fixed implant prostheses and adjacent natural teeth has been reported. Although several causes have been suggested, an obvious cause for this phenomenon remains elusive. To better understand this issue, Varthis et al. evaluated the prevalence of interproximal open contacts between single-tooth implant prostheses and adjacent natural teeth. Also evaluated were the presence of food impaction and the patient's awareness of the problem. Guidelines to prevent interproximal contact loss (ICL) were then considered.

This retrospective cross-sectional study included 128 male and female patients ranging from 19 to 91 years of age. This patient cohort possessed 174 single-implant restorations placed in a dental school postgraduate clinic and a dental faculty practice. One anterior or posterior implant restoration per patient was selected for inclusion in the study. The evaluation period following restoration placement was between 3 months and 11 years. Participants were seen at random intervals to investigate ICL. Interproximal contacts were evaluated with 0.07-mm-thick dental floss, radiographic identification, and clinical visual confirmation. Contact was considered open if floss passed through the interproximal area without resistance. Opposing occlusion consisted of natural dentition, single crowns, fixed partial dentures, removable partial dentures, and/or complete dentures.

The overall prevalence of ICL was 52.8% (92 of 174 instances of single-implant restorations). With regard to proximal involvement, 78.2% of the ICLs were identified on mesial and 21.8% on distal surfaces of the implant restoration. Eight implant restorations in women demonstrated both mesial and distal ICLs. With respect to oral location, 57.9% of the ICLs were associated with maxillary and 49% with mandibular implant restorations, whereas 53.5% involved posterior and 47.8% involved anterior restorations. Among the patients having ICL, a significant percentage (40%) were aware of its presence and of associated food impaction.

Within the limitation of this pilot study, the authors concluded that a substantial number of single-tooth implant restorations demonstrated ICL with adjacent natural teeth. Interproximal contact loss occurred more at the mesial proximal surface and in the maxilla. These finding generally confirmed previous reports. Potential causative factors may include craniofacial growth, anterior component of force, interproximal wear, and poor antirotation implant component stability but most likely is multifactorial. The high prevalence of ICL is ample justification for proper informed consent, and
interproximal contact evaluation between implant restorations and the adjacent teeth should be routinely monitored at recall. Obviously, further investigation is necessary to determine true causative factors and best practices to avoid this problem.

**Prostodontic materials**

Generally, ceramic restorations are popular because of their esthetic appeal. Monolithic ceramic restorations, compared with veneered restorations, have recently become popular because of their higher strength, reduced cost, and reduced wear of opposing teeth. However, surface characteristics of monolithic ceramic materials are not well understood, particularly with respect to clinical adjustment and polishing, as well as the potential for wear of opposing dentition. To investigate this issue, Amaya-Pajares et al. compared the surface roughness of glazed and polished monolithic ceramic with the surface roughness produced by different intraroral polishing systems on adjusted monolithic ceramics.

Milled ceramic disks (10-mm diameter × 2-mm thick) were manufactured and distributed to 6 experimental groups (10 specimens per group): zirconia, glazed and polished (BruxZir; Glidewell, USA); zirconia, glazed and polished (Zenostar; Ivoclar Vivadent AG); leucite-reinforced glass-ceramic, glazed (IPS Empress CAD; Ivoclar Vivadent AG); and lithium disilicate glass-ceramic, glazed (IPS e.max CAD; Ivoclar Vivadent AG). A fine diamond rotary instrument was used to simulate adjustment (5 seconds, 0.5 N). Zirconia specimens were polished using either their manufacturer’s system or the Dialite ZR system (Brasseler). Glass-ceramic specimens were polished using either the OptraFine system (Ivoclar Vivadent AG) or the Dialite LD system (Brasseler). All glazed specimens were produced by means of additive glaze followed by appropriate firing. Surface roughness (defined as absolute deviation of surface irregularities from the mean and expressed as Ra) was assessed using atomic force microscopy and profilometry before and after adjustment and finishing. Mean ± standard error (SE) for each material and finishing procedure were calculated and statistically analyzed.

Results indicated that all materials presented smoother surfaces at baseline than after adjustment and finishing. Generally, polished zirconia was less rough than glazed zirconia. With respect to polishing, BruxZir zirconia presented smoother surfaces with Dialite ZR than with the manufacturer’s system, whereas Zenostar zirconia demonstrated smoother surfaces with the manufacturer’s system than with Dialite ZR. For polishing IPS Empress CAD and IPS e.max CAD, the OptraFine system produced smoother surfaces than the Dialite LD system.

The authors indicated that these in vitro results provide clinicians with information regarding preferred polishing systems for the specific ceramic investigated. Polishing protocols were determined in a preliminary study as many of the manufacturers do not provide clear instructions on how to use their products. Results should be interpreted with caution and may not apply to other similar ceramic materials or when using different protocols of adjustment and polishing. As with all in vitro studies, true replication of clinical conditions limits practical interpretation.

Veneering yttria-stabilized tetragonal zirconia polycrystal (Y-TZP) substructures with glass-ceramic (porcelain) improves the restoration’s esthetics. However, despite the favorable biomechanical behavior of monolithic Y-TZP, porcelain-veneered T-TZP is susceptible to fractures and chipping much more so than with other ceramic and metal-ceramic restorations. Current studies suggest several factors may be related to this adverse clinical outcome. In an effort to gain better understanding of this problem, Meirelles et al. studied the influence of the porcelain composition and fabrication cooling protocol on the fracture strength and reliability of porcelain-YTZP bilayer specimens. The authors hypothesized that applying a porcelain veneer containing leucite and slower cooling during fabrication would yield superior mechanical properties.

A total of 120 bilayer porcelain/Y-TZP bar-shaped specimens were prepared with the dimensions 1.8-mm thick (0.8 mm Y-TZP plus 1.0 mm porcelain) × 4.0-mm width × 16.0 mm length. The specimens were divided into 4 experimental groups (30 specimens/group) according to the porcelain composition (leucite-containing or leucite-free) and cooling protocol. Sample materials included zirconia (Vita In-Ceram YZ), leucite-containing porcelain (Vita VM9; Vita Zahnfabrik), and leucite-free porcelain (Ceramco PFZ; Dentsply Sirona). Fast cooling was accomplished by opening the furnace chamber immediately upon achieving sintering temperature. For slow cooling, the chamber remained closed until it reached room temperature. The specimens were tested using 3-point bending (porcelain surface under tension), using a universal testing machine (0.5 mm/min crosshead speed) in 37°C water. After specimens were tested, they were analyzed using stereomicroscopy (×4 magnification with transillumination) to confirm the presence, extension, and propagation path of the initial crack.

The results demonstrated that Y-TZP veneered with porcelains of different microstructural composition presented similar flexural strength (σ) and reliability (m) values (P=.718). Somewhat surprisingly, the cooling protocol had no influence on the σ and m values of the experimental groups (P=.718). Cracking represented 95% of failures, whereas the initial flaw propagated from the porcelain surface toward the interface.

The authors concluded that Y-TZP veneered with leucite-containing and leucite-free porcelain presented
similar mechanical behaviors. These porcelains, at 1-mm thickness, did not appear to be sensitive to the variable cooling protocol.

The authors point out that the use of a small volume of veneering porcelain (1 mm as in the present study) is known to permit homogeneous cooling and reduced stress states in the material. However, when a greater thickness of porcelain is necessary (>1 mm), cooling the specimen/crown slowly becomes important in order to prevent transient and residual stresses, which could nucleate and propagate cracks inside the porcelain to catastrophic failure. Therefore, future in vitro studies should incorporate experimental protocols that test crown-shaped specimens, a challenging directive at best.

Recently, zirconia primers have been introduced to mediate the bonding of dimethacrylate resins to Y-TZP frameworks. Piloa et al.211 investigated the bonding mechanism of 2 commercially available zirconia primers with 3% Y-TZP disk surfaces. Polished Y-TZP disks (Lava; 3M ESPE) were ultrasonically cleaned (10 minutes in ethanol), rinsed with water, air dried, and distributed to 3 experimental groups: no treatment (control), treatment with Z Prime Plus (Bisco), and treatment with Z-Bond (Danville Materials). Primer films formed on Y-TZP surfaces were left intact for 5 days (dark storage, 37°C, 40% relative humidity), rinsed (10 mL of acetone) to remove the loosely bound fractions, and air-dried. The specimens were then subjected to reflection optical microscopy, reflection Fourier transform infrared microscopy (RFTIRM), and scanning electron microscopy/energy dispersive x-ray microanalysis (SEM/EDX).

The results indicated an amorphous, thick film on primed and acetone-rinsed Y-TZP-treated surfaces, whereas the controls presented a thinner film with phase-separated aggregates. Results of RFTIRM indicated that both of the primers induced carboxylate salt and phosphate salt formation on Y-TZP. SEM/EDX analysis showed increased C, O, and P content on the films, which masked substrate contributions.

The authors concluded that the primers tested produced strongly adsorbed films on Y-TZP, with evidence of carboxylate and phosphate salt formation that is known to promote chemical adhesion. The phosphate monomer (MDP) of both of the primers demonstrated a low to negligible molecular orientation toward the Y-TZP surface. Although a bonding condition was established between these primers and the Y-TZP surfaces, the hydrolytic sensitivity of the carboxylate salts formed may affect the stability of the interface. Thus, the differences in the film-forming properties and water solubility between the carboxylate and phosphate salts may affect the strength and durability of adhesive resin interfaces with Y-TZP, as mediated by these primers.

PERIODONTICS

This year’s review covered topics relating to the assessment, prevalence, and treatment regimens of periodontal disease, osteonecrosis of the jaw, systemic health conditions affecting periodontium and alveolar bone health, periodontal regeneration, soft tissue augmentation adjacent to teeth and implants, alveolar ridge preservation and augmentation techniques, and peri-implantitis.

Periodontal disease prevalence, cause, and treatment

Large-scale epidemiological studies examining the prevalence of periodontal disease are often plagued by inconsistency in the definition of adult periodontal disease. Through the use of optimal surveillance measures and standard case definitions, Eke et al.212 demonstrated it is now possible to determine more accurately population-average risk profiles for severe periodontitis and nonsevere periodontitis in adults (30 years of age and older) in the United States. Data from the 2009 to 2012 National Health and Nutrition Examination Survey (NHANES) were used. For the first time, the gold standard full-mouth periodontitis surveillance protocol was used to classify the severity of periodontitis following case definitions suggested by the US Centers for Disease Control/American Academy of Periodontology (CDC/AAP). Probabilities of periodontitis were identified by sociodemographics, behavioral factors, and comorbid conditions. These were assessed using prevalence ratios estimated by predicted marginal probability from multivariate generalized logistic regression models. This report found that total periodontitis (TP) increased with age overall and that nonsevere periodontitis increased more quickly than nonperiodontitis. Compared with non-Hispanic whites, TP was more likely in Hispanics and non-Hispanic blacks. A likelihood of at least 50% or more of TP in current smokers was found than with non-smokers. In men, the likelihood of TP in adults 65 years of age and older was greater than in adults 30 to 44 years of age. Total periodontitis was more likely in men with uncontrolled diabetes mellitus (DM) than in adults without DM. Cigarette smoking, specifically current smoking, remains an important modifiable risk for all severity levels of periodontitis. A higher likelihood of TP in older adults and in men with uncontrolled DM was also noteworthy.

Because this study identified the prevalence of periodontal disease in older adults, a behavior possibly erroneously associated with only younger adults may also influence the incidence of periodontal disease. Shariff et al.11 examined the relationship between frequent recreational use of cannabis and periodontitis in adults. Data from the NHANES (2011 to 2012) were analyzed. The primary outcome, periodontitis, was defined using the CDC/AAP classification as well as continuous
Periodontitis is a chronic infectious disease driven by dysbiosis, an imbalance between commensal bacteria and the host organism. Emerging evidence suggests that periodontitis is associated with mechanisms beyond bacteria-induced protein and tissue degradation. Martins et al. hypothesized that bacteria are able to induce epigenetic modifications in oral epithelial cells mediated by histone modifications. Histone modification is a covalent posttranslational modification to histone proteins which includes methylation, phosphorylation, among others changes to cell nucleus proteins. The posttranslational modifications made to histones can impact gene expression by altering chromatin structure. This study found that dysbiosis in vivo led to epigenetic modifications, including the acetylation of histones and downregulation of DNA methyltransferase 1. In addition, in vitro exposure of oral epithelial cells to lipopolysaccharides resulted in histone modifications, activation of transcriptional coactivators such as p300/CREB binding protein (CBP), and accumulation of nuclear factor-kB (NF-kB). The overall analysis of pathogen recognition receptors induced histone modifications. This study supports the hypothesis that the cause of periodontal disease is related to epigenetic modifications.

Alveolar bone destruction and clinical AL is commonly associated with the combination of plaque-induced periodontal disease and excessive mechanical loading. The underlining cellular and molecular mechanisms of this synergy are not clearly understood. Nogueria et al. evaluated the contribution of biomechanical loading to inflammation-induced tissue destruction. The limitation of this study is the animal model used. A total of 144 adult rats were randomly assigned to 4 experimental groups: control (C), ligature-induced periodontal disease (P), orthodontic movement (OM), and combination group (OMP). Evaluations were performed after euthanasia at 1, 3, 7, and 15 days after baseline. Bone volume fraction and bone mineral density were measured using microcomputed tomography. The expression and synthesis profiles of cytokines and receptors of inflammation in gingival tissues were evaluated by PCR array assay and multiplex immunoassay. At 15 days, the OMP group presented a significantly lower bone volume fraction and bone mineral density levels than all the other groups. The OMP group presented the highest number of upregulated protein targets in comparison with those of the other groups. Furthermore, the gene expression and protein levels of CCL2, CCL3, interleukin-1β (IL-1β), IL1-α, IL-18, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF) were significantly higher in the OMP group than in the P group. These results support the findings that mechanical loading modulates the inflammatory response of periodontal tissues to periodontal disease by increasing the expression of several proinflammatory mediators and receptors, which leads to increased bone resorption.

An increasing body of research supports the use of locally delivered hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins in the nonsurgical treatment of periodontal disease. Sinjab et al. conducted a systematic review of the research examining the efficacy of this treatment. An electronic search of 3 databases and a hand search of peer-reviewed journals for relevant articles were performed. Randomized clinical trials and prospective studies with data comparing use of adjunctive locally delivered statin with mechanical scaling and root planing and placebo. The overall analysis of defect fill presented a weighted mean difference (WMD) of 1.37 mm. The overall analysis of pocket depth reduction presented a WMD of 1.76 mm, and the overall analysis of clinical AL (CAL) gain presented a WMD of 1.58 mm. However, the comparison presented a considerable heterogeneity among studies. This systematic review and meta-analysis found the adjunctive use of locally delivered statins compared with mechanical scaling and root planing to be beneficial, increasing bone fill percentage with improved inflammatory and bleeding control as well as pocket depth reduction and CAL gain.

Osteonecrosis of the jaw

Considerable attention and controversy surrounds the topic of osteonecrosis of the jaw (ONJ) with the use of bisphosphonates (BPs) and, more recently, with other bone metabolism effector drugs such as receptor activator of NF-kB ligand (RANKL) inhibitors, antiangiogenic agents, and mammalian target of rapamycin (m-TOR)
inhibitors. The reported incidence, confounders, risk factors, and treatment outcomes appear to show that ONJ may have been initially underreported. Zhang et al\(^{217}\) examined ONJ data from US Food and Drug Administration’s (FDA) MedWatch or FDA Adverse Event Reporting System (FAERS).

The FAERS database was queried for the adverse drug events reported from the first quarter of 2010 to the first quarter of 2014. The odds ratios (ORs) were reported and the 95% confidence intervals (CIs) were calculated for each queried drug. A total of 17 119 unique ONJ cases were identified. In the overall analysis, the drugs with the highest reported ORs were BPs, including pamidronate (OR=498.9), zoledronate (OR=171.7), and alendronate (OR=63.6), whereas denosumab had lower ORs than all the BPs except for etidronate. The antiangiogenic and mTOR inhibitors had the lowest ORs. In patients with cancer who were treated for prevention of skeleton-related events, the ORs reported for zoledronate and denosumab were 125.2 and 4.9, respectively. In patients with osteoporosis, the ORs were 1.1 for zoledronate and 0.63 for denosumab. Their analysis of the FAERS database showed that intravenously administered BPs were associated with the highest risk for ONJ; RANKL inhibitor was associated with risk comparable to BPs used for osteoporosis such as etidronate; and the antiangiogenic agents and m-TOR inhibitors were associated with the lowest risk for ONJ. The high risk for ONJ with zoledronate and denosumab was mainly observed in those who were treated for prevention of skeleton-related events.

Osteonecrosis of the jaw most commonly presents as a localized infection of the alveolus, characterized by exposed necrotic bone. Jabbour et al\(^{218}\) investigated any link between bacteria colonizing ONJ sites and those from other oral cavity sites. Microbiota samples from 10 patients with antiresorptive agent-induced osteonecrosis of the jaws (ARONJ) were collected from exposed bone, adjacent teeth, contralateral teeth, and tongue. DNA checkerboard hybridization was used for microbiota analysis, with 43 genomic DNA probes prepared from human oral bacterial and Candida spp, using the Socransky bacterial complexes as a guide. Eikenella corrodens, Streptococcus constellatus, and Fusobacterium nucleatum were dominant in the ONJ sites and detected in most tooth specimens. Staphylococcus aureus also was dominant in the ONJ sites and tongue. Significant correlations were found among the mean proportions of bacterial species colonizing adjacent teeth, contralateral teeth, and tongue. No significant correlation was found between bacteria colonizing ONJ sites and other evaluated sites. The authors concluded that the primary sources of microorganisms colonizing ARONJ sites could be other sites such as teeth and tongue. The microbial profile of the necrotic bone is predominantly colonized with bacteria from Socransky green and orange complexes, as well as with species associated with bone infections.

The exact pathogenesis of BP-induced ONJ continues to be elucidated. One way BPs disrupt osteoclastic function is by affecting the osteoclast cytoskeletal adaptation necessary to establish the “ruffle border” interface between the osteoclast and resorbing bone surface. Another proposed mechanism is the effect that BPs have on local microvasculature. Sharma et al\(^{219}\) evaluated the effect(s) of various BPs on the differentiation of human placental mesenchymal stem cells (pMSCs) along the endothelial lineage and their subsequent functional and morphogenic capabilities. pMSC differentiation in the presence of noncytotoxic BP concentrations showed that nitrogen-containing BPs (N-BPs) had a significant inhibitory effect on cell migration and endothelial marker gene expression and compromised endothelial differentiation. This in vitro study also demonstrated that at noncytotoxic levels, N-BPs inhibit the differentiation of pMSCs into cells of an endothelial lineage and affect the downstream functional capability of these cells supporting a multimodal effect of BPs on angiogenesis as a pathogenic mechanism contributing to bone healing disorders such as BP-related osteonecrosis of the jaws.

Treatment of ONJ also remains controversial, with no one single treatment regimen being proven more effective than others. The administration of topical and systemic antimicrobial therapies, surgical removal of necrotic tissues, and hyperbaric oxygen therapies have been suggested but none has been shown to be superior.\(^{220}\) Pramanik et al\(^{221}\) examined the long-term oral and intravenous use of N-BPs associated with osteonecrosis of the jaw and suggested a treatment which attacked the way in which N-BP bind to bone. Although N-BPs bind strongly to bone surfaces through noncovalent bonds, extrinsic ions can dissociate bound N-BPs from mineralized bone by competitive desorption. Pramanik et al\(^{222}\) studied the effects and mechanism of using an ionic cocktail derived from borate bioactive glass for the sequestration of heterocyclic N-BPs bound to apatite. By using solid-state and solution-state analytical techniques, the authors confirmed that sequestration of N-BPs from BP-bound apatite occurs in the presence of the borate-containing ionic cocktail. The sequestration mechanism is due to the borate anion competing with BPs for similar electron-deficient sites on the apatite surface for binding. Thus, application of the borate-containing ionic cocktail represents a possible new topical lavage approach for removing apatite-bound heterocyclic N-BPs from exposed necrotic bone in BP-related osteonecrosis of the jaw.

**Relationship between periodontal and systemic health**

Periodontal disease is increasingly recognized as an emerging risk factor for various systemic diseases,
including diabetes, cardiovascular diseases, and cancer. A large study conducted by Chang et al.\textsuperscript{222} in Taiwan, using national health data, examined the association between periodontal disease and pancreatic cancer. A total of 139,805 individuals with periodontal disease and 75,085 individuals without periodontal disease were identified from the National Health Insurance Research Database of Taiwan. Cox proportional hazards regression was performed to compare the incidence of pancreatic cancer between the 2 groups. Periodontal disease was positively associated with pancreatic cancer risk (HR, 1.55; 95% CI, 1.02–2.33). This positive association occurred predominantly among those 65 years of age or older. It is interesting that further analysis showed that periodontal disease is a risk factor for pancreatic cancer independent of diabetes, hyperlipidemia, allergies, viral hepatitis, peptic ulcer, pancreatitis, chronic obstructive pulmonary disease (as a proxy for cigarette smoking), and alcohol-related conditions (as a proxy for alcohol drinking). This major study\textsuperscript{222} indicated a significantly positive association between periodontal disease and risk of pancreatic cancer. However, the underlying biological mechanisms for the positive association between periodontal disease and pancreatic cancer is unknown.

Few prospective studies have reported relationships between objective probing depth measurements and cancer risk. This association was examined in 1337 postmenopausal women participating in the Buffalo OsteoPerio Study.\textsuperscript{223} Oral alveolar crestal height (ACH) was measured using oral radiographs. Incident cancers were adjudicated with medical records. Hazard ratios and 95% CIs for associations between ACH and incident cancer outcomes were estimated using Cox proportional hazards models. In this study, 203 total incident cancer cases were confirmed during follow-up. After adjusting for age and smoking, the authors found no statistically significant associations between ACH-defined periodontal disease categories; and total cancer risk ACH-defined probing depth categories were not associated with common site-specific cancers. However, whole-mouth mean and worst-site ACH (per 1 mm loss) were significantly associated with increased risk of lung but not total or other site-specific cancer. Smoking status modified the associations between continuous ACH variables and total cancer risk; measurements of probing depth were associated with total cancer among smokers but not never-smokers. Alveolar crestal height-defined periodontal disease was associated with total cancer risk in ever- but not never-smoking postmenopausal women. Whole-mouth mean and worst-site ACH measurements were associated with increased lung cancer risk.

Schmickler et al.\textsuperscript{224} evaluated periodontal conditions and microbiological findings and their influence on rheumatological disease parameters in patients with rheumatoid arthritis (RA). A total of 168 RA patients were included. A healthy control group (n=168) was composed according to age and sex and smoking habits. Rheumatological data were extracted from patients’ records. Dental examination included dental findings decayed/missing/filled/teeth (DMFT), gingival inflammation, periodontal status (probing depth and AL). Subgingival biofilm was analyzed for 11 periodontopathogenic bacteria. Results showed mean DMF-T in RA patients was significantly higher than that in healthy controls, especially due to the number of missing teeth. Rheumatoid arthritis patients had a significantly higher number of increased probing depth AL compared with controls. Ninety-eight percent of patients with RA and 82% of the control patients had moderate to severe periodontitis. Rheumatoid factor-positive RA patients suffered from worse periodontal conditions than rheumatoid factor-negative patients.

The association between periodontitis and cardiovascular disease has been implied, as periodontal disease is common in patients with cardiovascular disease. Periodontal disease could be causally related to the risk for cardiovascular disease, a hypothesis tested in the Periodontitis and Its Relation to Coronary Artery Disease (PAROKRANK) study by Ryden et al.\textsuperscript{225} A total of 805 patients (<75 years of age) with a first myocardial infarction (MI) and 805 age-, sex-, and area-matched controls without MI underwent standardized dental examination. This study is unique as great efforts were made to collect information on possibly related confounders (≈100 variables). Periodontal disease was found to be more common in patients than in controls (P<.001). An increased risk for MI was found among those with periodontal disease and remained significant after adjusting for variables that differed between patients and controls (such as, smoking habits, diabetes mellitus, years of education, and marital status). These findings strengthen the possibility of an independent relationship between periodontal disease and MI.

Carotid calcification is a frequent finding on panoramic and cone beam computed tomography (CBCT) radiographic surveys. Bengtsson et al.\textsuperscript{226} sought to determine whether the presence of periodontitis is associated with carotid arterial calcifications found on panoramic radiographs in an elderly population. Study individuals were randomly selected from the Swedish civil registration database representing the aging population (60-96 years of age). Bleeding on probing and the deepest probing measurement at each tooth were registered. The proportions of teeth with a probing depth ≥5 mm and the proportion of teeth with bleeding on probing were calculated. Analog panoramic radiographs were made, and the proportion of sites with a distance of ≥5 mm between the alveolar bone level and cement-enamel junction were assessed. Readable radiographs were obtained from 499 individuals. Carotid
calcification was identified in 39.1%. Periodontitis was diagnosed in 18.4% of the participants. These data demonstrated a significant association between periodontitis and carotid calcification.

As the relationship between the functional anatomy of the oral cavity and obstructive sleep apnea (OSA) becomes more evident, investigators have examined the relationship between periodontal disease and OSA. Gamsiz-Isik et al. compared prevalence of periodontitis between control and OSA patients by assessing clinical periodontal parameters and levels of gingival crevicular fluid interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), and serum hs-CRP. A case control study was performed that included 163 individuals: 83 individuals with OSA and 80 non-OSA individuals as controls. The test group was classified according to OSA severity. Clinical periodontal measurements were recorded, and gingival crevicular fluid samples were collected. Gingival crevicular fluid hs-CRP, IL-1β, and TNF-α levels were analyzed using an enzyme-linked immunosorbent assay. Serum hs-CRP was measured. The prevalence of periodontitis in the OSA group (96.4%) was significantly higher than in the control group (75%). All periodontal clinical parameters and gingival crevicular fluid IL-1β concentrations were significantly higher in patients with OSA than in the controls. No significant differences were found between the mild OSA group and severe and moderate OSA groups.

**Periodontal regeneration**

A wide variety of materials have been proposed for treatment of periodontal intrabony defects (IBDs). Gold standard treatments include autogenous grafts and demineralized freeze-dried allografts (DFDBA). Recently, autologous blood products such as platelet-rich fibrin (PRF) have been suggested as a grafting material. Chadwick et al. conducted a study to measure changes in the CAL and bone fill of periodontal IBDs treated with DFDBA, compared with PRF in humans. Thirty-six patients contributed a single IBG, which was randomized to receive either DFDBA or PRF. Clinical and standardized radiographic data were collected at baseline and 6 months after treatment. Primary outcome measurements included radiographic bone fill and change in CAL. Both of the treatment groups had significant gains in CAL as well as in bone fill, with no significant differences in outcomes between groups. DFDBA had a mean CAL gain of 1.16 ±1.33 mm, a mean clinical bone fill of 1.53 ±1.64 mm, and a mean radiographic bone fill of 1.14 ±0.88 mm. Platelet-rich fibrin had a mean CAL gain of 1.03 ±0.86 mm, a mean clinical bone fill of 1.35 ±1.60 mm, and a mean radiographic bone fill of 1.10 ±1.01 mm. These data support the treatment of IBDs with either DFDBA or PRF.

Another variation of autologous blood products used for regenerative purposes is leucocyte- and platelet-rich fibrin (L-PRF). A systematic review of published reports conducted by Castro et al. examined the efficacy of L-PRF. Electronic and hand searches were conducted in 3 databases. Only randomized clinical trials were selected, and no follow-up limitation was applied. Pocket depth, CAL, bone fill, keratinized tissue width, recession reduction, and root coverage (%) were considered outcomes. Three subgroups were created: IBDs, furcation defects, and periodontal plastic surgery. Meta-analysis was performed in all subgroups. Significant probing depth reduction, CAL gain, and bone fill (1.7 ±0.7 mm, P<0.001) were found when comparing L-PRF with open flap debridement in IBDs. For furcation defects, significant probing depth reduction, CAL gain, and bone fill were reported when comparing L-PRF with open flap debridement. When L-PRF was compared with a connective tissue graft, similar outcomes were recorded for probing depth reduction, CAL gain, and recession reduction.

Despite this supportive evidence for the use of autologous blood products in regenerative therapies, which product, platelet-rich plasma (PRP), PRF, or L-PRF, is the most efficacious is controversial. Some investigators have suggested that leukocyte and platelet-rich preparations are better than platelet-poor preparations alone. The logic behind the use of these preparations is the presumed delivery of platelet-derived growth factor (PDGF), insulin-like growth factor (ILGF), and fibroblast growth factor (FGF) to the surgical site. Martinez et al. asked whether the platelet-poor fraction of the preparation had any biological effect on regeneration. In this study, the authors analyzed the content and specific effect of both PRP and platelet-poor plasma (PPP) on osteoblastic differentiation using primary cultures of human periodontal ligament stem cells (HPLSCs). The authors evaluated the growth factor content of PRP and PPP using a proteome profiler array and enzyme-linked immunosorbent assay. HPLSCs were characterized by flow cytometry and differentiation assays. The effects of PRP and PPP on HPLSC bone differentiation were analyzed by quantifying calcium deposition after 14 and 21 days of treatment. Albeit at different concentrations, the 2 fractions had similar profiles of growth factors, the most representative of which were the PDGF isoforms PDGF-AA, -BB, and -AB, and insulin-like growth factor binding protein (IGFBP)-2 and IGFBP-6. Both of the formulations exerted a comparable stimulus on osteoblastic differentiation, even at low doses (2.5%), increasing calcium deposits in HPLSCs. This study suggests that even the PPP fraction of the preparation may contain a high enough level of growth factor to stimulate regeneration successfully.
Fibroblast growth factor-2 (FGF-2) has recently been shown to have a positive effect on periodontal regeneration. A recombinant human form (rh-FGF-2) is now available for human clinical use. Cochran et al. conducted a prospective randomized controlled study to evaluate the safety and effectiveness of 3 doses of FGF-2 combined with a β-tricalcium phosphate (β-TCP) scaffold placed in vertical infrabony periodontal defects in adult patients. In this double-blinded, dose-verification, externally monitored clinical study, 88 patients who required surgical intervention to treat a qualifying infrabony periodontal defect were randomized to 1 of 4 treatment groups: β-TCP alone (control), 0.1% recombinant human FGF-2 (rh-FGF-2), 0.3% rh-FGF-2, and 0.4% rh-FGF-2 with β-TCP-after scaling and root planing of the tooth before a surgical appointment. Flap surgery was performed with ethylenediaminetetraacetic acid (EDTA) conditioning of the root prior to device implantation. When a composite outcome of gain in clinical attachment of 1.5 mm was used with a linear bone growth of 2.5 mm, a dose response pattern was detected within the 0.3% and 0.4% rh-FGF-2/β-TCP groups with significant improvements over the control and 0.1% rh-FGF-2/β-TCP groups. The success rate at 6 months was 71% in the 2 higher concentration groups compared with 45% in the control and lowest treatment groups. Percentages of bone fill in the 2 higher concentration groups were 75% and 71%, compared with 63% and 61% in the control and lowest treatment groups, respectively. No increases in specific antibody to rh-FGF-2 were detected, and no serious adverse events related to the products were reported. This well-controlled study is significant as the ideal concentration of the growth factor was identified. The advantage of this concentration-controlled growth factor product is evident from the results of this study compared with the variability of growth factor concentration of autologous blood products.

The 3D microenvironment of the extracellular matrix has been shown to influence the migration and differentiation of pluripotent cells. Reconstruction of a lost clinical attachment apparatus, including alveolar bone, periodontal ligament (PDL), and cementum/dentin surfaces is the ultimate regenerative goal of periodontal therapy. Pilipchuck et al. conducted a preclinical study developing poly(e-caprolactone) (PCL) scaffolds with mesoscale and microscale architectural cues specific to human ligament progenitor cells and assessed their ability to form aligned bone-ligament-cementum complexes in vivo. PCL scaffolds were designed to integrate a 3D printed bone region with a micropatterned PCL thin film consisting of grooved pillars. The patterned film region was seeded with human ligament cells, fibroblasts transduced with bone morphogenetic protein-7 genes seeded in the bone region, and a tooth-dentin segment positioned on the ligament region prior to subcutaneous implantation into a murine model. The results indicated increased tissue alignment in vivo using micropatterned PCL films compared with random-porous PCL. At week 6, 30-μm groove depth significantly enhanced oriented collagen fiber thickness, overall cell alignment, and nuclear elongation relative to the 10-μm groove depth. This study demonstrated for the first time that scaffolds with combined hierarchical mesoscale and microscale features can align cells in vivo for oral tissue repair with potential for improving the regenerative response of other bone-ligament complexes.

**Soft tissues adjacent to teeth and implants**

Chambrone and Tatakis conducted a systematic review to assess the long-term outcomes of untreated buccal gingival recession (GR) defects and the associated reported esthetic and functional alterations and also to evaluate which factors influence the progression/worsening of dental and periodontal tissue conditions of untreated GR defects. Considered eligible for inclusion were interventional and observational studies of ≥24 months reporting outcomes from adult patients with localized or multiple GR defects not treated by root coverage or gingival augmentation procedures. Of 378 potentially eligible articles, 8 (reporting 6 studies) met the inclusion criteria. Of 1647 GR defects with baseline and follow-up information, 78.1% experienced GR depth increase during the follow-up period, whereas the remaining experienced decrease or no change. Moreover, a 79.3% increase was noted in the number of GR defects among the patients followed (that is, new GR defects). The authors concluded that untreated recession defects in individuals with good oral hygiene have a high probability of progressing during long-term follow-up.

Coronally repositioning the flap with or without the adjunctive use of a connective tissue graft is a commonly used therapy in the treatment of gingival recession. Cairo et al. conducted a study to assess the clinical efficacy of a coronally advanced flap (CAF) with or without connective tissue graft (CTG) for the treatment of multiple adjacent gingival recessions in the upper arch. Thirty-two patients with a total of 74 gingival recessions were randomly allocated to 1 of the 2 groups. Outcome measurements, recorded by a blinded examiner, included complete root coverage (CRC), recession reduction (RecRed), keratinized tissue (KT) gain, increase in gingival thickness, patient satisfaction, and root coverage esthetic score (RES). At 1 year, CAF plus CTG resulted in better outcomes in terms of CRC and RecRed than CAF alone at sites with thin gingiva. No differences were found between CAF alone and CAF plus CTG at sites with thick gingiva (>0.8 mm). Coronally advanced flap resulted in higher RES than CAF plus CTG at sites with thick gingiva. Coronally advanced flap plus CTG was...
Many clinical surgical procedures exist to correct gingival recession. A confounding problem in comparing the efficacy of these clinical procedures is the variability in the technical aspects of the procedures. Subtleties such as suturing techniques and materials used may affect outcomes. Tatakis and Chambrone\(^2\) conducted a systematic review of published articles to investigate whether suturing protocols (suture removal timing and/or type of suture material) influence root coverage outcomes in recession defects treated with a CAF procedure. MEDLINE and EMBASE databases were searched for randomized controlled trials (RCTs) that assessed single-tooth, Miller class I/II recession defects, surgically treated by CAF. Mixed-effects linear regression analysis evaluated differences on CRC between RCTs with early (<10 days postoperatively) and late (≥10 days) suture removal, as well as between RCTs using absorbable and nonabsorbable sutures removed ≥10 days postoperatively. Seventeen RCTs were eligible for inclusion. Overall, data from 325 single gingival recession defects revealed a statistically significant superior proportion of sites exhibiting CRC when sutures were removed ≥10 days postoperatively compared with those in which sutures were removed <10 days. Conversely, no significant differences were found in CRC outcomes between absorbable and nonabsorbable sutures removed ≥10 days postoperatively. The majority of included RCTs (59%) reported the use of nonabsorbable suture materials.

The long-term stability of the augmented gingival tissues can be influenced by many patient-centered behaviors. The type of toothbrush, the technique used, and the duration of use have been suggested as possible factors. Acunzo et al.\(^2\) evaluated gingival margin stability with the use of an oscillating-rotating toothbrush compared with a manual toothbrush.

Sixty healthy individuals with at least 1 Miller class I or II gingival recession underwent a surgical root coverage procedure. Soft-bristle manual and powered toothbrushes were given to participants randomly assigned to control and test groups, respectively. Full-mouth plaque score, full-mouth bleeding score, probing depth, and recession depth were recorded at baseline and 1, 3, and 6 months after completion of the surgical procedure.

Data analyses and temporal trend differences across treatments were then tested by including treatment-time interaction terms. The use of a powered toothbrush resulted in a significantly greater reduction of recorded periodontal clinical indices than a manual device. No significant differences were noticed between the 2 experimental groups, both for probing depth and clinical attachment level. Complete root coverage was significantly higher in participants who used the powered toothbrush than those who used the manual toothbrush at 6 months, with control participants demonstrating 66.67% complete coverage and test participants 96.67%.

The influence of soft tissue thickness on early marginal bone loss (MBL) adjacent to endosseous dental implants has been recently demonstrated. Suárez-López et al.\(^2\) conducted a systematic review to evaluate the influence of soft tissue thickness on early MBL around dental implants. Electronic and manual searches of articles were performed by 2 independent reviewers in several databases for articles up to May 2015, reporting soft tissue thickness at time of implant placement and MBL with ≥12-month follow-up. Meta-regression analysis was conducted to investigate any potential influences of confounding factors, that is, platform switching design, cement- or screw-retained restoration, and flapped or flapsless surgical techniques. Only 8 articles were included in the systematic review, and 5 were included in the quantitative synthesis and underwent meta-analysis. Meta-analysis for the comparison of MBL among selected studies showed a WMD of −0.80 mm (P<.001), favoring the thick tissue group. Meta-regression of the selected studies failed to demonstrate an association among MBL and confounding factors.

The descriptive parameters of soft tissue thickness and keratinized tissue should be differentiated. Peri-implant soft tissues may be of sufficient thickness to benefit marginal bone levels but not necessarily be keratinized. Rocuzzo et al.\(^2\) investigated the clinical conditions around dental implants placed in the posterior mandible of healthy or moderately periodontally compromised patients in relation to the presence, or not, of keratinized mucosa (KT). A total of 128 patients who needed an implant in the posterior mandible were consecutively enrolled in a private specialist practice. Only 1 implant per patient, originally placed either in KT or alveolar mucosa (AM) was examined. At 10 years, clinical and radiographic measurements were recorded by a calibrated operator. Ninety-eight patients completed the 10-year study. The absence of KT was associated with a higher plaque accumulation, a greater soft tissue recession, and a higher number of sites that required additional surgical and/or antibiotic treatment. Patient-reported outcomes regarding maintenance procedures presented major differences between the groups. In 11 of the 35 AM placements, additional FGG was successfully used to reduce discomfort and to facilitate optimal plaque control. Implants that are not surrounded by KT are more prone to plaque accumulation and recession, even in patients exercising sufficient oral hygiene and receiving adequate supporting periodontal therapy.

Clearly, secondary soft tissue augmentation procedures adjacent to implants are often necessary in areas associated with greater KT gain and greater postoperative morbidity.
presenting with shallow vestibules or prior ridge augmentation procedures. Treatment alternatives include, but are not limited to, free gingival autografts and collagen matrix (CM) xenografts. Schmitt et al.239 examined the predictability for long-term stability of the use of CM (Mucograft) or free gingival autografts in the treatment of mandibular posterior implants. The study included 48 patients with atrophic edentulous or partially edentulous mandibles that had undergone implant treatment. In the context of implant exposure, a vestibuloplasty was performed using either 2 FGGs from the palate (n=21 patients) or the CM (n=27 patients). Surgery time was recorded from the first incision to the last suture. Follow-up examinations were performed at 10, 30, 90, and 180 days and at 1, 2, 3, 4, and 5 years after surgery. The width of keratinized mucosa was measured at the buccal aspect of each implant, and augmented sites were evaluated in terms of their clinical appearances (texture and color). The groups showed similar healing with increased peri-implant keratinized mucosa after surgery (FGG, 13.06 mm ±2.26 mm; and CM, 12.96 mm ±2.86 mm). The maximum follow-up was 5 years (5 patients per group). After 180 days, the width of keratinized mucosa had decreased to 67.08% ±13.85% in the FGG group and 58.88% ±14.62% in the CM group, with no statistically significant differences. The total loss of the width of keratinized mucosa after 5 years was significant between the FGG (40.65%) and the CM (52.89%) group. Although the use of a CM has the advantages of procedure time and patient comfort, the increased posttreatment shrinkage and cost are factors to include in the patient selection process.

Alveolar ridge preservation, ridge augmentation, and sinus augmentation procedures

The preservation of alveolar bone volumes after tooth extraction is important for subsequent successful implant placement. Clinicians and patients also continually search for procedures to decrease time from tooth extraction to restoration. If an immediate implant is not placed, evidence to date is limited concerning the timing of ridge preservation healing and reentry for implant placement. Whetman and Mealey240 conducted a study to evaluate histologically new bone formation at 8 to 10 weeks versus 18 to 20 weeks after extraction of nonmolar teeth and ridge preservation using DFDBA. The authors also compared dimensional changes including ridge width and height at the 2 healing time points. Forty-four patients had tooth extraction and ridge preservation with DFDBA obtained from a single donor. Clinical measurements were made to evaluate ridge height and width. Patients were randomly allocated to short-term (8 to 10 weeks) and long-term (18 to 20 weeks) healing groups. Sites were reentered at the appropriate healing time, a core biopsy was obtained, and a dental implant was placed. The same ridge dimensions were measured at the time of implant placement. Histomorphometric analysis was performed to determine the percentage of new vital bone formation, residual graft, and connective tissue or other. The authors found a significantly higher percentage (47.41%) of new vital bone formation in the long-term healing group than in the short-term healing group (32.63%; P=.01). No significant differences were found in the percentage of residual graft, percentage of connective tissue or other, or ridge dimensional changes. These data support the placement of dental implants in preserved alveolar bone sites augmented with DFDBA after a healing period of 5 months.

Most ridge preservation studies compare the efficacy of a particulate graft placed in the socket with that of another material or no treatment. A prevailing assumption is that a particulate graft is mandatory to preserve the alveolar bone volumes. Crespi et al.241 challenged this notion and proposed techniques which emphasize the stability of clot and reactive soft tissues. The authors conducted a study assessing the bone healing of large bone defects grafted with collagen sheets and the maintenance of the reactive soft tissue by evaluating CBCT scans and analyzing histomorphometric results. Patients presented large bone defects after tooth extractions. Reactive soft tissue was left in the defects filled by collagen sheets. Vertical bone volume was assessed by CBCT examinations before tooth extractions and again 3 months later. At 3 months, cylinder bone specimens were obtained for histology and histomorphometry analyses. Twenty-six patients were included in the clinical study. Examined defects reported mean bone gain of 12.13 ±3.91 mm, and mean vertical bone levels showed a statistically significant increase at 3 months after extraction. Histological examinations revealed bone formation; mean vital bone measurements were 41.59%, and connective tissue percentages averaged 50.37%. The authors concluded that reactive soft tissue left in large bone defects after tooth extraction and grafted collagen may support significant vertical bone gain and vital bone formation.

Alveolar bone regeneration procedures to enhance the successful placement of implants have been used for more than 20 years. Two studies examined the long-term success of implants placed in regenerated bone. Simion et al.152 conducted a retrospective clinical study evaluating the performance of 91 turned implants placed in vertically augmented ridges in 33 patients by means of guided bone regeneration techniques after a mean follow-up of 15 years. A total of 88 implants were in function (97% survival rate), whereas 9 showed peri-implantitis (9.9%). A mean radiographic bone loss of 1.02 mm between the baseline evaluation (1 year after loading) and the final visit (13-21 years later) was recorded. Turned implants placed in vertically augmented bone seemed to remain
stability after many years of function. As discussed later in this review, the incidence of peri-implantitis is relatively low in this study. Likewise, the authors found that, in sites which did demonstrate alveolar bone loss, the rate of bone loss was not progressive. The authors suggested that the low rate of peri-implantitis and lack of disease progression may be related to the turned or “mached” implant surfaces used in this study.

Camps-Font et al. conducted a systematic review comparing vertical bone augmentation techniques in the atrophic posterior areas of the mandible and compared these procedures with alternative treatments. Electronic searches of studies were conducted to identify all relevant articles published up to July 1, 2015. Eligibility was based on inclusion criteria, and quality assessments were conducted. The primary outcome variables were implant and prosthetic failure. After data extraction, meta-analyses were performed. Of 527 potentially eligible papers, 14 randomized clinical trials were included. Of these 14 studies, 4 trials assessed short implants (5-8 mm) as an alternative to vertical bone augmentation in sites with a residual ridge height of 5 to 8 mm. No statistically significant differences were found in implant or prosthetic failure after 12 months of loading. However, complications at treated sites increased with the augmentation procedures. No evidence was found to suggest one vertical augmentation procedure was of greater benefit than any other for the primary outcomes (implant and prosthetic failure). The authors suggested that short implants in the posterior area of the mandible seem to be preferable to vertical augmentation procedures, which present similar implant and prosthetic failure rates but greater morbidity.

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is approved by the U.S. Food and Drug Administration as a viable alternative to bone graft in spinal fusion and maxillary sinus lift procedures. Kelly et al. conducted a systematic review and meta-analysis to examine whether rhBMP-2 is an effective bone graft substitute in localized alveolar ridge augmentation as well as for maxillary sinus floor augmentation. Databases were searched for studies in which the primary outcome was bone formation measured as change in bone height on a computed tomogram. A systematic review of adverse events was also performed. A random-effects model was chosen. Ten studies met the criteria for systematic review; 8 studies were included in the meta-analysis. Five studies assessed localized alveolar ridge augmentation and findings resulted in an overall standardized mean difference of 0.56 (95% CI, 0.20-0.92) in favor of BMP; this result was statistically important. Three studies assessed maxillary sinus floor augmentation and findings resulted in an overall standardized mean difference of -0.50 (95% CI, -0.93 to -0.09), which was meaningfully different in favor of the control group. Adverse events were inconsistently reported, ranging from no complications to widespread adverse events. For localized alveolar ridge augmentation, this meta-analysis showed that rhBMP-2 substantially increased bone height. However, rhBMP-2 did not perform as well as the autograft or allograft in maxillary sinus floor augmentation. This study supports clinical opinion questioning the need for biologically active substances in sinus grafting procedures.

Zill et al. presented data showing that spontaneous bone fill of the maxillary sinus cavity after a graftless osteotomy technique can be expected in many clinical situations. The authors conducted a study to examine the outcome of the graftless osteotomy sinus floor elevation technique and to determine whether the gain in apical bone depended on the initial residual bone height and whether the initial residual bone height influenced the amount of marginal bone loss. The study also assessed whether perforations of the Schneiderian membrane or residual bone height were potential predictors of implant survival. Patients having 1 to 11 mm of residual bone height underwent crestal sinus lift elevation procedure. A cohort of 113 patients with 233 implants were included in this study. The follow-up period was 5 years post loading for all patients. The average initial bone level height was 5.9 ±1.7 mm. No bone graft or substitute material was used. All implants healed transgingivally and were loaded 3 months after insertion. Outcome measurements were prosthetic success, implant success, complications, radiographic crestal bone level changes, and apical (sinus floor) bone height. A high number of patients (63) dropped out during the 5-year post-loading follow-up. Seven implants in 7 patients failed. The implant survival rate 5 years after loading was 93.8% at patient level. Implants succeeded in 92.7% of all cases. In 6 patients (5.3%), prostheses failed and had to be remade. Average marginal bone loss at 5 years of follow-up was 0.5 ±0.8 mm per patient. No correlation was found between marginal bone loss and initial residual bone height. Average bone height gained was 4.5 ±1.4 mm after 5 years of loading. However, initial residual bone height is also a predictor for implant survival; that is, survival increases by 1.6 times with every additional millimeter of initial residual bone height. The apical bone gain was higher in situations with less residual bone.

Peri-implant disease prevalence, pathogenesis, treatment, and prevention

Although information for the estimation of prevalence of peri-implantitis is currently available, data describing onset and progression of the disease are limited. Derks et al. conducted a long-term study using 9-year follow-up examinations of 596 randomly selected implant-carrying individuals. Sixty-two patients with moderate or severe peri-implantitis were identified. Longitudinal
assessments of peri-implant marginal bone levels were used to construct a statistical model with bone loss as the dependent variable. A multilevel growth model estimated the pattern of bone loss for each implant or patient. Onset of peri-implantitis was determined by evaluating the cumulative percentage of implants or patients presenting with estimated bone loss at each year following prosthetic delivery. The analysis showed a nonlinear, accelerating pattern of bone loss at the 105 affected implants. The onset of peri-implantitis occurred early, and 52% and 66% of implants presented with bone loss of >0.5 mm at years 2 and 3, respectively. A total of 70% and 81% of participants presented with ≥1 implant, with bone loss of >0.5 mm at years 2 and 3, respectively. The authors concluded that peri-implantitis progresses in a nonlinear, accelerating pattern and that, for most patients, the onset occurred within 3 years of function.

The ability to predict which patients are more likely to develop peri-implantitis would be of great benefit to clinicians. Canullo et al.246 investigated whether specific predictive profiles for patient-based risk assessment and diagnosis can be applied in different subtypes of peri-implantitis. This study included patients with at least 2 implants. Anamnestic, clinical, and implant-related parameters were collected. Dental implant was chosen as the unit of analysis, and a complete screening protocol was established. The implants affected by peri-implantitis were then clustered into 3 subtypes in relation to the identified triggering factor, as follows: purely plaque-induced, prosthetically triggered, or surgically triggered peri-implantitis. Statistical analyses were performed to compare the characteristics and risk factors between peri-implantitis and healthy implants and to compare clinical parameters and distribution of risk factors among plaque-, prosthesis-, and surgery-triggered peri-implantitis. A total of 926 patients previously treated with 2812 dental implants were screened for eligibility. Fifty-six patients (6.04%) with 332 implants (4.44%) met the study criteria. Data from 125 peri-implantitis and 207 healthy implants were therefore analyzed and included in the statistical analysis. Within the peri-implantitis group, 51 were classified as surgically triggered (40.8%), 38 as prosthetically triggered (30.4%), and 36 as plaque-induced (28.8%) peri-implantitis. The variables identified as predictors of peri-implantitis were female sex (OR=1.60), malpositioning (OR=48.2), overloading (OR=18.70), and bone reconstruction (OR=2.35). The predictive model showed 82.35% of accuracy and identified distinguishing predictive profiles for plaque and prosthetically and surgically triggered peri-implantitis. It was concluded that plaque-induced and surgically triggered peri-implantitis are different entities associated with distinguishing predictive profiles; hence, the appropriate causal treatment approach remains necessary. Clinically, these results suggest that patients with surgical (such as, malpositioned implant placement) or prosthetic compromises are more likely to develop peri-implant disease and warrant interceptive therapies.

For patients with plaque-induced peri-implantitis, understanding the microbiological profile of the affected site provides needed information for appropriate treatment. Rakic et al.247 conducted a systematic review of the microbiological profile associated with peri-implantitis. Online and manual searches of other articles were conducted to identify articles potentially relevant to the review. Screening, data extraction, and quality assessment were conducted independently and in duplicate. Twenty-one articles were eligible for inclusion in this review. Early studies focused on the identification of target periodontal pathogens, whereas more recent studies used advanced molecular techniques for comprehensive overview of the peri-implantitis-associated microbiome. In summary, the microbiologic profile in peri-implantitis is complex and variable; it consists of gram-negative anaerobic periodontal pathogens and opportunistic microorganisms in almost the same ratio; it is frequently associated with Epstein-Barr virus and nonsaccharolytic anaerobic gram-positive rods; it is not so strictly associated with S. aureus; and it is different from that of periodontitis. The authors suggest that the microbiological profile of peri-implantitis consists of aggressive and resistant microorganisms and is distinct from that of periodontitis. The qualitative characteristics of the microflora cohabitants seem to represent the key determinant of disease, rather than the qualitative composition, which is very similar in healthy and peri-implantitis states. This implies that efforts which aim to reduce the quantity of per-implant plaque may be of equal or more benefit than directed antimicrobial therapies.

Heightened awareness of cement-induced peri-implantitis has influenced clinical decisions between screw-retained and cement-retained prostheses. However, many factors influence the iatrogenic retention of cement on the abutment surface. Among these factors are the designs of the abutment, the quality of the peri-implant tissues, and the material choice of cement. Kotsakis et al.248 examined the association between retention type (cement- versus screw-retained restorations) and prevalence of peri-implant diseases in a German university population. Data were analyzed from individuals who underwent clinical and radiographic peri-implant examinations as part of a university-based, cross-sectional study. Data from 139 individuals with 394 implants were analyzed: 192 implants supported single crowns and 202 fixed partial dentures. Overall, 11.9% of participants had peri-implantitis, whereas 68.9% had peri-implant mucositis. Crude OR for peri-implantitis and peri-implant mucositis for cement versus screw-retained restorations were 1.43 and 0.89, respectively. Results remained nonsignificant in multivariate models, adjusting for type of restoration.
and smoking. There was also no effect of splinting on restorations. The authors concluded that no association existed between type of prosthesis retention and peri-implant diseases and suggested that, when appropriate selection and removal of cement is performed, cement retention is not a risk indicator for peri-implant diseases. What is important to understand when evaluating this study is that all cemented restorations were placed with a eugenol-based temporary cement. The cytotoxicity, microbiology, and ability to remove the cement from both the abutment and the peri-implant tissues is critical.

Methods of preventing peri-implantitis have focused upon controlling iatrogenic factors. It is an accepted belief that cementing dental restorations on implants poses the risk of undetected excess cement. The effect of excess cement on the bacterial profile is not yet known. Korsch et al analyzed the effect of 2 different dental cements on the composition of the microbial peri-implant profile. In a cohort of 38 patients, samples of the peri-implant tissue were taken with paper points from 1 implant per patient. In 15 patients, the suprastructure had been cemented with a zinc oxide-eugenol cement (Temp Bond [TB]) and in 23 patients with a methacrylate cement (Premier Implant Cement [PIC]). The excess cement and suppuration found were documented. Subgingival samples of all patients were analyzed for taxonomic composition, according to 16 S amplicon sequencing. None of the TB-cemented implants had excess cement or suppuration. In 14 (61%) of the PIC implants, excess cement was found. Suppuration was detected in 33% of the PIC implants without excess cement and in 100% of the PIC implants with excess cement. Taxonomic analysis of the microbial samples revealed an accumulation of oral pathogens in the PIC patients independent of the presence of excess cement. Significantly fewer oral pathogens occurred in patients with TB implants compared with patients with PIC implants. The authors concluded that, compared with TB cement, PIC cement favored the development of suppuration and growth of periodontal pathogens.

Once peri-implantitis has been diagnosed and the decision has been made to treat the site, the best method for decontaminating the implant and restoring the lost alveolar bone must be chosen. Unfortunately, there is no universally accepted evidenced-based treatment for peri-implantitis. Schwarz et al assessed the long-term outcomes (>4 years) following combined surgical resective/ regenerative therapy of advanced peri-implantitis lesions using 2 surface decontamination methods. Fifteen patients (n=15 combined supra- and intrabony defects) completed a follow-up observation period of 7 years. The treatment procedure included access flap surgery, granulation tissue removal, and implantoplasty at buccally and supracrestally exposed implant parts, and a randomly assigned decontamination of the unmodified intrabony implant surface areas using either treatment with Er:YAG laser treatment or with plastic curettes plus cotton pellets plus sterile saline. Intrabony defects were filled using a natural bone mineral and covered by a native collagen membrane. At 7 years, both Er:YAG laser and plastic curettes plus cotton pellets plus sterile saline were associated with similar mean reductions in bleeding on probing and clinical attachment level gains. The authors concluded that combined surgical resective/regenerative therapy of advanced peri-implantitis was effective in the long-term but not influenced by the initial method of surface decontamination.

Implant surfaces demonstrating peri-implantitis have been conventionally treated with topically applied chemotherapeutic agents (ChAs) based on their antimicrobial effect. Despite the proven antimicrobial effect of ChAs on titanium-bound biofilms, studies have elucidated an unexpected disassociation between bacterial reduction and biologically acceptable treatment outcomes. Kotsakis et al hypothesized that ChA residues altered titanium physiochemistry and thus compromised cellular response to decontaminated surfaces. This in vivo study examined grit-blasted acid-etched titanium disks which were contaminated with multispecies microcosm biofilms grown from in vivo peri-implant plaque samples. To simulate implant decontamination, the contaminated disks were burned with 0.12% chlorhexidine, 20% citric acid, 24% EDTA-1.5% NaOCl, or sterile saline and assessed for surface physicochemical properties. Sterile untreated surfaces were the controls. The biological effects of decontamination were assessed using cell proliferation and differentiation assays. Bacterial counts after decontamination confirmed that the ChAs were antimicrobial. X-ray photoelectron spectroscopy invariably detected elemental contaminants associated with each ChA molecule or salt that significantly altered wettability compared with controls. Notably, all surfaces with ChA residues showed some cytotoxic effect compared with controls. Increased cell counts were consistently found in the saline-treated group compared with chlorhexidine. Interestingly, no association was found between antimicrobial effect and cell counts. ChA-specific residues left on the titanium surfaces altered titanium physical properties and adversely affected the osteoblastic response regardless of their observed antimicrobial effect. Chlorhexidine may compromise the biocompatibility of titanium surfaces, but the authors suggest not using it to detoxify implants. Sterile saline, citric acid, and EDTA-NaOCl may be proposed for use in the treatment of peri-implantitis. Contrary to previous studies that recommended the selection of ChAs for the decontamination of titanium implants according to their antimicrobial effects, this study demonstrated that the restoration of the biocompatibility of contaminated
titanium surfaces is also contingent on the preservation of titanium material properties.

Wheelis et al. investigated the impact of treatments used to detoxify dental implants on the oxide layer morphology and to infer how changes in morphology created by these treatments may impact the reosseointegration of an implant. Pure titanium (cpTi) and the alloy Ti6Al4V were subjected to a series of chemical treatments and mechanical abrasion simulating surface decontamination of dental implants. The morphology and roughness of the surface layer before and after treatment with these solutions were investigated with optical and atomic force microscopy. The solutions used are typically used to detoxify dental implants, including citric acid, 15% hydrogen peroxide, chlorhexidine gluconate, tetracycline, doxycycline, sodium fluoride, and peroxyacetic acid and treatment with carbon dioxide laser. The microscopy investigation showed that corrosion and pitting of the specimens were present in both metal grades with immersion and rubbing methods when more acidic solutions with a pH <3 were used. Mildly acidic solutions caused surface discoloration when coupled with rubbing but did not cause corrosion with immersion. Neutral or basic treatments resulted in no signs of corrosion with either method. Energy dispersive spectrometry (EDS) results revealed the presence of titanium particles on all rubbing samples. This study demonstrated that acidic environments coupled with rubbing are able to introduce noticeable morphological changes and corrosion on the surface of both titanium grades.

From these 2 studies, we can infer that implant surface decontamination for microbiological reasons may negatively affect our ability to regenerate osseous tissues on the affected implant surface. These decontamination procedures may also release titanium (Ti) ions into the surrounding tissues as peri-implantitis represents a disruption of the biocompatible interface between the TiO2 layer of the implant surface and the peri-implant tissues. Data also suggest that the peri-implantitis microbiota may not only trigger an inflammatory immune response but also cause electrochemical alterations of the Ti surfaces, that is corrosion, that aggravate this inflammatory response. Saffioti et al. hypothesized that an association exists between the dissolution of Ti from dental implants, which suggests corrosion, and peri-implantitis in humans. The authors conducted a study to compare the levels of dissolved Ti in submucosal plaque collected from healthy implants and implants with peri-implantitis. Submucosal plaque from 20 implants with peri-implantitis and 20 healthy implants was collected using sterile curettes (N=30 participants). Levels of Ti were quantified using inductively coupled plasma mass spectrometry and normalized for bacterial DNA mass per sample to exclude confounding by varying amounts of plaque per site. Implants with peri-implantitis harbored significantly higher mean levels of Ti (0.85 ±2.47) than healthy implants (0.07 ±0.19) after adjusting for the amount of plaque collected per site (P=.033). Greater levels of dissolved Ti were detected in the submucosal plaque around implants with peri-implantitis than in healthy implants, indicating an association between Ti dissolution and peri-implantitis.

Despite our concern for implant surface alterations, many current surgical protocols treating peri-implantitis use chemical surface decontamination and bone grafting procedures. Rotenberg et al. described a retrospective case series of a novel approach using porcine collagen-coated bovine bone to treat peri-implantitis. Eleven patients with no history of periodontitis and presenting with peri-implantitis around a single restored dental implant were included in the study. After surgical debridement of the peri-implant defect and treatment of the implant surface with a 0.12% chlorhexidine gluconate solution, bony defects were grafted with collagen-coated bovine bone. All patients had 12 months of follow-up. Results showed the average pocket depth at the deepest site was 7.6 ±1.9 mm. At the time of surgery, excess cement was found around 9 implants (81%). All patients healed uneventfully without postoperative complications. At 6 and 12 months, all implants showed favorable results with average reduction of deepest site probing depth of 3.9 ±1.5 mm and 4.1 ±1.6 mm, respectively. All implants showed radiographic signs of bone fill, whereas the gingival margin level showed no changes from preoperative measurements at either 6 (0.1 ±0.5 mm) or 12 (0.0 ±0.6 mm) months.

Recent bone biology studies have confirmed that elevating Wnt signaling promotes bone formation. For example, increasing Wnt signaling by inhibiting Wnt antagonists such as sclerostin is an effective method of inducing bone formation under pathological conditions such as multiple myeloma and osteoporosis. Anti-sclerostin antibodies can increase bone formation around implants placed in the medullary cavities of long bones. Yin et al. tested whether a WNT protein therapeutic could rescue a failed, fibrous encapsulated dental implant. Titanium implants were placed in oversized murine oral osteotomies with a lack of primary stability, verified by mechanical testing. Histology coupled with histomorphometry confirmed the lack of peri-implant bone. After fibrous encapsulation was established, peri-implant injections of a liposomal formulation of WNT3A protein (L-WNT3A) or liposomal phosphate buffer saline (L-PBS) were then initiated. Quantitative assays were used to analyze the effects of L-WNT3A treatment. Implants in gap-type interfaces exhibited high interfacial strains and no primary stability. After verification of implant failure, L-WNT3A or L-PBS injections were initiated. L-WNT3A induced a rapid,
significant increase in Wnt responsiveness in the peri-implant environment, cell proliferation, and osteogenic protein expression. The amount of peri-implant bone and bone in contact with the implant were significantly higher in L-WNT3A cases. These data demonstrated that L-WNT3A can induce peri-implant bone formation even in situations where fibrous encapsulation predominates.

DENTAL MATERIALS

Research bias and industry sponsorship
Studies of dental materials in 2016 evaluated the potential for bias in studies with industry sponsorship, restoration repair, adhesives, sealants and infiltration, silver compounds, endodontic materials, composite resins, and amalgam. One question that has haunted dental research is whether clinical trials sponsored by industry are influenced by inherent or introduced bias. A systematic review of RCTs of dental restorative materials published between 2005 and 2015 was conducted in an attempt to assess the potential for sponsorship effects on research design, choice of material for comparison to the sponsored product, and findings. Overall, 114 studies were included in a comparison between industry-sponsored and nonsponsored research that included more than 15,000 restorations in more than 5000 patients. The findings were reassuring in that sponsorship did not significantly affect most of the assessed factors and that most material rankings were similar between sponsored and nonsponsored trials. This is an important finding when we consider the sheer volume of sponsored trials in the published research and the economic dependence of the dental research community upon private research sponsorship. It also provides a degree of confidence in the results of clinical trials that constitute a higher level of evidence.

Restoration repair and replacement
Two papers from investigators in Norway explored dentists’ choices of repair or replacement and their experiences with the repair of defective amalgam restorations. The second question, regarding amalgam repair, is especially relevant in a country where amalgam has not been used since 2008 and restorations placed prior to that date are reaching their service life. When it came to time spent placing restorations, dentists spent on average 58% of their time placing or replacing restorations. The major reason for treatment was primary caries at 55%, with repair making up 27% and replacement 18% of treatments. The favored material combination was composite resin with 2-step etch-and-rinse adhesive at 49% of restorations. When it came to dealing with failed amalgam restorations, composite resin was the restorative material preferred by 99% of dentists, and secondary caries was the highest reason for failure at 73%, followed by restoration fracture at 25%. Composite resin was suggested as the repair method for amalgam restored teeth with fractured cusps by 25% of dentists surveyed. Both of these reports emphasized the fact that Norwegian dentists demonstrated positive attitudes toward composite resin as a restorative material and toward minimally invasive approaches to restoration repair over replacement.

Adhesives
A comprehensive systematic review of RCTs was performed of restorative and adhesive materials published between 2005 and 2015. Comparative survival was evaluated for more than 11,000 restorations in nearly 4000 patients. Thirty-six trials included cervical restorations, and 36 were in load-bearing restorations. Resin-modified glass ionomer had the highest chance of survival in cervical lesions, whereas composite resin or composites placed using 2-step self-etch and 3-step etch-and-rinse adhesives performed best, and those placed with 2-step etch-and-rinse and 1-step self-etch adhesives performed worst. Conventional composite resin also appeared to outperform siloranes in load-bearing restorations. Unfortunately, most studies showed a high risk of bias, and the evidence was still considered insufficient to make specific recommendations with regard to adhesive strategies.

A report generated by a practice-based research network (Ceramic Success Analysis) tracked over 5000 ceramic inlay/onlay restorations placed by 167 dentists over 20 years. The mean annual failure rates were 1.0% and 1.6% at 3 and 10 years of service, respectively. Not surprisingly, restorations with cervical margins in dentin had a 78% higher risk of failure than those with margins in enamel. Restorations placed with a liner or base demonstrated twice the risk of failure compared with those with no liner or base, and restorations placed with simplified adhesive systems consisting of 2-step etch-and-rinse or 1-step self-etch presented a 142% higher risk of failure than restorations placed with 3-step etch-and-rinse and 2-step self-etch systems. The most common mode of failure was fracture of the tooth or restoration at 44.5%. Another trial of ceramic restorations compared a self-adhesive luting material (RelyX Unicem) applied both with and without selective enamel etching. After 6.5 years, the survival of restorations with the selective enamel etching was significantly higher than those without. This study also demonstrated that restorations with foundations or cavity linings had higher failure rates. Taken together, these studies continue to confirm the superiority of enamel etching as a component of a multistep adhesive procedure and higher risk of failure for restorations with bases and liners.

Last, an updated systematic review was published that analyzed the use of adhesively bonded versus
nonbonded amalgam restorations. Unfortunately, this update included only a single RCT with 31 patients and 113 restorations. As with so many of these reviews, the studies concluded there is no evidence to either claim or refute the superiority of bonded amalgam restorations. The authors did point out, however, that clinicians should be mindful of the added costs of this as-yet un-proven procedure.

**Sealants and infiltration**

Concurrent updates of the clinical evidence and the clinical guidelines for pit and fissure sealants were published in 2016. The review of evidence compared the effect of dental sealants for the prevention and management of pit and fissure lesions in primary and permanent molars compared with no sealants, fluoride varnishes, or other direct comparisons. Twenty-three studies were included, resulting in moderate-quality evidence that sealants reduced the risk of developing carious lesions on the occlusal surfaces of permanent molars compared with nonsealed molars after 7 or more years of follow-up (OR=0.15; 95% CI, 0.08-0.27). Similar results were found when sealants were compared with fluoride varnishes (OR=0.19; 95% CI, 0.07-0.51), but the evidence in this case was considered low quality. The head-to-head comparisons of different types of sealant materials did not provide a clear hierarchy of effectiveness. As a result of this review, the guideline panel convened by the American Dental Association Council on Scientific Affairs and the American Academy of Pediatric Dentistry formulated updated clinical recommendations with 3 conclusions, as follows: first, that sealants are effective in preventing and arresting occlusal caries in both primary and permanent molars in children and adolescents compared with either no sealants or the use of fluoride varnishes. Second, sealants could minimize the progression of noncavitated occlusal caries lesions that receive a sealant. Third, the current evidence does not distinguish the superiority of one type of sealant material over another.

A series of public health papers investigated school-based sealant programs from both a prevention and cost effectiveness standpoint. School-based sealant programs have proven to be an effective way of delivering prevention to children of low socioeconomic status. A systematic review updated the cost and benefit information for school-based sealant programs from an original 2002 review and added 10 new studies. The results showed that the median cost per tooth sealed was $11.64 with labor accounting for two-thirds of that cost. Over 4 years, the median economic benefit of a sealed tooth would exceed costs by $11.37, and 3 analyses of Medicaid claims data showed that the benefits in averted treatment exceeded sealant costs in all cases. One factor cited as instrumental in achieving cost effectiveness was the ability to target schools attended by large numbers of at-risk children.

A French study compared use of sealants with non-sealant controls in first- and second-grade students from low-income backgrounds in a school-based program. The children (228) were followed for 3 years, and survival analysis showed the first permanent molars receiving sealants had 67% less risk of developing carious lesions. A related school-based paper looked at the impact of a policy change in the state of Wisconsin that allowed dental hygienists to place and bill for sealants placed in public health settings after September 2006. Medicaid claims were analyzed for sealant use from 2001 to 2009 for a total of 479 847 children with 64 546 dental visits. Results were revealing in that the rate of visits for sealants by dentists increased from 3% per year before policy to 11% per year after policy, and sealant visits of nondentists remained relatively steady at 20% after policy. Apparently, the awareness generated by nondentists in public health settings such as school-based programs may have increased sealant use in private settings.

High-viscosity glass ionomer cements are placed as sealants by pressing the material into the occlusal surface using an index finger coated with petroleum gel. The assumption is that this method will increase material penetration into pits and fissures and increase sealant retention. It may also provide a method of forensically identifying the operator in more than just amalgam occlusal surfaces. A systematic review was conducted to compare this high-viscosity glass ionomer method with conventional resin-based sealants. Six clinical trials were included with data combined for meta-analysis. Results suggest equivalence between the 2 materials after 48 months and perhaps some advantage for the high-viscosity ionomer after 60 months for caries prevention, but the 60-month results were imprecise and require further confirmation. Several papers reported the impact of applying adhesives under pit and fissure sealants.

Two systematic reviews compared sealant retention after the use of an adhesive with no adhesive, as well as the performance of self-etch adhesives with traditional etch-and-rinse adhesives. On the question of adding an adhesive, both reviews indicated a positive effect on retention. Both of the reviews also reported that etch-and-rinse adhesives were superior to self-etching adhesives in retaining sealants. A third clinical study of 228 sealants placed on 57 children’s caries-free first permanent molars did a similar comparison. That study also concluded that enamel etching was key to sealant retention and that addition of an adhesive with that etching improved retention rates.

One long-term paper presented a case series of clinical sealants where retention was analyzed after 22 years
of service by visual inspection, photography, and scanning electron microscopy of epoxy replicas. A total of 41 teeth were sealed with either resin-modified glass ionomer (Vitrebond or Fuji II LC) or polyacid-modified resin composite (VariGlass VLC). Within these teeth, sealant loss was detected visually and photographically, but scanning electron analysis revealed that none of the teeth had total loss of sealant material, regardless of the material used. No caries were noted after 22 years in any of the sealed surfaces. This study demonstrates that residual sealant protection often remains in teeth with visually observed sealant loss.

A systematic review compared caries prevention using resin-based sealants with fluoride varnish. Eight RCTs with a total of 1747 children between 5 and 10 years of age were included. After 2 years, sealants prevented more caries (OR=0.69; 95% CI, 0.50-0.94), and follow-up at 4 and 9 years found that this caries-preventive benefit for sealants was maintained. The authors concluded that there was some low quality evidence suggesting the superiority of resin-based sealants over fluoride varnish application for preventing occlusal caries on permanent molars.

One paper reported the safety of dental sealants as related to the potential for exposure to 6 synthetic phenolic antioxidants added as preservatives or polymerization inhibitors in sealant formulations. The most common of these, 2,6-di-tert-butyl-4-hydroxytoluene (BHT), was found in all 63 dental sealant products tested, but the estimated daily intake following sealant placement based upon a worst-case scenario was still several orders of magnitude lower than the current acceptable daily intake proposed by the European Food Safety Authority.

One paper of note reported results from resin infiltration of proximal caries lesions in a split-mouth, randomized, and placebo controlled trial performed in the private offices of several dentists. The study included 238 pairs of proximal lesions in 87 children and young adults. Lesions extended radiographically into the inner half of enamel or the outer third of dentin and were randomly allocated to either resin infiltration or a mock treatment control. All patients were given the same home care instructions. After 18 months, lesion progression was observed in 5% of test lesions and 31% of the mock control lesions. This study confirms results reported by similar studies conducted in university settings.

Overall, studies continue to confirm that pit and fissure sealants are one of the most effective tools in our preventive arsenal. The evidence clearly shows that there is a public health benefit to school-based sealant programs and that the preventive value is cost effective when applied to higher risk populations. The Dental Quality Alliance has established measures around sealant placement in at-risk children that have been adopted by the National Quality Forum as part of its basic set of pediatric quality measures. These measures are being rapidly adopted by state and federal public health programs and will become an ever more important driver of dental public policy.

Silver compounds
There continues to be growing interest in the use of silver nitrate and silver diamine fluoride in the arrest of carious lesions. One systematic review of fluoride therapies in caries remineralization included 7 studies reporting arrest in dentin caries, using silver diamine fluoride. A meta-analysis of 5 of these studies demonstrated a 65.9% proportion of arrest in dentin caries. A randomized clinical trial looked at the ability of silver diamine fluoride to arrest root caries in an elderly population in Hong Kong. A total of 157 root surfaces were randomly allocated to receive an annual placebo application of soda water, a similar application of silver diamine fluoride, or an application of silver diamine fluoride followed by potassium iodide solution to reverse the black lesion discoloration. After 30 months, the arrest rates were 45% in the soda water control, 90% in the silver diamine fluoride group, and 93% in the group receiving silver diamine fluoride followed by potassium iodide. The darkening of the silver diamine fluoride-treated lesions was not negated by the addition of the potassium iodide. A related paper reported cost effectiveness of silver diamine fluoride and other preventive measures in the control of root caries. The results of cost modeling showed that in populations with a high number of teeth and high tooth-level risk, silver diamine fluoride was the least costly and most effective option.

A study in young children between 3 and 4 years of age compared the arresting ability of 3 topical fluoride regimens on dentin caries. Children with at least 1 active carious lesion into dentin were allocated to receive either 1 application of 30% silver diamine fluoride, 3 applications at weekly intervals of 30% silver diamine fluoride, or 3 applications at weekly intervals of 5% sodium fluoride varnish. A total of 304 children with 1670 tooth surfaces were included, and after 18 months, the arrest rates were 40% for 1 application of silver diamine fluoride, 35% for 3 weekly applications of silver diamine fluoride, and 27% for 3 weekly applications of sodium fluoride varnish. It was concluded that both of the silver diamine fluoride regimens were more effective than the fluoride varnish in arresting active dentin caries in these young children.

A second pediatric-related paper compared silver diamine fluoride use among US pediatric dental residency programs. This survey found that more than a quarter of programs reported using silver diamine fluoride and that 68.9% expected to increase use. No regional or program-type associations were noted. Most program directors felt silver diamine fluoride should be used only
with high-risk patients in both primary and permanent teeth. The most frequently reported barrier was parental acceptance. The evidence supporting use of silver diamine fluoride for caries management continues to grow slowly. Although it is certainly not a panacea when it comes to caries control, this compound provides a promising option for situations such as root caries and severe early childhood caries, where few options currently exist. Most importantly, it provides an option for treating patients with access and health limitations that often represent the greatest challenge.

**Endodontic materials**

Two papers reported clinical trials of mineral trioxide aggregate (MTA). The first paper evaluated single-visit treatment of permanent teeth with chronic apical abscesses using either MTA or conventional gutta percha and sealer for obturation. 282 Teeth were randomly assigned to 1 of the 2 methods, and the outcomes evaluated were obturation length, periapical healing, resorption of extruded material, and survival rate at 2.5 years or longer. Of 32 teeth evaluated, complete healing was observed in 87.5% of teeth treated with MTA and 75.0% of teeth treated with gutta percha. Complete resorption of extruded material was observed in 83.3% of MTA-treated teeth and 100% of gutta percha-treated teeth. The survival rate of MTA-treated teeth was 100%, whereas that of gutta percha was 83.3%. Although MTA appeared to perform better than gutta percha, the small sample size in this study did not provide enough power to establish significant differences.

A second paper compared MTA with another base material, Intermediary Restorative Material (IRM), in primary teeth with furcation lesions. 283 Fifty primary teeth were randomly assigned to the 2 treatment methods, and after pulpal therapy, the pulpal floor was lined with either MTA or IRM. After restoration, the teeth were followed for 18 months and assessed for any signs of clinically visible or radiographic pathology. Once again, both materials proved to be highly successful, with no differences, other than the noted observation that MTA-treated teeth appeared to heal more rapidly than those treated with IRM. MTA continues to demonstrate good versatility and performance as an endodontic repair and obturation material.

A novel antimicrobial material called 3Mixtatin was reported as a repair material for bony defects caused by pretreatment endodontic perforations. 284 3Mixtatin is described as a mixture of 3 antibiotics (metronidazole, minocycline, and ciprofloxacin) combined with simvastatin. In this study, 80 primary molars in 65 children between 3 and 6 years of age who exhibited interradicular or periapical root resorption and/or perforations were assigned to either 3Mixtatin or MTA therapy prior to pulpectomy and restoration. The teeth were followed for 24 months, and in the 3Mixtatin group, 96.8% showed no signs or symptoms of pathology, and resorption appeared to be arrested on radiographs. Signs and symptoms of pathology were present in 48.6% of MTA-treated teeth with only 18.9% showing radiographic arrest of resorption. These are promising early results, and hopefully more research related to this material will be conducted in the future.

**Composite resin**

A systematic review assessed the effect of the use of cavity liners on postoperative sensitivity and other performance factors in class I and class II composite resin restorations. 285 Eight studies with more than 700 patients were included in the review, and all studies were either unclear or at high risk of bias. The evidence evaluating liner effect on postoperative sensitivity was inconsistent, and restoration failure rates were too low to establish any impact on longevity. Another publication of a clinical trial evaluated placement technique (incremental or bulk fill) and the use of either self-etch or etch-and-rinse adhesives on sensitivity of posterior composite resin restorations. 286 The findings from 236 teeth in 72 patients were that postoperative sensitivity was not affected by either filling technique or adhesive strategy and that the overall risk for sensitivity was 20.3% and typically occurred within 48 hours of restoration placement.

One very interesting review compared the published success rates for posterior composite restorations placed between the decade between 1995 and 2005 to those placed between 2006 and 2016. 287 Only studies with at least 24 months of restoration service were included. The overall survival rate during the earlier decade was 89.4% and that of the most recent decade was 86.9%. Although survival rates were seemingly unchanged over time, the reasons for failure were very different. Reasons for failure in the earlier decade were 29.5% secondary caries, 28.8% material fracture, and 3.5% tooth fracture. During the later decade, secondary caries was similar at 25.7%, but composite resin fracture had increased to 39.1% and tooth fracture to 23.8%. The authors speculated that this increase in composite resin and tooth fracture was due to the placement of larger composite resin restorations during the second decade.

Several studies and reviews reported the performance of composite resin restorations. One systematic review assessed differences in clinical performance of direct versus indirect composite resin restorations in permanent posterior teeth. 288 Again, only RCTs with at least 2 years of follow-up were included. Nine studies were included in the analysis, 5 of which were considered at low risk of bias. Results showed that the overall risk differences in longevity for direct versus indirect restorations did not reach statistical significance for any teeth or time point.
and the study concluded that there were no differences in longevity regardless of the type of material or restored tooth. A second, similar systematic review and meta-analysis evaluated the risk of failure up to 11 years and came to similar conclusions in that no differences could be found other than in marginal discoloration between direct and indirect restorations.\textsuperscript{289} These findings are important and affect the additional cost and complexity of indirect composite restorations.

Two studies examined the differences between bulk and incremental filling techniques for composite resin restorations. The first study was a 5-year RCT that compared a flowable bulk-filled composite resin (SureFil SDR) with the incremental placement of CeramX Mono+ nano-hybrid.\textsuperscript{290} The materials were randomly assigned to class I and class II restorations in a split-mouth design. After 5 years, the annual failure rate was 1.1% for bulk-filled and 1.3% for incrementally filled restorations, which was not a significant difference. The second study looked at early postoperative sensitivity, comparing bulk-filled to incrementally filled restorations.\textsuperscript{291} Seventy-two teeth were randomly assigned to the 2 methods, and although a small difference in sensitivity was noted at day 2 postoperatively, by day 7, there were no differences in sensitivity between the 2 filling techniques, with 8.3% of teeth overall reporting tenderness on biting. The authors did note, however, that class I cavities were found to be more tender on biting than class II cavities, a phenomenon that has been reported in other studies.

Two papers reported potential exposure to bisphenol A (BPA) from dental composite resin. The first study assessed urinary BPA levels in children and adolescents who received bisphenol A-glycidyl methacrylate (bis-GMA)-based composite resin restorations.\textsuperscript{292} Urinary levels from 91 participants were measured before restoration until 6 months after restoration placement. The mean change from preplacement was 0.87 nanograms/mL at day 1, but no associated increase could be detected at day 14 or at 6 months after treatment. The conclusion was that after the placement of a few restorations, a transient increase might have occurred in urinary BPA concentrations that was no longer detectable by 14 days because of the high level of variation in background exposure from other sources. A second paper reported urinary levels of BPA from participants who took part in the 2003 to 2004 and 2010 to 2012 NHANES surveys.\textsuperscript{293} The 2003 to 2004 survey included 7514 participants and the 2010 to 2012 survey 7189 participants. The analysis compared blood levels of BPA to dental surface restorations. An increase in overall urinary BPA concentration was noted from the earlier to the later survey periods, but when adjusted for dental surface restorations, no significant associations were found in either period. This lack of association between dental restoration surfaces and urinary BPA again indicates that other environmental exposures play a more pivotal role.

Research continues to be related to bioactive restorative materials in published reports, but this class of materials is still early in development, and no clinical studies are yet available. Many different approaches are being tested, but whether these materials can be made commercially viable remains to be seen.

**Amalgam**

The biggest news related to amalgam in 2016 was the publication of the final ruling by the US Environmental Protection Agency, “Effluent Limitations Guidelines and Standards for the Dental Category.”\textsuperscript{294} This ruling was long in the making and covers technology-based pretreatment standards under the Clean Water Act to reduce discharges of mercury from dental offices into municipal sewage treatment plants. The ruling came after nearly 2 decades of calls for voluntary adoption of amalgam waste best management practices, which since 2007, included the installation of amalgam separators. Many states and municipalities had already put in place mandatory requirements for adoption, and this federal ruling now expands this mandate nationally.

The guidelines and standards call for 3 areas of compliance, as follows. The first guideline is the installation and operation of amalgam separators that meet the requirements of the American National Standards Institute/American Dental Association standard 108 for amalgam separators. The second guideline relates to prohibiting the use of oxidizing cleansing agents such as bleach, iodine, and peroxides for flushing of vacuum systems. The third guideline prohibits the rinsing or flushing of any amalgam waste, such as chairside trap waste, down a drain. A One-Time Compliance Report requirement is also included in the ruling to document the fact that the dental discharger meets the requirements of the applicable performance standard. Dental offices that do not place or remove amalgam restorations are exempted from this regulation. Those offices with existing amalgam separators that do not meet the performance requirements are given 10 years to replace them with compliant technology. Dental offices have until the end of 2019 to comply with this regulation.

Dental amalgam continues to be one of the most studied and scrutinized of dental materials. Four papers were published related to mercury exposure in pregnant women. One paper determined the contribution of dental amalgam to the total blood mercury level in 4484 pregnant women enrolled in the Avon Longitudinal Study of Parents and Children.\textsuperscript{285} Linear regression models were used to estimate the relative contribution of dental amalgam to total blood mercury level. The dental contribution was estimated to be 6.5%, whereas that shown for seafood consumption was a comparable

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*Donovan et al.* THE JOURNAL OF PROSTHETIC DENTISTRY
8.75%. A second study used the Norwegian Mother and Child Cohort Study to assess possible associations between exposure to amalgam fillings and adverse pregnancy outcomes.296 This potential association was explored in 69,474 pregnancies, and regression models revealed no significant associations between the number of teeth with amalgam fillings and early preterm delivery, late preterm delivery, low birthweight, infant malformation, or stillbirth. A third study determined the extent to which mercury is transmitted from mother to fetus through the umbilical cord in mothers with dental amalgam fillings.297 A comparison was made between mothers with amalgam fillings and those without. Not surprisingly, the women with amalgam fillings had both maternal and umbilical cord mercury levels that were higher than those women without amalgam fillings. Those levels, however, did not affect any of the fetal biometric measurements. A fourth paper described an investigation of whether in utero exposure to mercury may affect the neurological development of sons born to Swedish dental personnel.298 The national Swedish registry was used to investigate possible adverse effects on the sons of 16,909 female dentists and 10,420 dental auxiliaries, and comparisons were made with a cohort of female nondental health workers. This analysis was carried out over the decades of the 1960s, 1970s, and 1980s in order to look at differing exposure levels. The results found no elevated risk for neurological disease, epilepsy, or intellectual development among the sons of dental personnel during any of the study decades. Thus, the evidence continues to find no association between dental amalgam exposure in women and adverse birth outcomes, child health, or child development.

Another study involving healthcare workers compared 1,409 dental workers with 462 nondental workers measuring urinary mercury levels as related to personal restorations and work-related amalgam exposure.299 The median urinary mercury level for dental workers was 2.75 μg/L and 2.66 μg/L for nondental workers. No significant risk factors were found among dental workers other than for those who used squeeze cloths, and the factor of greatest significance was between respondents who ate seafood more than five times per week compared with those who ate seafood less frequently or not at all. Also significant was the exposure to mercury from cosmetic products.

A study performed in Taiwan examined the association between dental amalgam filling exposure and the risk of Parkinson’s disease.300 This was a retrospective cohort comparison of patients with fillings placed between 2000 and 2008, identified in the National Health Insurance Research Database, and the nonamalgam cohort was chosen from the same database, including patients who had received no new amalgam fillings during this same time period. The results indicated that individuals receiving amalgam fillings had a significantly higher risk (OR=1.583; 95% CI, 1.122–2.234) of Parkinson’s disease than those who did not receive amalgam fillings during this time period. Adjustments were made for comorbidities in this comparison, but one major deficiency was not knowing the history of amalgam exposure or other sources of mercury exposure in either cohort. This is a good example of the limitations of retrospective studies where important contributory factors simply cannot be accounted for or controlled.

Several papers were published that studied the impact of the 2013 Minimata Convention on Mercury and how this global agreement has impacted the use of dental amalgam. The Minimata Convention called for a global phasing out of amalgam use in order to reduce environmental mercury pollution. The impact of this agreement is likely to be felt differently in countries where there is a greater dependence on amalgam as a restorative material. The first paper looked at the impact in the United Kingdom, where amalgam is still extensively used.301 The British Society of Prosthodontics published the proceedings of its Annual Conference, where discussions elicited concerns regarding the suitability of mercury-free alternatives for larger restorations and anecdotal reports of dentists not being trained adequately in the use of dental amalgam. Clinicians expressed concern that amalgam should remain available, even in the event of a complete phasing out, for clinical circumstances such as restoration of posterior teeth and situations where moisture control is challenging. In contrast, the attitudes of 400 Saudi dentists in the city of Riyadh were surveyed related to the use of dental amalgam.302 In that population, 80.7% of respondents reported that they did not use dental amalgam frequently in their practice. Furthermore, a large portion of those dentists reported that they would replace existing well-placed amalgam restorations. The author attributed this to their market-oriented attitude, which had been reported in other earlier surveys. Another survey of Jordanian dentists showed that only 13.8% were aware of the Minimata Convention and that 17% had training that favored the placing of composite resins in posterior teeth.303 Only 28.1% of those dentists were in favor of discontinuing use of amalgam. These surveys reflect the wide range of awareness as well as attitudes related to the goals set forth in the Minimata Convention.

Once again, 2 rather bizarre papers were somehow published that related to the effect of electromagnetic fields on amalgam mercury exposure. The first paper presents a rather twisted compilation of conjectures that attempt to connect amalgam mercury release with microwave radiation emitted by mobile phones to maternal exposure to electromagnetic fields and increases in autism disorders.304 Unfortunately, in this paper,
supporting data demonstrating any of the cited interdependencies or the authors’ call for additional studies are lacking. Some of the same authors reported on the effect of Wi-Fi signals on mercury release from amalgam in extracted teeth.265 The specimens exposed to Wi-Fi purportedly release approximately twice the concentration of mercury into artificial saliva than the non-Wi-Fi exposed specimens released. No data were provided to demonstrate this same phenomenon in a more realistic clinical situation, but the conclusions made the completely unsupported statement that Wi-Fi devices can increase mercury release from amalgam restorations in patients.

One systematic review compared the in-service performance and longevity of bonded amalgam restorations with nonbonded restorations.263 Only 1 trial with 31 patients who received 113 restorations was included in the final analysis, and no differences could be distinguished in any aspect of clinical performance. A second study reported the 12-year survival of composite resin and amalgam class II restorations placed on premolars by Canadian dental students.306 Over the 12 years, 1695 composite resin and 1125 amalgam 2-surface restorations were placed with a cumulative failure rate of 7.9% for the composite resin and 5.9% for amalgam. Amalgam outperformed composite resin in both short-term (2 years or less) and long-term (greater than 2 years) failure rates, and the differences in survival curves were statistically significant.

Silver amalgam, while continuing to wane in use worldwide, is still supported by science as a safe and effective restorative material. Actions such as those taken by the Environmental Protection Agency and Minimata Convention will hopefully address environmental concerns while retaining it as a restorative choice for those clinical situations where few viable alternatives are available.

**OCCLUSION AND TEMPOROMANDIBULAR DISORDERS**

The section on occlusion and temporomandibular (TM) disorders covers investigation of education, diagnostic criteria, jaw injury, TM joint (TMJ) imaging, TM disorders and headaches, orthognathic surgery, and occlusal and facial changes.

**Education**

The need for education in occlusion and TM disorders (TMDs) becomes evident in the article by Adibi et al.307 The aims of that study were to determine whether patients in the clinic of one US dental school reported existing signs and symptoms of TMJ disorders/orofacial pain (OFP); whether the dental students diagnosed the condition based on the reported signs and symptoms; and whether the condition was then treated. The study was based on a retrospective analysis of electronic health record data over a 3-year period. Results showed that, during the study period, 21 352 patients were treated by student providers. Of those patients, 5.33% reported signs or symptoms associated with TMD/OFP; 5.99% received a TMD/OFP diagnosis; and 0.26% received at least one form of TMD/OFP treatment that had either a diagnosis or signs/symptoms of TMD/OFP. In addition, a small percentage of patients (0.24%) with no documented diagnosis received some sort of TMD/OFP-related treatment. A randomly selected sample of 90 patient charts found that no diagnoses of TMD/OFP were recorded in any of them. The results suggested that students had only marginally diagnosed the problems.

Training for students, including comprehensive didactic courses and clinical experiences to gain knowledge, context, and skill, may be required to ensure they reach the required level of competence and prepare them to face the diagnostic challenges of TMD/OFP after graduation. The authors feel there are 2 significant potential pitfalls for novice or inexperienced practitioners in diagnosing and treating TMD/OFP. One pitfall involves the ability to understand the patients’ chief complaint and underlying complex causes with thorough history-taking skill, and the other is claiming premature success in an not necessarily evidence-based treatment modality prescribed when patient compliance is absent or the patient’s return for evaluation is an issue.

The study found that the numbers of patients with TMD/OFP-related diagnoses documented in their charts and those who received some sort of TMD/OFP treatment were below that expected based on the preponderance of these conditions in the general population. As students only marginally diagnosed the problems, stronger didactic courses in both basic and clinical sciences, along with improved training in diagnosing TMD/OFP conditions, seem to be needed. In addition, more research is needed to explore evidence-based treatment modalities in order to enhance the profession’s ability to provide care for patients suffering from these debilitating disorders.

Where Adibi et al.307 assessed predoctoral students, Candirli et al.308 investigated how practicing dentists approached the use of occlusal splint therapy for myofascial pain and TMJ disorders. A total of 400 general dentists registered on the list of the Turkish Dental Association were selected by systematic random sampling as research participants in this study. A 12-item questionnaire was developed to determine dentists’ knowledge of TMJ disorders and splint treatments. The questionnaire also gathered sociodemographic and descriptive information, such as the dentist’s age, sex, and year of graduation. The dentists were asked about their knowledge and experience with different splint types and TMJ disorders. The final section of the questionnaire investigated the dentist’s approach to TMJ
disorders and bruxism. In addition, treatment results and success criteria were gathered. The dentists were divided first into 3 groups according to the time passed since graduation (group A: 0 to 5 years; group B: 5 to 15 years; and group C: more than 15 years) and then also divided into 2 groups according to knowledge about TMJ disorders and treatment modalities (group 1: sufficient knowledge; group 2: insufficient knowledge) in accordance with the assertion of the participants.

The mean age of the dentists was 33.12 ±9.24 years old (range: 23-69 years of age). Of dentists participating in the study, 211 (57.1%) were male and 159 (42.9%) were female; 174 (82.5%) male dentists and 114 (71.7%) female dentists implemented the use of occlusal splints (P<.05). A total of 42% of dentists (n=121) reported using soft splints, 44.8% (n=129) hard splints, and 13.2% (n=38) reported using both soft and hard splints; 77% (n=221) used maxillary splints, whereas 23.3% (n=67) used mandibular splints. Regarding the duration of the splint therapy, 37.5% (n=108) of the participants used the splint for 3 months, 10.1% (n=29) for 6 months, 12.2% (n=35) for more than 6 months, and 40.3% (n=116) used the splints until the patients reported that the symptoms had disappeared.

A total of 52% (n=149) of the dentists were using additional therapy such as thermal, pharmacological, and cryotherapy, and 48.3% (n=139) of the dentists claimed that they used no additional therapy with occlusal splint therapy. When the dentists were asked whether they had information about joint diseases, 30.2% of participants (n=87) reported that they had sufficient information about the joint disease; however, 69.8% (n=201) of dentists using occlusal splints had insufficient information relevant to the joint disease (causes, pathophysiology, and therapy), and 87% (n=250) of the dentists using occlusal splints reported that they did not pay attention to occlusal adjustment of the splints. Although 80.2% (n=231) of the dentists reported that occlusal splint therapy successfully treated patients, 19.8% (n=57) reported that splint therapy was not successful. Patient satisfaction was the most common success criterion (52.1%; n=150), followed by pain reduction or disappearance (44.8%; n=129). Improvement in clinical parameter rates were success criteria infrequently used by the dentists (3.1%; n=9). When the dentists were asked whether they had considered the clinical parameters during the treatment, 32.3% of participants (n=93) reported that they had taken into account various clinical parameters, and 67.7% (n=195) of dentists using occlusal splints reported they did not evaluate clinical parameters.

A total of 56% of young dentists (0 to 5 years of experience) had sufficient knowledge of TMJ disorders, whereas only 16% of dentists in other groups demonstrated such knowledge (P<.001). Dentists with 0 to 5 years of experience generally used hard occlusal splints (P<.001). The rate of hard occlusal splint application decreased with increased experience. Less than 16% of dentists in each group had performed occlusal splint adjustment (P>.05). The authors speculated that these differences between young dentists and those with more experience may be due to 2 main factors. First, a soft splint is readily used and does not require occlusal adjustment, thereby reducing chair time in comparison with the use of a hard splint requiring occlusal adjustment. Second, it is possible that dentists’ knowledge decreases over time.

Dentists’ knowledge of the cause and treatment of TMJ disorders and bruxism is important. Occlusal splints were the first treatment choice among male and female dentists in the sample. The effectiveness of hard occlusal splints has been demonstrated. Soft occlusal splints have been shown to increase pain and nocturnal electromyograph activity compared with hard splints. Thus, hard occlusal splints should be used in patients with these problems. The survey results indicated that female dentists had more knowledge of TMJ disease than male dentists and used hard occlusal splints more frequently (P<.05).

Dentists participating in this survey showed insufficient knowledge of TMDs, bruxism, and occlusal splints. Their knowledge decreased with increasing experience. The dentists’ therapeutic methods are incompatible with those accepted or recommended on the basis of scientific knowledge in dental practice in Turkey. Thus, national dental associations and dental faculties should work together to organize postgraduate training symposia, and all dentists should be encouraged to attend to reinforce and augment their education.

While occlusal appliances are typically the first course of treatment for patients, the structural damage in the TMJs of some patients requires a surgical approach. Elledge et al309 reviewed the perceptions of oral and maxillofacial surgeons training in the United Kingdom regarding the frequency and nature of exposure to procedures on the TMJ, anticipated confidence at completion of specialty training, and likelihood of pursuing TMJ surgery as a subspecialty after training. Respondents were also asked to give their current level of training and region.

A prospective audit was undertaken of all OMFS trainees in the United Kingdom by using the electronic survey tool Survey Monkey. The survey was distributed to all members of an online Yahoo group forum reserved for specialty trainees in OMFS. A total of 52 trainees responded to the survey from 134 members of the Yahoo groups OMFS trainees forum (a response rate of 39%), and a wide range of training grades and UK training regions were accounted for by the respondents. Although 39 trainees (75%) took part in more than 5 arthrocenteses of the TMJ, only 11 (21%) had experience
with a similar number of arthroscopies of the TMJ and 11 (22%) an equivalent number of alloplastic TMJ replacements. Those respondents who were involved in more than 5 alloplastic joint replacements were from a diverse range of training regions. As expected, the nature of involvement became more observational as procedures become more complex. Of the total number of potential respondents, 34 (65%) had been involved in an arthrocentesis in some capacity (either supervised or independently), whereas only 11 (21%) had performed an alloplastic TMJ replacement.

Respondents were asked how confident they were that they would be competent in different surgical procedures on the TMJ at the time of completion of specialist training and asked to rate this on a 5-point Likert scale. As can be seen, the scores were higher for simpler procedures such as arthrocentesis and intramuscular botulinum toxin injections but low for alloplastic and autogenous TMJ replacements. Participants were asked to rate how likely they would be to consider TMJ surgery as a subspecialty interest in their future careers. The mode score, based on a 5-point Likert scale, was 1 (signifying not at all likely), and 22 (44%) of respondents returned this result. Results of the present survey highlight the fact that few higher trainees in OMFS will be interested in pursuing a career in TMJ surgery, and the need to focus attention on those trainees who will go on to take up this challenging subspecialty is paramount.

**Diagnostic criteria**

Given the difficulties outlined above in predoctoral students, practicing dentists, and specialists, attempts have been made to summarize the diagnostic criteria for TMJ disorders for clinical and research applications. Schiffman and Ohrbach\(^\text{310}\) published an update of the 1992 Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) model. The RDC/TMD model went beyond standard classification approaches for TMD and proposed a dual-axis assessment. Axis I included the standard diagnostic criteria for the most common TMDs and was based on TMD clinical signs and symptoms. Axis II took the assessment further by including the assessment of psychosocial and behavioral factors. Thus, Axis I described the most common physical disorders, and Axis II described aspects of the person who had the disorder.

When using Axis I diagnoses, the clinician must first rule out odontogenic disease and other pain disorders that can occur in the masticatory system. Numbness, swelling, and redness typically are not present with common TMDs, and when they are present, the clinician must rule out clinically significant disease, including infections, neoplasms, and systemic conditions. In addition, the clinician also must consider the uncommon TMDs.

For pain-related TMDs, the patient must report that the pain or headache is located in the jaw or temple area and that the pain or headache is modified (made better or worse) with jaw movement, function, or parafunction. The diagnostic criteria for myalgia, and its subtypes, require palpation of only the masseter and temporal muscles as the minimum. However, examination of the other masticatory muscles may be indicated, especially when the patient’s pain complaints have not been replicated by the standard examination.

The diagnostic criteria for TMJ intra-articular disorders, with the exception of disc displacement (DD) without reduction with limited opening, can be used only for screening purposes because of inadequate criterion validity. Definitive diagnoses require TMJ magnetic resonance imaging (MRI) for DD and TMJ CT for degenerative joint disease (DJD). Routine occlusal assessment is recommended because occlusal status may change with treatment. Also, TMD can cause transient or persistent malocclusions. For example, with unilateral arthralgia, if an effusion (such as, swelling) is present, an ipsilateral posterior open-occlusal relationship can be present; or with bilateral DJD, an anterior open occlusal relationship may occur. Therefore, clinically significant occlusal findings should be documented. Clinical observations using the DC/TMD model can be the basis for future research. Future research will lead to diagnostic protocols based on causes and mechanisms to allow for more targeted, personalized treatment plans for the patients we serve.

**Jaw injury**

Many of the problems in TMJ patients are the result of some type of injury to the jaw. Barbosa et al\(^\text{311}\) evaluated the awareness of the possible relationship between jaw pain or TMD symptoms, facial and jaw injury (FJI), orthodontic treatment (OT), and third molar removal (TMR) in the presence of TMD. Temporomandibular disorder research is controversial, and many clinicians and researchers differ in their views of TMD origins, diagnosis, and management. The reason for these differences lies in the fact that TMDs are a multifactorial group of musculoskeletal disorders that involve the TMJ, masticatory muscles, and all associated tissues. Temporomandibular disorders commonly present with combined causes and a patient’s perception of how a specific occurrence affected their TMD can influence the clinician’s perception. Patients frequently believe that procedures such as orthodontic treatment or third molar removal are important causative factors in the development of their TMD, thus considering the professionals who carried out these treatments responsible for their symptoms.

The study was carried out from March 2014 to July 2014. A total of 1381 students participated from the
University of Oporto in Oporto, Portugal. Before undergoing the clinical examination, each student completed a questionnaire that included demographic data (sex and age) and the questions from the Portuguese version of the RDC/TMD patient history questionnaire, which yield Axis I RDC/TMD classification (TMD symptoms of facial pain, difficulty on mouth opening, clicking, crepitus, and headache), as well as questions of the RDC/TMD Axis II that are used for application of the Graded Chronic Pain Scale. The students were divided into 2 groups according to age: 18 to 25 years of age and 25 years and older. Three groups of questions were added to this questionnaire, each group containing 3 dichotomous questions (yes/no) about the students’ experience with FJI (“Have you had a recent injury to your face or jaw?”), OT (“Did you undergo orthodontic treatment [dental correction] with fixed or removable appliances?”), and TMR (“Were you subject to third molar extraction [wisdom teeth] even if you had only one extracted?”). All students were required to answer these first 3 questions. If they answered “no” to the entire RDC/TMD patient history questionnaire (and thus were not symptomatic) but answered “yes” to the first question of any group, they were requested not to answer the 2 following questions. If symptomatic students answered “yes” to the first question of any group, they were also required to answer the other 2 questions in the group: “Did you have jaw pain before [FJI, OT, or TMR]?” and “Do you relate the beginning of your jaw pain or symptoms with [FJI, OT, or TMR]?”

Of the 1381 students who participated in this study (mean ±SD age=21.7 ±3.9 years), 75.5% (n=1042) were female, and 24.5% were male (n=339). The mean age of women was 21.3 ±7.2 years, and that of men was 22.6 ±4.5 years; statistically significant differences in the age of women and men were observed (t test, P<.001). With respect to the distribution of TMD diagnoses, 60.7% (n=838) of the students had no TMD diagnosis, and 39.3% (95% CI, 36.7% to 41.9%; n=543) had some type of TMD. Of these, 23.2% had a single TMD diagnosis, and 16.1% had combined TMD diagnoses. The prevalence of TMD in women was 41.7% and 31.9% in men. With regard to the prevalence of TMD by age, students 18 to 25 years of age had a prevalence of 38.4% and those older than 25 years of age had a prevalence of 47.7%. Therefore, the assessment of the relationship of TMD with sex and age group indicated that being female (chi-square test, P=.001) and older than 25 years (P=.038) were significantly associated with TMD.

Recent FJI affected 23.2% of the students, and significantly more of these students were male (chi-square, P<.001). These students had greater awareness of the relationship between their pain or other symptoms and FJI (P=.007). In addition, 44.5% of the students and significantly more women had undergone OT (P=.004). Also, TMR was experienced by 26.2% of the sample and by significantly more women than men (P=.024). Univariate analyses showed significant associations between OT and a TMD diagnosis (P=.044) and between TMR and a TMD diagnosis (P=.003). Jaw pain before FJI or OT was not found to be a significant risk factor for TMD (P>.05), but jaw pain before TMR was found to be a risk factor for TMD (P=.005). A significant positive correlation between awareness of the relationship between jaw pain or other TMD symptoms and a history of FJI and TMD was shown (P<.001), and 72.0% of students with such an awareness actually had TMD. A significant positive correlation between OT and awareness was also shown (P=.002); 68.7% of these students had TMD. Multivariate analyses revealed that FJI was not found to be associated with any of the single or combined TMD diagnoses. Orthodontic treatment and TMR were not associated with any of the single TMD diagnoses; nonetheless, both were significantly associated with different combined RDC/TMD diagnoses. Orthodontic treatment was found to be a significant risk factor for groups II and III (OR=2.0; P=.017), whereas TMR was found to be a significant risk factor for groups I and III (OR=1.69; P=.045), and groups I, II, and III (OR=2.15; P=.006). Upon completion of multiple regression analysis that included the variables FJI, OT, TMR, OT×TMR interaction, sex, and age, the model only retained TMR (OR=1.50; P=.041), sex (OR=1.59; P=.001) and age (OR=1.04; P=.013) as significant and independently associated with the TMD outcome.

In this university student population, TMR, female sex, and older age were independent risk factors for TMD. Additionally, when the students’ awareness of the relationships between jaw pain or other TMD symptoms and FJI, OT, or TMR were taken into account, there were significant associations between awareness and FJI and between awareness and OT. Based on these results, screening patients for their awareness of potential risk factors for TMD could help evaluate TMD risk factors at the individual patient level.

**Temporomandibular joint imaging**

Injuries to the TMJ can cause structural alterations to both the soft tissue and the hard tissue in the TMJ. The ability to recognize and diagnose these structural changes has increased since the advent of 3D imaging over 25 years ago. Alarabawy et al analyzed MRI criteria to compare the role of MRI with arthroscopy. Temporomandibular joint pain and dysfunction are common but important clinical problems and, according to some studies, affect up to 28% of the population. The most frequent cause of TMJ dysfunction or TMJ disorder is internal derangement, which is defined as an abnormal relationship of the disk to the condyle. MRI
helps in the assessment of signs of TMJ dysfunction. Since the advent of MRI, improvements have been made in both hardware and software that currently allow better visualization of small structures such as retrodiscal layers or lateral pterygoid muscle attachment. MRI is accepted as the most advanced imaging modality for the diagnosis of TMJ abnormalities. It is noninvasive and has the potential to yield high quality tomographic imaging in any plane with bone as well as soft tissue spatial resolution. Additionally, the patient is not exposed to ionizing radiation or any biological hazards. Other advantages of MRI are its sensitivity, specificity, and diagnostic accuracy. MRI represents the best method of studying clinically affected joints, evaluating the morphological status of TMJ, and analyzing the dynamic process during mouth opening. This is not true dynamic imaging, but it is pseudodynamic MRI obtained from the serial multiple static images. MRI is the best technique for correlating and comparing TMJ components such as bone, disk, fluid, capsule and ligaments with autopsy specimens.

Fifty consecutive patients (80 joints) referred from dentists’ and rheumatologists’ clinics were included in this retrospective study. This study was performed from April 2013 to October 2015. The clinical inclusion criteria for the study group were limited mouth opening, crepitation or deflection of the mandible, or pain at mouth opening. The exclusion criteria for the study group were patients with systemic disease that affects TMJ such as rheumatoid arthritis, patients with obvious skeletal jaw deformity or previous trauma, or patients who have contraindications to MRI such as claustrophobia, uncooperative patients, or patients who had a cerebral aneurysm clip and cardiac pacemaker.

A detailed history was taken from each patient in the study, with special emphasis on the history of the present illness, a clinical examination including palpation of joint sounds, evaluation of joint stability, and measurement of range of motion. Also included were laboratory investigations such as complete blood evaluations, rheumatoid factors, and erythrocyte sedimentation rate (ESR) and diagnostic examinations and imaging.

MRI scans were performed using a (General Electric Signa) high-speed 1.5-T system in the MRI unit of the Radiodiagnosis and Medical Imaging Department at Tanta University Hospital. The patient was placed in the supine position with both arms adducted. The special TMJ dual coil was applied for the examination. Arthroscopy was performed in 40 individuals (49 joints) after MRI in patients with relatively advanced complaints, who agreed to arthroscopy based on the recommendations of the surgical team. Both TMJs were examined for disk position, disk configuration, presence or absence of joint effusion in TMJ space, and morphology of the mandibular condyle.

A comparison study between MRI and arthroscopy for evaluation of TMJ internal derangement was done in a selected 40 patients (of 49 TMJs, 31 unilaterally, and 9 bilaterally affected) showing that MRI detected anteriorly displaced disks in 41 of 49 joints, representing 83.7%, whereas 8 TMJs (16.3%) showed normal disk position. Magnetic resonance imaging revealed 14 TMJs (28.6%) with anterior disk displacement with reduction (ADDWR) and 27 TMJs (55.1%) with anterior disk displacement without reduction (ADDWOR). Arthroscopy revealed 39 of 49 TMJs (79.6%) were true positives, with anteriorly displaced disks. Two (4.1%) were false positives. Seven TMJs (14.3%) were true negatives, whereas 1 joint (2%) was a false negative. Arthroscopy revealed 13 TMJs (26.5%) with ADDWR, and 26 TMJs (53.1%) showed ADDWOR.

Disk displacement or internal disk derangement is the most prevalent disorder. A statistically significant association exists between anterior disk displacement without reduction and deformed disk configuration, joint effusion, and secondary osteoarthritic changes. Magnetic resonance imaging is a proper diagnostic modality for TMJ disorders, in comparison with arthroscopy, because of its noninvasiveness, excellent soft tissue contrast, and multiplanar capabilities.

Al-Saleh et al 313 evaluated the effect of MRI and CT image registration on inter- and intraexaminer consistency when they evaluated TMJ internal derangement compared with MRI alone. Magnetic resonance imaging and CBCT images of 25 patients (50 TMJs) were obtained and coregistered using mutual-information rigid image registration, using Mirada XD software. Two experienced radiologists independently and blindly evaluated 2 types of images (MRI alone and MRI-CBCT-registered images) at 2 different times (T1 and T2) for TMJ internal derangement based on sagittal and coronal articular disk position in relation to the head of the condyle and the posterior slope of the articular eminence.

The intraexaminer consistency with MRI alone (examiner 1=0.85 [0.74-0.92]; examiner 2=0.91 [0.84-0.95]) was lower than for the MRI-CBCT registered images (examiner 1=0.95 [0.91-0.97]; examiner 2=0.97 [0.96-0.99]). The interexaminer consistency of evaluating internal derangement with MRI alone (0.52 [0.18-0.73] at T1; 0.71 [0.45-0.84] at T2) was lower than for the MRI-CBCT-registered images (0.97 [0.95-0.98] at T1; 0.98 [0.96-0.99] at T2). When disk position classification was dichotomized to normal versus anteriorly displaced, intraexaminer agreement for the 2 examiners was 0.52 and 0.63 for MRI alone but 0.91 and 0.92 for MRI-CBCT-registered images. IntereXaminer agreement for MRI alone was 0.29 at T1 and 0.42 at T2 but 0.96 at both examination times for MRI-CBCT-registered images.
results of this study show MRI-CBCT-registered images improved intra- and interexaminer consistency in the evaluation of the internal derangement of the TMJ. Results of this study may conflict with the experience of well-trained clinicians who have experience in reading MRI and CBCT scans.

**Temporomandibular disorders and headache**

Graff et al\(^ {314} \) discussed TMDs and headaches that may be related to structurally altered TMJs that can be identified with MRI and CBCT imaging. In assessing the prevalence of TMD in a headache population, they stated that 56.1% of headache patients had TMD. This percentage increased if the study population had both migraine and tension-type headache. If the population is limited to women, 86.3% of migraine and 91.3% of chronic migraine patients had TMDs.

Understanding the mechanisms whereby facial pain (TMD) and head pain (migraine) may be linked physiologically may provide clues as to their clinical association and elucidate common targets for therapy. Whereas, in the face, maxillary and mandibular trigeminal nerve divisions are clearly separated anatomically from the ophthalmic division and cervical spine, pain referral clearly occurs between these sites. For this referral to occur, anatomic links must be proven between these distant sites. These referrals may be facilitated by central sensitization, reducing activation thresholds, increasing the responsiveness to afferent stimuli, and expanding the receptive field.

Graff et al\(^ {314} \) discussed disk displacements and claimed it is relatively uncommon for a disk displacement with reduction to progress to disk displacement without reduction. This may not match the clinical findings of practitioners who have significant experience imaging TMJs. Graff et al\(^ {314} \) also claimed the most prevalent diagnosis in the TMD patient population is myofascial pain. This again may not match the clinical findings of practitioners with significant experience imaging TM joints. The authors discussed treatment options, and the TMD symptoms are often self-limiting resolving in most patients within 7 years. This again may not match the clinical findings of practitioners with significant experience imaging TMJs.

In patients presenting with comorbid TMD and headache, each disorder should be separately identified and diagnosed using standardized diagnostic criteria. Once the disorders are identified, the predisposing, causative, and perpetuating factors of each condition should be addressed and minimized.

**Occlusal and facial changes secondary to TMJ structural alterations**

Although the historical focus has been on occlusal factors creating structural changes in the TMJ, the current thinking is that occlusal and facial changes occur as a result of structural changes in the TMJ. Caldas et al\(^ {315} \) contended that the relationship between TMDs and malocclusion is an extremely critical issue in dentistry. Contrary to the old concept that malocclusion causes TMD, occlusal changes, especially those observed as sudden, may be secondary and reflect joint or muscle disorders because of the obvious connection between these structures.

In the 1980s, the results of a lawsuit implied that orthodontic treatment was the main cause of TMDs. Since then, a significant number of studies have been conducted to investigate this association. In the past, studies have suggested that malocclusion and occlusal interferences were main factors in TMD development, thus validating irreversible occlusal therapies as the definitive treatment for the disorder. Based on that, occlusal adjustments, complete-mouth rehabilitation, and orthodontic treatment became popular as the treatment of choice for TMDs. However, most recent studies have shown no differences in the signs and symptoms of TMDs among individuals with malocclusion and those with normal occlusion or between orthodontically treated and nontreated individuals.

In the early 1990s, well-conducted studies demonstrated that some occlusal and skeletal factors, such as anterior open occlusal relationship, unilateral posterior reverse articulation, horizontal overlap greater than 6 to 7 mm, absence of 5 or more posterior teeth, and centric relation to maximum intercuspatation discrepancy greater than 2 mm, could be considered occlusal risk factors for TMD. However, most people presenting with these alterations have never experienced any TMD symptoms. An appropriate adaptation capacity is probably able to compensate for small alterations in function created by the presence of the malocclusion.

The purpose of the article was to present some conditions of occlusal change and TMJ conditions to help the dental professional recognize and evaluate the signs and symptoms of TMD before treatment planning. When an occlusal alteration is caused by TMD, the resulting mandibular position and occlusal relationship depend on the TMJ structures and/or muscles involved. Patients can demonstrate any of a number of clinical conditions that interfere with their comfort and ability to function. Therefore, clinicians must be able to recognize these conditions before treatment planning so that patients are not submitted to irreversible treatment (orthodontic treatment, occlusal adjustment, prosthetic rehabilitation, orthognathic surgery) based on an unstable occlusal relationship produced by articular and/or muscular disturbances. Immediate treatment would not only worsen the patient’s symptoms but also aggravate TMD severity.

A common clinical manifestation of an occlusal change secondary to structural changes in the TMJ is an
anterior open occlusal relationship. If the joint collapse occurs in both TMJs, condylar resorption causes morphologic breakdown of the TMJs and a subsequent decrease in ramus height, which results in progressive mandibular retrusion with an anterior open occlusal relationship. The diagnosis is usually confirmed by appropriate TM images. Cone beam computed tomography is an excellent option because of its capacity to adequately detect bone changes, and MRI allows visualization of the disk position and articular cartilage alterations. Frequent radiographic findings are erosion and flattening of the articular surface of the condyle and articular eminence, osteophytes, articular cysts, and loss of joint space.

Another common clinical manifestation of occlusal change secondary structural changes in the TMJ is a unilateral posterior open occlusal relationship associated with unilateral condylar resorption. When condylar resorption occurs unilaterally, an intrusion of the condyle, associated with a mandibular shift to the affected side, is a common finding. The result is an anterior open occlusal relationship associated with a posterior open occlusal relationship on the contralateral side, with occlusal contact occurring only in the posterior region of the affected side.

Based on the fact that there is an evident connection between the TMJ, masticatory muscles, and dental occlusion, occlusal changes may reflect the presence of TMD. Therefore, all plans for irreversible therapy such as orthodontics or prosthetic rehabilitation should be preceded by a meticulous analysis of TMD signs and symptoms. When present, TMD symptoms must always be controlled to reestablish a normal occlusion and allow proper treatment strategy.

Hsieh et al316 discussed facial morphology in children and adolescents with juvenile idiopathic arthritis and moderate to severe TMJ involvement. Juvenile idiopathic arthritis is a chronic autoimmune, inflammatory joint disease. It may affect the TMJ and cause severe growth disturbances such as mandibular micrognathia, retrognathia, a steeper mandibular plane angle, and increased facial convexity. The purposes of this study were to assess lateral facial morphology in children and adolescents with juvenile idiopathic arthritis with and without moderate to severe TMJ involvement to compare lateral facial morphology between these groups using lateral cephalograms and lateral 3D facial photographs and to compare and correlate the results of the photographic and cephalometric analysis.

This retrospective study included children and adolescents with juvenile idiopathic arthritis (mean age, 12.7 ±3.2 years; range, 4 to 18.5 years) attending annual TMJ examinations at the School of Dentistry, Faculty of Health and Medical Sciences, at the University of Copenhagen in Denmark between 2008 and 2014. The inclusion criteria were juvenile idiopathic arthritis diagnosed and treated medically according to the guidelines of the Department of Pediatric Rheumatology at Copenhagen University Hospital Rigshospitalet, cephalometric and panoramic films and 3D photographs available at the same visit, no history of maxillofacial surgery, and no genetic diseases, syndromes, or other congenital deformities. Diagnosis of the TMJ involvement was confirmed by both clinical and radiographic findings. TMJs were scored on a 4-point scale on the panoramic radiographs, as follows: no involvement (score 0), slight erosion or breakdown of the superficial cortical bone of the condyle (score 1), manifest erosion and flattening of the condyle (score of 2), or complete destruction of the condyle (score of 3).

Twenty children and adolescents with juvenile idiopathic arthritis and without TMJ involvement were consecutively enrolled in group 1 (bilateral TMJ involvement, score of 0). Twenty children and adolescents with juvenile idiopathic arthritis and a unilateral TMJ involvement score of 2 or 3 (the other side scored 0) were enrolled in group 2, and 20 children and adolescents with juvenile idiopathic arthritis and a bilateral TMJ involvement score of 2 or 3 were enrolled in group 3. The lateral projection of the 3D photograph was manually superimposed on the cephalogram by translation and rotation until the best fit of the profiles of the 2 images was reached.

The results showed patients with juvenile idiopathic arthritis and either unilateral or bilateral TMJ involvement had a more retrognathic mandible and retruded chin, steeper occlusal plane and mandibular plane angles, and a more hyperdivergent pattern than those without TMJ involvement. However, patients with juvenile idiopathic arthritis and unilateral TMJ involvement showed a lower degree of these characteristics than those with bilateral TMJ involvement. This indicates that moderate to severe condylar destruction, either unilateral or bilateral, can affect the facial profile and patients with bilateral TMJ involvement will have more severe growth disturbances than those with unilateral involvement. Compared with other cephalometric variables, the mandibular plane angle and the hyperdivergent pattern showed greater differences among the 3 groups; this may indicate that a vertical facial pattern is more affected by TMJ involvement than a sagittal facial pattern in participants with juvenile idiopathic arthritis. However, the hyperdivergent pattern of patients with juvenile idiopathic arthritis is different from that of the long-face syndrome that usually results from maxillary alveolar hyperplasia or maxillary vertical excess. The results showed a more steeply inclined maxillary occlusal plane in patients with TMJ involvement than in patients without TMJ involvement. This result is consistent with those of previous studies and indicates that deficient vertical growth of the maxillary posterior alveolar process
may be due to subnormally erupted maxillary molars hindered by an abnormal growth pattern or dentoalveolar compensation for the abnormal skeletal growth pattern.

This study suggests that children and adolescents with juvenile idiopathic arthritis and either unilateral or bilateral moderate to severe TMJ involvement will have severe growth disturbances, including retrognathic mandible, retruded chin, steep occlusal and mandibular planes, and severe discrepancies between the size of the maxilla and mandible. The vertical pattern is more affected by TMJ involvement than the sagittal facial pattern. Patients with juvenile idiopathic arthritis and unilateral TMJ involvement have similar facial patterns but less growth disturbance than those with bilateral TMJ involvement. Early intervention for patients with juvenile idiopathic arthritis and moderate to severe growth disturbances, including retrognathic jaw, is recommended to prevent unfavorable facial development.

Manfredini et al317 systematically reviewed published cases for the relationship between facial skeletal structures and TMJ joint disorders. A systematic search of dental and medical articles was performed to identify all studies of humans, assessing the relationship between TMJ disorders and facial morphology. Articles were included based on study design, regardless of TMJ disorder (disk displacement, osteoarthrosis, or unspecified), skeletal features, diagnostic strategies (imaging techniques or clinical assessment), and population (demographic features of participants) under investigation. The selected articles were assessed according to a format based on patients, problem, and population, intervention, comparison, and outcome, and quality was evaluated based on the Newcastle-Ottawa Scale.

Thirty-four articles were included in the review, 27 of which concerned adult samples and 7 concerned adolescent samples. Quality was generally moderate. The articles dealt with the relationship between facial morphology and the following TMJ disorders, assessed clinically or by MRI: disk displacement (n=20), osteoarthritis or osteoarthrosis (n=8), and temporomandibular disorder signs and symptoms (n=6). The different approaches featuring the various investigations and the presence of some potential methodologic biases complicated a summary of the findings. Most studies reported that some features related to the vertical dimension of the face may help distinguish patients with potential TMJ disk displacement or MRI-detected signs of osteoarthrosis from those without TMJ disorders.

The quality of the available studies is not adequate to provide an evidence base for the topic. Despite the heterogeneity of design and findings of the reviewed articles, it seems reasonable to suggest that skeletal class II profiles and hyperdivergent growth patterns are likely associated with an increased frequency of TMJ disk displacement and degenerative disorders.

**Occlusion**

Cimic et al318 evaluated the possible differences in centric slide values between different angle classes of occlusion. The study included 98 participants divided into 4 groups: angle class I, angle class II, subdivision 1, angle class II, subdivision 2 and angle class III. All recordings were obtained using an ultrasonographic jaw tracking device with 6 degrees of freedom. The distance between the maximum intercuspation (reference position) and the centric occlusion was recorded at the condylar level. Anteroposterior, superoinferior, and transversal distance of the centric slide were calculated for each participant, and the data were statistically analyzed (using analysis of variance and Newman-Keuls post hoc tests). No statistically significant differences were found in the anteroposterior and transversal distances of the centric slide between tested groups, whereas angle class II, subdivision 2 showed a smaller vertical amount of the centric slide than the angle class I and class II, subdivision 1. None of the 98 participants showed coincidence of the maximum intercuspidation with the centric occlusion should not be expected. Smaller extent of the vertical distance of the centric slide could be morphological and a functional expression characteristic of the angle class II, subdivision 2.

A major flaw in this study that makes the results questionable was that no manipulation or investigator guidance occurred during the recording of the centric occlusion. Every participant was trained to move the mandible to the back and close to the first tooth contact/contacts so that the position of the condyles at the centric occlusion could be measured. If the condyles are not verifiably fully seated in the condylar position, the magnitude of the centric slide cannot be accurately assessed.

Cimic et al319 also investigated the influence of an occlusal interference on the condylar position within the TMJ. This study included 10 completely dentate participants (apart from third molars) without signs and symptoms of TMD (mean age 26.0 ±3.7 years old) and without previous orthodontic therapy. The participants had angle class I relationship of the permanent first mandibular molar without reverse articulation/open occlusal relationship and without previous extensive restorative treatment.

Composite resin was added as an artificial occlusal interference on the lingual cusp of the lower left second premolar with a layer thickness of 1 mm and polymerized without application of adhesive (for easier removal of the composite resin). Subsequently, the condylar deviations...
were measured. The participants had to occlude, and the condylar position was recorded at the occlusal position defined by the contact with the artificial occlusal interference on the mandibular left second premolar. Using the corresponding computer program, the authors measured deviations of the recorded left and right condylar positions.

The average condylar linear deviation between the maximum intercuspal position and the position of the occlusion with artificial occlusal interference was 0.48 mm (±0.29; minimum, 0.17 mm; maximum, 1.19 mm). Within the limitations of this study, it can be concluded that the introduction of occlusal interferences leads to immediate changes of the condylar position in the occlusal position of maximum intercuspation. The inevitable superior condylar position at occlusion in the presence of artificial occlusal interference confirms the immediate lever creation in dental arches. Further research of the TMJ adaptation upon occurrence of occlusal interference is necessary, especially in patients with different types of temporomandibular disorders.

Manfredini and Poggio systematically reviewed published reports to evaluate the relationship between prosthetic rehabilitation and TMD and bruxism. No clinical trials of the reviewed topics were found, and a comprehensive review relying on the best available evidence was provided. Bruxism is not linearly related to TMDs, and both of these conditions are multifaceted. Based on the diminished causal role of dental occlusion, prosthetic rehabilitation cannot be recommended as a treatment for the 2 conditions. In theory, they may increase the demand for adaptation beyond the stomatognathic system’s tolerability. No evidence-based guidelines were available for the best strategy for managing prosthetic needs in patients with TMDs and/or bruxism.

This systematic review of publications revealed an absence of RCTs of the various topics concerning the relationship between TMD and bruxism and prosthodontics. Based on the best available evidence, prosthetic changes in dental occlusion are not yet acceptable as strategies for solving TMD symptoms or helping an individual stop bruxing. Clinicians should take care when performing irreversible occlusal changes in healthy individuals and in patients with TMD and/or bruxism.

**Orthognathic surgery**

Kuhlefelt et al studied the impact of forward bilateral sagittal split osteotomy (BSSO) on TMD. One of the reasons retrognathic patients seek treatment or dentists refer patients for orthognathic surgery is TMD. Bilateral sagittal split osteotomy is the standard treatment for the correction of a congenitally small and retrognathic mandible. Whether orthognathic surgery is itself a predictable treatment for patients whose primary reason for referral is TMD is a question that needs to be answered.

The question of predictability of TMD in patients with orthognathia has been one of the controversies in oral and maxillofacial surgery, and it is well known that TMD symptoms and clinical findings fluctuate over time. The symptoms can originate from the joint or from the surrounding musculoskeletal structures. Patients often experience pain, joint sounds, muscle tenderness, or deviations or restriction of movement of the mandible.

This study included adult patients with class II mandibular retrognathia. All patients were at least 18 years of age and were to undergo advancement of the mandible with the aid of standard BSSO at the Helsinki University Hospital’s Department of Oral and Maxillofacial Diseases during a period of 18 months. Patients who underwent any other preplanned surgical procedures of the mandible or maxilla during the first postoperative year were excluded. Patients with any other malocclusions or facial syndromes were also excluded, as were patients who had any other surgical procedures in the maxillomandibular region, either before BSSO or during the follow-up, except for patients with surgical complications after BSSO.

A total of 42 consecutive patients with retrognathia met the inclusion criteria, and all patients consented to participate in the study. Two patients did not appear at the 1-year follow-up, so their data were excluded, leaving the data of the 40 patients who completed the study for analysis. Twenty-six patients (65%) were female. The mean age of the study population was 36.9 years old (range, 22.2-59.4 years of age). The patients were generally healthy. Three patients were taking medication for hypothyreosis, 1 patient had migraine, and 1 was obese. Six patients (15%) were smokers. All 40 patients had mandibular retrognathia, 33 patients (82.5%) had an excessive vertical overlap, and 4 patients (10%) had a slight mandibular asymmetry. Four patients were seen to have a slight flattening of the condyle in the preoperative radiographic orthopantomogram, and the condyles appeared normal for the other 36 patients. Seventeen patients (42.5%) had a notation of TMD as one of the reasons for seeking treatment at the first appointment, and 12 patients (30%) had a history of an occlusal device for TMD.

Orthognathic treatment is lengthy and costly and can have complications. Its efficacy for improving TDM symptoms is still controversial. The outcome with regard to the alleviation of TMD symptoms is still unpredictable, and in light of our current knowledge, there is no sure way to predict the final result of TMD in an individual patient. Patients and referring colleagues should obtain appropriate information about this lack of certainty to reduce unrealistic expectations and thereby circumvent
patient dissatisfaction after treatment. Occlusion and TMD should be treated as 2 separate entities. Most patients are highly satisfied with orthognathic treatment, and the improvement of occlusion and facial esthetics is unquestionable. An urgent need exists for more studies that use a well-known TMD index with a well-defined follow-up time and a robust study design. TMD symptoms in individual patients fluctuate over time, and thus studies with multiple measuring points, better differentiation among TMD pathologies, and a longer follow-up time would improve our current understanding of TMD.

Miao et al clarified the correlation between pretreatment anterior disk displacement and mandibular stability after orthognathic and orthodontic treatment among patients with a skeletal class II malocclusion and without pretreatment condylar resorption. Thirty-seven patients were included (7 men, 30 women). The mean length of follow-up was 6.76 ± 3.06 years. Patients with condylar resorption before treatment were excluded. Magnetic resonance images and lateral cephalometric radiographs were made before treatment (T0), after treatment (T1), and at follow-up (T2).

The results showed the condyle moved posteroinferiorly after treatment and then moved anteriorly to a more concentric location during the long follow-up period. Condylar movement was found not to correlate with disk displacement. The degree of disk displacement before treatment did not correlate with the postsurgical mandibular positional change in either the sagittal or vertical direction. To conclude, the mandibular bilateral sagittal split ramus osteotomy was stable in the long-term after orthognathic and orthodontic treatment. In the absence of pretreatment condylar resorption, the degree of initial anterior disk displacement did not have a significant influence on the stability of mandibular advancement. Although the study did not show instability in the absence of pretreatment condylar resorption, it would be prudent to discuss the potential for future changes given the potential for structural changes in TMJs where the disk is anteriorly displaced.

Sleep-disordered breathing
Dental professionals are becoming an integral part of the multidisciplinary team of health care providers offering treatment for individuals with sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA). Results of the Sleep Apnea Cardiovascular Endpoints (SAVE) trial found that therapy with continuous positive airway pressure (CPAP) plus usual care, compared with usual care alone, did not prevent cardiovascular events in patients with moderate to severe OSA and established cardiovascular disease. Mandibular advancement devices (MAD) continue to provide an important alternative for those who are unwilling or unable to use CPAP. However, many barriers still exist for practitioners to produce a MAD with predictable outcomes. A method of titration and appliance design that gives a foreseeable result has not been identified. A report released by the Rand group this year found that up to $680 billion is lost each year across 5 Organization for Economic Co-operation and Development countries because of insufficient sleep. Given the large impact on work productivity and medical expenditures, dentists will increasingly be relied on to care for those with SDB.

Oral appliance therapy
No study has been published on the standardization of mandibular advancement splint (MAS). Therefore, without standardization, the probable outcomes of studies will be inconclusive and show wide variation.

One study set out to assess the effect of anatomic balance, which is the ratio of upper airway soft tissue volume to maxillomandibular enclosure volume, on MAS responders versus nonresponders. Patients with OSA having an apnea-hypopnea index (AHI) of >10 events/hour were selected for MAS therapy. Upper airway MRI was performed while participants were awake, both with and without the appliance in place. Images were processed for volumetric analysis of upper airway soft tissues (including tongue, soft palate, parapharyngeal fat pads, and lateral pharyngeal walls) and 3D cephalometry to determine the intramandibular space area and total maxilla-mandibular volume. Anatomic balance ratios were examined between treatment responders (AHI <10/hour and 50% reduction) and nonresponders. Sixty-nine patients underwent imaging and subsequent analysis and included 36 responders. Soft tissue volumes did not differ between MAS responders and nonresponders; however, nonresponders had increased soft tissue/intramandibular space areas compared with responders. The authors concluded that anatomic imbalance as determined by intramandibular space area was associated with poor MAS treatment response. The authors noted that changes in anatomic balance with mandibular advancement did not reflect treatment outcome as static imaging may not be sufficient to capture dynamic improvements in the upper airway function accurately.

A group from the Netherlands examined the effect of combining oral appliance therapy (OAT) with CPAP therapy as an alternate modality to CPAP alone. Such hybrid therapy may allow for reduced CPAP pressures and increased patient comfort, leading to increased patient compliance. Seven patients with moderate to severe OSA syndrome who tolerated their existing CPAP treatment at pressures of ≥10 cm H₂O were fitted with hybrid therapy. The mandible was advanced to 70% of C2/C21 and increased patient comfort, leading to increased patient compliance. Seven patients with moderate to severe OSA syndrome who tolerated their existing CPAP treatment at pressures of ≥10 cm H₂O were fitted with hybrid therapy. The mandible was advanced to 70% of the participant’s maximum protrusion, and CPAP pressure was set at 6 cm H₂O; pressure was increased as needed if the patients’ subjective complaints persisted. Polysomnography (PSG) was performed at 3 months;
patients also completed questionnaires at baseline and after 3 months of combination therapy to assess comfort, compliance, and satisfaction with treatment; excessive daytime sleepiness and quality of life (QOL). Four of the 7 participants reported hybrid therapy to be more comfortable and effective, preferring it over conventional CPAP alone. No differences were reported in baseline and follow-up scores in compliance, satisfaction, excessive daytime sleepiness, and QOL. No statistical differences were found in effectiveness between conventional CPAP and combination therapy (median AHI pretreatment, 64.6/hour; median AHI with hybrid, 1.5/hour; median AHI with CPAP, 2.4/hour). The authors concluded that combination therapy is possible in OSA syndrome, and RCTs are warranted to assess comfort and long-term compliance.

A systematic review and meta-regression analysis was performed to investigate the effectiveness of different amounts of mandibular advancement in reducing the AHI in patients with OSA; the existing publications do not provide evidence elucidating the most effective mandibular advancement. An electronic search included MEDLINE, Cochrane Database, Google Scholar Beta, ISI Web of Knowledge, Scopus, and LILACS to select RCTs examining the efficacy of MADs in decreasing AHI in adult sleep apnea patients. Inclusion criteria were a diagnosis of OSA, efficacy testing with PSG within a maximum of 12 months, and protrusion amount as reported as a percentage of maximum mandibular advancement. Thirteen RCTs performing advancements from 50% to 89% of maximum protrusion were analyzed. The authors concluded that AHI improvement was not proportional to the mandibular advancement increase; the success of the treatment is likely influenced by a combination of variables that warrant further study.

Another study sought to explore long-term adherence and clinical effects of OAT. Participants consisted of all sleep apnea patients treated at the University of Helsinki, Department of Dentistry between 2006 and 2013, with a total sample size of 1208 patients. After a 1-month follow-up appointment, questionnaires about oral appliance adherence, asthma symptoms, and general health were sent to all participants continuing OAT (N=811). The response rate was 37.4% (99 women, 204 men); the mean ±SD age was 58.7 ±10.3 years, and the mean body mass index (BMI) was 27.3 ±4.0 kg/m². During the average follow-up period of 3.3 years, no substantial variations in BMI were found. Forty-one participants discontinued OAT, for an adherence rate of 86%. Ninety-seven percent of patients used the appliance ≥4 hours per day, and the mean daily use was 7.2 ±1.1 hours per night. Asthma control scores improved, and the AHI decreased from 27 ±19 at baseline to 10 ±10 events/hour with OAT (P=.001). The authors concluded that after a 1-month trial period, long-term adherence to OAT was good and contributed to a significant reduction in AHI as well as improvement in respiratory and asthma symptoms.

A systematic review was performed to investigate the accuracy of a number of clinical and experimental tests for predicting oral appliance treatment outcomes in OSA. Prediction of OAT efficacy may be important for efficient disease management, as successful outcomes may not be solely based on AHI. A review of published reports was conducted, and 17 studies were selected for the review, and quality assessment of diagnostic accuracy studies was used. The predictive accuracy varied depending on the definitions of treatment success used as well as the type of index test. A multisensor catheter was used in the studies with the best predictive accuracy and lowest risk of bias and concerns of applicability. One remotely controlled mandibular positioner study demonstrated high accuracy but also a high risk of bias. The authors concluded that the available information on the validity of predictive index tests is very useful in clinical practice and allows for greater disease management efficiency.

A group from Japan investigated complications in oral appliance therapy for OSA syndrome that may prevent continuous use of these devices. Ninety participants being treated in a university hospital for OSA syndrome with OAT were mailed questionnaires to assess their progress; all patients had been treated for more than 1 year. Forty participants responded to the questionnaire, of whom only 18 patients were still wearing the appliance. The average time before discontinuing OAT was 9.6 months. The main reasons for stopping OAT were that it was bothersome to use and/or it did not effectively prevent sleep apnea. Comparison of complications between current oral appliance users and nonusers illustrated significant differences in “difficulty sleeping,” and a “stifling feeling.” Users reported better scores for sleep quality than nonusers. Those patients choosing to discontinue therapy did so because the device was “bothersome to use” and because it had “little or no effect.”

A prospective intervention study compared adherence and treatment effects with OAT in patients with 2 different types of OSA: those with mainly respiratory arousals (arousers) and those with oxygen desaturation (desaturaters) at PSG. Seventy-two “tired snorers” with normal home sleep study results were later diagnosed with OSA through PSG and accepted oral appliance therapy. The authors were offered evaluation with a follow-up PSG and questionnaires, including the Epworth Sleepiness Scale (ESS), general health (GH), satisfaction, and side effects. Sixty-six patients using OAT were designated arousers (n=33) or desaturaters (n=33). The 1-year adherence rate was 85% among the arousers versus 55% for the desaturaters. Thirty-six of the original
66 patients underwent follow-up PSG; the AHI was substantially reduced in 22 arousers from a median of 14 to 3 events/hour and in 14 desaturaters from 18 to 7 events per hour. The ESS and GH showed no significant improvements in either group; however, sleepy arousers significantly improved their ESS. Sex analysis showed a significant predominance of women classified as arousers. The authors concluded that OSA patients with mainly arousals at PSG exhibited higher adherence to OAT than those with desaturations. The authors suggest that “tired snorers” with a normal home sleep test result should be offered PSG and OAT if OSA is indeed diagnosed.

Another study explored the feasibility, efficacy, and mechanism of MADs in the treatment of persistent sleep apnea following surgery for OSA. Nineteen patients for whom uvulopalatopharyngoplasty (UPPP) or UPPP plus genioglossus advancement and hyoid myotomy failed were given a nonadjustable MAD for treatment. All participants had PSG at least 6 months after UPPP, with and without the appliance. Seventeen patients underwent CT examinations as well. With the MAD in place, the AHI decreased significantly from 41.2 ±13.1 events per hour to 10.1 ±5.6 events/hour in the responder group (11 of 19 [57.9%]). When sleep was induced through sedation, CTs were performed, and the responders exhibited significant enlargement in the cross-sectional area, anterior-posterior dimension, and lateral dimension of the velopharynx; velopharyngeal and glossopharyngeal collapsibility also decreased. The investigators concluded that a MAD can be an effective alternative treatment for patients with moderate to severe OSA for whom surgical intervention has failed.

The Predicting Therapeutic Outcome of Mandibular Advancement Device treatment in the OSA (PROMAD) study aimed at identifying predictive screening methods for treatment success with MADs, assessing upper airway evaluation methods with the following: awake nasendoscopy including the Müller maneuver; drug-induced sedation endoscopy to identify the level, degree, and pattern of upper airway collapse; and CT-based computational fluid dynamics to evaluate changes in upper airway volume and resistance. The prospective, single-center cohort study enrolled 100 consecutive patients with diagnosis of OSA for treatment with a custom-fabricated, titratable MAD. Primary endpoints were positive and negative predictive values of awake nasendoscopy including the Müller maneuver, drug-induced sedation endoscopy, and computational fluid dynamics with and without the appliance, toward reduction in AHI. Univariate and multivariate analyses were performed to determine which of the investigations and/or combinations thereof predict success. The authors predicted that the results would allow translation of the assessments into optimal OSA patient selection, leading to evidence-based decision making and targeted MAD therapy.

Another prospective single-center study investigated factors associated with long-term adherence to MAD therapy. All patients with OSA who had started MAD therapy in the previous year were prospectively contacted to evaluate long-term effectiveness and compliance. Adherence was based on continuation of treatment (yes/no). Predictors of long-term adherence were analyzed using an adjusted multivariate analysis. Median follow-up was 1002 days for 279 participants (mean 58 years of age; range, 50 to 64 years old). Sixty-three percent of patients were continuing appliance treatment with good efficacy, tolerability, and compliance. In adjusted multivariate analysis, significant predictors of continuing MAD therapy were ≥50% reduction in AHI and complete symptom resolution. In the 37% of individuals who stopped the appliance therapy, median treatment duration was 351 (174-752) days. The main reasons for discontinuing treatment were unsuccessful outcome (26.2%), discomfort (25.2%), and side effects (21.4%). The authors concluded that after 3 years of therapy, MAD was effective for two-thirds of patients who continued treatment, and short-term control of OSA was predictive of long-term treatment adherence.

A different group set out to assess the methodological quality of published systematic reviews and meta-analyses about the efficacy of oral appliances in the treatment of adult and pediatric SDB. Multiple electronic databases were searched for relevant research in any language from the beginning of each database through January 2016. Two reviewers independently selected and then evaluated the methodological quality of the studies, using the Assessment of Multiple Systematic Reviews measurement tool. Thirteen reviews of adult SDB were included: 2 systematic reviews and 11 systematic reviews with meta-analyses. Of these, 6 were high quality, and 7 were medium quality. Four reviews were included of pediatric SDB, 3 systematic reviews and 1 was a systematic review with meta-analysis. Three of these were high quality, and 1 was medium quality. Limitations of these studies included failing to reference excluded studies or describe reasons for exclusion, lack of applying valid criteria to assess the quality of included studies, lack of publication bias assessment, and lack of conflict of interest reporting. The authors concluded that overall systematic reviews with meta-analyses of OAT for adult and pediatric SDB were conducted with acceptable methodological quality. More primary studies are warranted of OAT for pediatric SDB, and that information can then be synthesized through further systematic reviews.

A randomized crossover study sought to determine how oral appliances alter AHI and 4 phenotypic traits of OSA (upper airway anatomy/collapsibility and muscle function, loop gain, and arousal threshold), and baseline...
predictors from which patients gain the greatest benefit from therapy. One possible adverse effect of statin therapy can be muscle problems. Participants (n=104) were recruited consecutively to undergo treatment with a custom-fabricated oral appliances. Muscular side effects included pain that was referred, spontaneous, or induced under palpation; and myofascial pain, mandibular rigidity and fatigue, and tension and sensitivity of the masticatory muscles. Side effects were collected by anamnesis (by verbal request and questionnaires), psychological status, and clinical assessment (manual muscle palpation in the masticatory and cervical muscle groups) at baseline and during MAD treatment. Of the total sample, 22.1% of participants exhibited muscular side effects with the oral appliance. In patients taking statins, 57.1% had muscular side effects compared with 16.7% of those not taking the medication (P<0.001). The authors concluded that treatment with statins could give rise to the appearance of undesirable side effects among patients with MADs for OSA.

Another systematic review assessed the effectiveness of different MADs in treating OSA -hypopnea syndrome (OSAHS) based on PSG measurements such as AHI and oxygen saturation and on changes in the upper airway and improvements in the most common symptoms, snoring and hypersomnolence. Adverse effects were also noted. An extensive search was performed in Medline, Scopus, and Cochrane Library databases for articles published over the previous 10 years; 22 articles met quality and inclusion criteria. Using MAD during sleep helps to prevent snoring and excessive daytime sleepiness, reduces the AHI significantly, and contributes to beneficial changes in the upper airway. Adjustable, custom-made appliances confer better results than fixed, prefabricated devices. Monobloc appliances contribute to more adverse events, which are generally mild and transient. The review concluded that MADs increase the area of the upper airway; and bring the tongue, soft palate, and hyoid bone forward and activate the masseter and submental muscles, preventing closure. These effects collectively lead to a reduction in AHI, increased oxygen saturation, and reduction of symptoms.

A prospective 1-year study was conducted to examine the effect of MAD treatment on arterial stiffness, glucose metabolism, and certain inflammatory markers as predictors of cardiometabolic risk in patients with mild to moderate OSA. Eighteen patients were prospectively enrolled in the study. The effects of MAD were examined at 3 months and 1 year following delivery of the device. Results of sleep studies, arterial stiffness assessment, and laboratory analyses were obtained at baseline and at follow-up. Data gathered at 1 year were compared with baseline values. A significant reduction in AHI was found.
at 1 year compared with that at baseline (22.9 ±5.9 versus 9.7 ±4.5 events/hour, respectively; P<.001). Mandibular advancement device treatment was also associated with decreased levels of fasting plasma glucose levels at 1 year and fasting plasma insulin values and homeostatic model assessment of insulin resistance. Pulse wave velocity was also substantially improved at 1 year, as were plasma levels of fibrinogen, an inflammatory marker. The authors concluded that treatment with MAD improved arterial stiffness, glucose metabolism, and insulin resistance in individuals with mild to moderate OSA after 1 year of therapy.

Another study set out to determine the utility of nasoendoscopy of the upper airway as a predictor of the efficacy of OAT in OSA.644 Sixty-one consecutive patients with moderate to severe OSA, as diagnosed using PSG, participated in the study. Nassoendoscopy was used to assess the velopharynx and oro-/hypopharynx in each participant while awake and in a supine position. A cross-sectional area, defined by anteroposterior and lateral diameters of the airway before and after mandibular advancement, was measured and expressed as dimensional changes and expansion after-to-before ratios. Measurements in responders to OAT were compared with those in OAT nonresponders. The expansion ratio for the cross-sectional area was greater in responders than in nonresponders in the velopharynx (2.9 [2.3-5.0] versus 1.7 [1.5-1.9] mm; P<.001) and in the oro/hypopharynx (3.4 [2.5-5.6] versus 2.4 [1.8-3.7 mm]; P<.05). Baseline AHI.s and cross-sectional area expansion ratios of the velopharynx were independent predictors of OAT outcome based on multivariate logistic regression analysis. The estimated area under the receiver operator characteristic curve was 0.87, and the cut-off value of the expansion ratio was 2.0. These results indicated that nasoendoscopy may have significant clinical utility in predicting the success of OAT.

A different trial studied patients with positional OSA (P-OSA) and compared the efficacy of MADs with nasal CPAP (nCPAP).645 At a single sleep center, from January 2008 to May 2014, male patients with moderate OSA were recruited and rigorously categorized as having P-OSA when their lateral-AHI-to-supine-AHI ratio was ≤0.5, their lateral sleep time was >60 minutes, and their lateral rapid eye movement (REM) sleep time was longer than 10 minutes. Treatment efficacy in P-OSA individuals treated with MAD (n=34) was compared with that in those with nCPAP (n=34) after matching for age, BMI, and baseline AHI. There were no significant differences in baseline or follow-up AHI between the 2 groups (the MAD group resulted in 20.6 ±3.9/hour versus 4.7 ±3.5/hour, respectively; the nCPAP group resulted in 21.3 ±1.7/hour versus 3.4 ±3.7/hour, respectively). Mandibular advancement devices decreased the AHI to the same extent as they did in nCPAP participants. The authors concluded that MAD treatment for patients with P-OSA may be a promising patient-tailored and first-line approach to OSA.

Another study evaluated the effect of individually adjusted custom-made mandibular advancement devices in the treatment of patients with moderate to severe OSA who were nonadherent to CPAP therapy.644 From 2007 to 2013, 116 patients with moderate (n=82) and severe (n=34) OSA who were nonadherent to CPAP were seen for management with an oral appliance at a specialist sleep clinic. Ten participants were lost to follow-up, leaving the final cohort with 106 individuals (71 men, 35 women; mean 57 years of age; range, 28-90 years). Nocturnal respiratory polygraphic recordings were performed at baseline and followed 12 months later, on average. Successful OAT was based on polygraphy at follow-up and divided into 3 groups: AHI<5; 5 ≤ AHI <10 and >50% reduction in baseline AHI; and >50% reduction in baseline AHI at follow-up. Treatment failure was defined as ≤50% reduction in baseline AHI at follow-up. The overall treatment success rate was 75%, with no significant differences between patients in the moderate groups and those in the severe groups (69% and 77%, respectively). The authors concluded that MAD therapy for patients nonadherent to CPAP is promising, especially for patients with severe OSA.

Tongue stabilization devices (TSDs) are a potential alternative to MAD therapy for patients with OSA. At a single multidisciplinary sleep center, a study was undertaken to document the outcomes of TSD treatment.644 Of 551 patients who were referred for oral appliance therapy, 76 individuals were prescribed a TSD; of particular concern were individuals for whom MAD therapy was contraindicated because of dental and or TMJ issues. Six patients were acclimated to TSD (8%); 22 were intolerant (29%); 26 were lost to follow-up (34%); and 6 discontinued use for other reasons (8%). Of the 16 participants (21%) who completed follow-up testing with PSG, the mean baseline AHI was reduced from 21.8 ±8.6 to 9.3 ±5.8 events/hour (P<.01) with a TSD in use. In 5 responders (7%), the device improved AHI from 14.2 ±2.9 to 2.1 ±1.3 events/hour (<.01). The authors concluded that the efficacy of the TSD was similar to that reported for MAD as long as the device was tolerated, especially in patients with mild OSA. The high percentage of treatment dropout and/or those lost to follow-up suggests the potential need for appliance redesign or modification to improve adherence to therapy.

**Pathophysiology and medical implications**

Patients with asthma have a higher incidence of OSA; the association between OSA and the exacerbation of severe asthma is unclear. This project sought to investigate the prevalence of OSA in a cross-sectional study of patients with asthma and to prospectively explore the
significance of the effect of OSA on severe asthma exacerbation. A total of 146 patients with asthma and 157 matched control participants were involved in the study. The patients with asthma were prospectively studied for 1 year, and exacerbation episodes were noted based on the patients' medical histories. Lung function and percentage of eosinophils in induced sputum samples were assessed, and frequencies of severe asthma attacks during the previous year were evaluated in the patients with asthma. The rates of OSA were 19.2% (28 of 146 asthmatic patients) and 9.6% (14 of 157 matched control patients; \( P=.016 \)). The frequency of severe asthma exacerbations was significantly higher among the patients with asthma and OSA compared than in those who did not have sleep apnea (\( P<.001 \)). The AHI correlated significantly with the number of severe asthma flare-ups (\( r=0.507; 95\% \) CI, 0.357-0.637; \( P<.001 \)). Logistic regression analyses determined that the AHI was significantly associated with the occurrence of severe asthma exacerbation (\( OR=1.322; 95\% \) CI, 1.148-1.523; \( P<.001 \)). The authors concluded that individuals with asthma had a high prevalence of OSA, which was an important factor associated with severe asthma exacerbation.

A retrospective cohort study set out to investigate the long-term risk of incident chronic kidney disease (CKD) events following sleep apnea diagnosis and compared the relative contributions of OSA, diabetes, and hypertension (HTN). Taiwan’s National Health Insurance Research Database provided information from 2000 to 2010. The cohorts were composed of patients \( \geq 20 \) years old with newly diagnosed OSA and matched controls without sleep apnea. The 2 groups were followed until the occurrence of CKD, death, or the end of 2010. A total of 8687 patients with OSA and 34 747 non-OSA controls were followed. A total of 157 new CKD events in patients with sleep apnea and 298 events in the matched non-OSA cohort were noted during a mean follow-up period of 3.9 years (incidence rates, 4.5 and 2.2/1000 person-years, respectively). The risk of CKD development was more elevated among patients with OSA than in the control group (adjusted \( HR=1.58; 95\% \) CI, 1.29-1.94). The contribution of OSA to the CKD hazard was similar to that of HTN (adjusted \( HR=1.17; 95\% \) CI, 0.68-2.01; \( P=.56 \)), whereas that of diabetes was significantly higher (adjusted \( HR=2.17; 95\% \) CI, 3.90; \( P=.01 \)). The authors concluded that OSA was associated with an increased risk of CKD incidence, similar to that of HTN.

A 2-center, open, prospective, case-control, parallel design study explored whether CPAP added to treatment with an antihypertensive agent had an impact on blood pressure (BP) levels. Obstructive sleep apnea is common in people with HTN, especially resistant HTN. Treatment with an antihypertensive medication alone is often insufficient to control HTN in patients with OSA. In the initial 6-week period, all patients (OSA-to-no OSA ratio of 2:1) began treatment with losartan, an angiotensin II receptor antagonist, 50 mg daily. In the second 6-week study of the group, the cohort was sex-stratified, open, randomized, and parallel design; all participants continued to receive losartan and were randomly assigned to either nightly CPAP as add-on therapy or no CPAP. Twenty-four-hour BP monitoring included measurement every 15 minutes during daytime hours and every 20 minutes during the night. Ninety-one patients with untreated HTN underwent a home sleep test; 55 had OSA, and 36 did not. Losartan significantly reduced systolic, diastolic, and mean arterial BP in both groups (changes without OSA were 12.6, 7.2, and 9.0 mm Hg, respectively, and 9.8, 5.7, and 6.1 mm Hg with OSA, respectively). Add-on CPAP therapy caused no significant changes in 24-hour BP values but did reduce nighttime systolic BP by 4.7 mm Hg. All 24-hour BP values were reduced substantially in the 13 patients with OSA who used CPAP \( \geq 4 \) hours/night. The authors concluded that losartan reduced BP in OSA but that the reductions were lower than in those without OSA. Add-on CPAP treatment led to no significant changes in 24-hour BP values, except in individuals using CPAP efficiently.

An observational study investigated the influence of SDB on weight loss in overweight/obese veterans participating in MOVE!, a nationally implemented behavioral weight management program administered by the National Veterans Health Administration health system. Participants had weight loss evaluated by SDB status from May 2008 to February 2012, with at least 2 MOVE! visits, and baseline weight and at least 1 follow-up weight (N=84 770). Sleep-disordered breathing was defined by the International Classification of Diseases, 9th revision, Clinical Modification codes. Primary outcome was weight change (pounds) from MOVE! enrollment to 6- and 12-month follow-up examinations. Weight change over time was modeled with repeated measures analyses. One-third of the study population (n=28 269) had a diagnosis of SDB. At baseline, participants with SDB weighed 29 lb (\( \equiv 13 \) kg) more than those without SDB (\( P<.001 \)). Participants attended 8 visits, on average. Weight loss patterns over time were statistically different between veterans with and those without SDB (\( P<.001 \)). Those participants with SDB lost less weight (~2.5 lb [\( \equiv 1.13 \) kg]) than those without SDB (~3.3 lb [\( \equiv 1.49 \) kg]; \( P=.001 \)) at 6 months. At 12 months, participants with SDB continued to lose weight, whereas veterans without SDB started to regain weight. The authors concluded that veterans with SDB had significantly less weight loss over time than those without SDB. Sleep-disordered breathing should be considered in the development and implementation of weight loss programs.
A cross-sectional analysis was performed of the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey from 2005 to 2010 to determine whether gastroesophageal reflux (GER) was significantly associated with OSA when simultaneously adjusted for the presence of potential confounding conditions and to quantify the magnitude of any existing association. Adults with a diagnosis of OSA or GER and potentially confounding conditions were identified. Univariate and multivariate logistic regression analyses were performed, and sensitivity analyses based on increasingly narrow diagnostic definitions were also computed. A significant, positive association between GER and OSA was observed, even after adjustments for age, sex, race/ethnicity, sinonasal and laryngopharyngeal obstructive and inflammatory disorders, obesity, asthma, and lung disorders. This positive association remained significant regardless of broad (OR=1.94; 95% CI, 1.07-3.54; P=.030) or narrow (OR=2.13; 95% CI, 1.17-3.88; P=.014) diagnostic criteria. The authors concluded that GER is independently associated with OSA, with double the odds of concurrent occurrence, even when controlling for potentially related conditions.

A meta-analysis of prospective cohort studies was conducted to elucidate the association between OSA and future risk of all-cause mortality. PubMed and EMBASE databases were searched for articles published through July 2015. Pooled HRs and corresponding 95% CIs were calculated to estimate the association between OSA and risk of all-cause mortality. Sources of heterogeneity were designated by subgroup and meta-regression analyses. Twelve prospective cohort studies including 34,382 participants were included in the meta-analysis. The pooled HR of all-cause mortality was 1.262 (95% CI, 1.09-1.43) with substantial heterogeneity. Subgroup analyses indicated that the pooled HRs of all-cause mortality in patients with mild, moderate, and severe OSA were 0.946 (95% CI, 0.81-1.08), 1.178 (95% CI, 0.97-1.38), and 1.601 (95% CI, 1.29-1.90), respectively. Obstructive sleep apnea severity may be contributing to the heterogeneity. Existing publication bias produced a minor contribution to effect size. The investigators concluded that severe, but not mild or moderate, OSA was significantly associated with increased risk of all-cause mortality.

Another study compared the head posture of patients with OSA having different levels of severity with that of controls. A total of 100 individuals participated in the study. Seventy-five participants underwent overnight PSG in a sleep laboratory and were classified as having mild, moderate, or severe OSA. Twenty-five participants with no sleep complaints were allocated to 1 group and served as controls. Cephalometric radiographs were obtained from all participants in natural head positions. Craniovertical, craniocervical, and cervicovertical angles were determined in each group. Data were analyzed using least significant difference. Significant differences were found between those with OSA and the control group, as well as among the different OSA groups. The authors concluded that head posture demonstrated significant differences in patients with OSA. Generally, the more severe the OSA, the more extended the natural head position as indicated by increases in the craniovertical angles. The cervical posture parameters may indicate the presence of OSA.

A different group explored the relationship between tooth loss and signs of OSA in a representative sample of the general US population. Data were gathered from 7305 men and women ≥25 years of age participating in the 2005 to 2008 National Health and Nutrition Examination Survey. Tooth loss, occlusal contacts, and prosthesis use were determined by dental examination. Four cardinal signs and symptoms were evaluated by questions based on American Academy of Sleep Medicine criteria. Adults with ≥2 signs and symptoms of OSA were classified as high risk of OSA. Prevalence ratios and 95% confidence limits (CL) from log binomial regression analyses estimated the strength of association between tooth loss and high risk for OSA after adjusting for demographic characteristics, BMI, use of dentures, and sleep duration. Prevalence of high risk for OSA was found to increase 2% for each additional lost tooth (PR=1.02; 95% CL, 1.01, 1.03) among adults 25 to 65 years of age. When tooth loss was modeled as an ordinal variable with 0 to 4 lost teeth as the referent category, the adjusted prevalence of high risk for OSA was as follows: 25% greater in those missing 5 to 8 teeth (PR=1.25; 95% CL, 1.07, 1.46), 36% greater in those missing 9-31 teeth (PR=1.36; 95% CL, 1.06, 1.73), and 61% greater in the edentulous (PR=1.61; 95% CL, 1.11, 2.33). The authors concluded that tooth loss may be an independent risk factor for OSA.

A review was performed to provide an overview of normal breathing physiology, as well as a discussion of pathophysiologic mechanisms that promote central sleep apnea (CSA) and the mechanisms that are specific to different manifestations of CSA. The transition from waking to sleeping is accompanied by many physiological changes which result in major alterations in respiratory control and may lead to sleep-related breathing disorders (SRBD). Central sleep apnea is a group of SRBDs characterized by recurrent episodes of airflow decrease or cessation as a result of a temporary reduction or absence of central respiratory drive. The prime hallmark of CSA conditions is the presence of ventilatory control instability; however, additional mechanisms play a role in one or more specific variants of CSA. Central sleep apnea may manifest itself during conditions of eucapnia/hypocapnia or chronic
hypercapnia, which is a useful clinical designation that lends understanding to the underlying pathophysiology and possible therapies.

Another group sought to determine whether treatment of OSA in patients with type 2 diabetes improves glycemic control. Participants were randomized to type 2 diabetes and no previous diagnosis of OSA, with a glycated hemoglobin level of 6.5% to 8.5%, and an oxygen desaturation index of 15 or more events per hour to CPAP therapy or usual care. A total of 416 participants met the entry criteria and were randomized. Of the 298 participants who met centrally adjudicated entry criteria, no differences between the study groups were noted for change in glycated hemoglobin. Moreover, there were no between-group differences when analyses were restricted to those with poorer baseline glycemic control, those with more severe OSA, or those who were adherent to treatment. A larger drop in diastolic BP occurred in the CPAP group than in the usual care group (−3.5 mm Hg versus −1.5 mm Hg, respectively; P=.07); this difference was significant in those who were adherent to CPAP therapy (−4.4 mm Hg versus −1.6 mm Hg, respectively; P=.02). There was a significant decrease in sleepiness in the CPAP group (P<.001), as well as improvements in vitality, mental health, and mental component summary scores. The authors concluded that positive airway pressure therapy had no effect on glycemic control in patients with relatively well-controlled type 2 diabetes and OSA.

A randomized trial assessed whether exercise training would decrease the severity of OSA and CSA in patients with coronary artery disease (CAD). Over-night fluid shift from the legs to the neck and lungs may contribute to the pathogenesis of OSA and CSA; exercise may decrease daytime fluid accumulation in the legs and, therefore, rostral fluid shift. Participants with CAD and OSA or CSA (AHI >15 events/hour) were randomized to 4 weeks of aerobic exercise training (n=17) or to a control group (n=17). Polysomnography and measurements of leg, thoracic, and neck fluid volumes and upper airway cross-sectional area before and after sleep were performed at baseline and follow-up. Apnea-hypopnea index decreased significantly more in the exercise group than in the controls (31.1 ±12.9-20.5 ±9.4 versus 28.1 ±13.5-27.0 ±15.1 events per hour; P=.047), in association with a larger reduction in the overnight change in leg fluid volume (579 ±222-466 ±163 versus 453 ±164-434 ±141 mL; P=.04) and by a significantly larger increase in the overnight change in the upper airway-cross-sectional area in the exercise group (P=.04). The investigators concluded that exercise training decreased sleep apnea severity through attenuation of overnight fluid shift and an increase in upper airway cross-sectional area in individuals with CAD and sleep apnea.

A prospective long-term observational study (Wisconsin Sleep Cohort study) attempted to characterize the prospective associations of OSA with future echocardiographic measures of adverse cardiac remodeling. Participants underwent overnight PSG followed by transthoracic ECG 18.0 ±3.7 years later. Obstructive sleep apnea was characterized by the AHI. Echocardiography was used to assess LV systolic and diastolic function and mass, left atrial volume and pressure, cardiac output, systemic vascular resistance, and right ventricular RV systolic function, size, and hemodynamics. Multivariate regression models estimated associations between log10(AHI+1) and future ECG findings. Secondary analysis examined oxygen desaturation indices and future ECG findings. At the outset, 601 participants were 47 ±8 years of age (47% female). After adjustment for age, sex, and BMI, baseline log10(AHI+1) was significantly associated with future LV ejection fraction and tricuspid annular plane systolic excursion (TAPSE) ≤15 mm. After further adjustment for cardiovascular risk factors, authors determined that participants with higher baseline log10(AHI+1) had lower future LV ejection fraction (β=−1.35 [±0.6 SE]/log10[AHI+1]; P=0.03) and higher odds of TAPSE ≤15 mm (OR=6.3/log10[AHI+1]; 95% CI, 1.3-30.5; P=.02). SaO2 desaturation indices were associated independently with LV mass, LV wall thickness, and RV area (all P<.03). The authors concluded that OSA is independently associated with decreasing LV systolic function and with reduced RV function. Echocardiography measurements of adverse cardiac remodeling are strongly associated with OSA but are confounded by obesity. Hypoxia may be a stimulus for cardiac hypertrophy in individuals with sleep apnea.

Another project examined longitudinal and cross-sectional associations of previously undiagnosed OSA, including OSA occurring in REM sleep, with HTN. The Men Androgens Inflammation Lifestyle Environment and Stress (MAILES) study is a longitudinal study of community-dwelling men in Adelaide, South Australia. Assessments at baseline (2002-2006) and follow-up (2007-2010) identified HTN (systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, or medication) and risk factors. From 2010 to 2011, of 837 men without a previous diagnosis of OSA underwent full in-home unattended PSG, and 739 participants recorded ≥30 minutes of REM. Hypertension at follow-up (along with OSA status) was defined as prevalent HTN. Recent-onset HTN was defined as HTN at follow-up (56 months mean follow-up [range, 48-74 months]) in men free of HTN at baseline. Severe REM OSA (AHI ≥30/hour) exhibited independent adjusted associations with prevalent (OR=2.40; 95% CI, 1.42-4.06), and recent onset HTN (OR=2.24; 95% CI, 1.04-4.81). Significant associations with non-REM AHI were not seen. In men with AHI less than 10, REM OSA (AHI) ≥20/hour was
significantly associated with prevalent HTN of 92.67 (range, 1.33-5.38) and the relationship with recent-onset HTN was positive but not statistically significant (2.32 [0.79-6.84]). Similar results were seen when analyses included only men with non-REM AHI<10. The authors concluded that HTN was associated with OSA during REM sleep in men with AHI<10. Rapid eye movement OSA may need consideration as an important clinical entity requiring treatment; further assessment and evidence is warranted.

A different study investigated the impact of sleep-disordered breathing on long-term outcomes in patients with acute coronary syndrome (ACS). Overnight cardiorespiratory monitoring was performed in 241 patients with ACS who were successfully treated with primary percutaneous coronary intervention between January 2005 and December 2008. The presence of SDB was defined as AHI ≥5 events per hour. The end point was incidence of major adverse cardiocerebrovascular events (MACE; a composite of all-cause death, recurrence of ACS, nonfatal stroke, and hospitalization for congestive heart failure). Participants were followed for a median of 5.6 years. Among the 241 patients who were enrolled, comorbidity of SDB with ACS was found in 126 patients (52.3%). The cumulative incidence of MACE was significantly higher in individuals with SDB than in those without (21.4% versus 7.8%, respectively; P=.006). Multivariate analysis revealed that the presence of SDB was a significant predictor of MACE (HR=2.28; 95% CI, 1.06-4.92; P=.035). The authors concluded that the presence of SDB among patients with ACS following primary percutaneous coronary intervention was associated with an elevated incidence of major adverse cardiocerebrovascular events during long-term follow-up.

A historical observational study sought to determine whether obesity increases the effect of nocturnal hypoxemia on the incidence of cardiovascular events in adults with suspected OSA. All adults with suspected OSA who underwent PSG at a large academic hospital between 1994 and 2010 were linked to provincial health administrative data to ascertain a composite cardiovas-cular outcome (hospital admission because of heart failure, myocardial infarction, stroke or revascularization procedures). Using a competing-risk model and controlling for confounding variables, authors compared hazards among 4 groups: (1) obese (BMI ≥30 kg/m²) with oxygen desaturation (>9 minutes of sleep spent with SaO₂<90%); (2) obese without desaturation; (3) non-obese with desaturation; and (4) nonobese without desaturation. Interaction was measured using the relative excess risk due to interaction (RERI). A total of 10 149 patients were followed, with 17%, 25%, 8%, and 50% in groups 1 through 4, respectively. Over a median of 7.8 years, 896 first cardiovascular events (8.8%) occurred. Group 1 was associated with the highest hazard compared with the others, using group 4 as a reference (group 1 HR=1.84; 95% CI, 1.46-2.32; group 2 HR=1.59; 95% CI, 1.29-1.95; group 3 HR=1.51; 95% CI, 1.15-1.98). The RERI was −0.25 (95% CI, −0.78 to 0.27), indicating no interaction. The authors concluded that, in adults with suspected OSA, the greatest cardiovascular risk was found in obese patients with nocturnal oxygen desaturation; however, the effect of these 2 factors together does not exceed the effect of each factor considered individually.

Another group evaluated the effect of an employer-mandated OSA program on the risk of serious preventable truck crashes. Data were taken from the first large-scale, employer-mandated program to screen, diagnose, and monitor OSA treatment adherence in the US trucking industry. A retrospective analysis of cohorts was compiled: PSG-diagnosed operators (OSA positive n=1613; OSA negative n=403) were matched to control drivers unlikely to have OSA (n=2016) on 2 factors affecting crash risk, experience-at-hire, and length of job tenure. Tenure was matched on the date of each diagnosed driver’s PSG. Auto-adjusting positive airway pressure therapy was provided to all OSA-positive employees. Treatment adherence was objectively monitored. Individuals were grouped by treatment adherence: full adherence (n=682), partial adherence (n=571), or no adherence (n=360). Preventable Department of Transportation reportable crashes per 100 000 miles were compared across study subgroups; robustness was assessed. After the matching date, non-adherent individuals had a preventable Department of Transportation reportable crash rate that was 5-fold greater (incidence rate ratio=4.97; 95% CI, 2.09-20.63) than that of matched controls (0.070 versus 0.014, respectively, per 100 000 miles). The crash rate of full-adherence cases was statistically similar to controls (incidence rate ratio=1.02; 95% CI, 0.48-2.04; 0.014 per 100 000 miles). The investigators concluded that non-treatment-adherent OSA-positive truck drivers had a 5-fold greater risk of serious preventable crashes but were discharged or quit rapidly, being retained only 1/3 as long as other participants. The mandated program removed high-risk non-treatment-adherent drivers and retained adherent drivers at the study company. The authors noted that current regulations allow non-adherent OSA cases to drive at another firm by keeping their diagnosis private.

A meta-analysis was performed to accurately determine the prevalence of OSA in patients with epilepsy and to evaluate the efficacy of seizure control after treating OSA. Articles were selected from MEDLINE and Embase, and data were extracted independently by 2 authors. The variables were calculated using the DerSimonian and Laird random effects model and odds ratio. The prevalence of mild to severe OSA in patients with
epilepsy was found to be 33.4% (95% CI, 20.8-46.1%), and patients with epilepsy were more susceptible to OSA than healthy control participants (OR=2.36; 95% CI, 1.33-4.18). Men were more likely than women to have OSA (OR=3.00; 95% CI, 2.25-3.99). The analysis also indicated that the prevalence of OSA in individuals with refractory epilepsy is not higher than the prevalence of OSA in patients with epilepsy overall (17.5% versus 33.4%, respectively). Obstructive sleep apnea prevalence was not significantly different for different seizure types or in the number of antiepileptic drugs. Patients who had been treated with CPAP were shown to have better seizure control than those who were untreated (OR=5.26; 95% CI, 2.04-13.5). The authors concluded that the prevalence of OSA in patients with epilepsy was higher than in the general population. Treatment of CPAP may result in a reduction of seizures.

Another study hypothesized that OSA was associated with low-density lipoprotein-cholesterol (LDL-C) variability, which may be a predictor of adverse cardiac events. A cohort of 190 patients with CAD were prospectively recruited for PSG. Statin therapy was prescribed upon discharge for 186 patients. Serum LDL-C levels were measured every 3 to 6 months. Severity of OSA (AHI) was correlated with visit-to-visit LDL-C variability (on the basis of variation independent of mean [VIM]) in outpatient clinic. The mean AHI was 21.9 ±18.9. Using AHI cut offs of 5-14.9, 15-29.9, and ≥30, the prevalence of mild, moderate, and severe OSA was 26.3, 18.9, and 27.4%, respectively. After 53.2 ±25.3 months, LDL-C was recorded over 8.1 ±4.2 laboratory draws. The VIM values positively correlated with AHI (Pearson r=0.183, P=.016) but not with BMI, baseline, and mean follow-up LDL-C levels, and number of LDL-C measurements. In multiple linear regression analysis, AHI remained an independent predictor of VIM after adjusting for type 2 diabetes and hyperlipidemia. A 10-unit increase in AHI led to a 3.8% increase in VIM (95% CI, 0.1-7.4%; P=.044). The authors claimed that this was the first study to demonstrate the independent correlation between OSA severity and visit-to-visit LDL-C variability.

A systematic review and meta-analysis was conducted to explore the relationship between OSA and work accidents. The nearly 2-fold increased odds of work accidents in participants with OSA calls for workplace screening in selected safety-sensitive occupations.

A systematic review of international publications was performed to evaluate the role of the epiglottis in snoring and OSA and to explore possible treatment options. Databases included PubMed, Scopus, Embase, Google Scholar, Book Citation Index-Science, CINAHL, Conference Proceedings Citation Index-Science, Cochrane Collaboration Databases, and Web of Science. Searches were performed from the first year of each database through March 5, 2015. Fourteen studies of the prevalence of epiglottal collapse in OSA were reviewed. Most studies involved drug-induced sleep endoscopy (drug-induced sedation endoscopy) studies that indirectly reported findings concerning epiglottal collapse. The data suggested that the prevalence of epiglottal collapse in OSA was higher than previously reported and that the epiglottis is implicated in 12% of individuals who snore, with a higher pitch than palatal snoring. Surgery, CPAP, and positional therapy were considered treatment options for epiglottal collapse. Lateral position of the head may diminish the frequency of epiglottal collapse. With regard to CPAP, reports suggest it may accentuate collapse of the epiglottis. Surgery may help decrease snoring in some patients with a lax epiglottis and improve OSA in patients undergoing multilevel surgery. The authors concluded that knowledge regarding the role of the epiglottis in adult OSA is limited. The prevalence seems to be greater than previously reported, and further research is warranted to understand its role in OSA and optimal treatment options.

Another study set out to evaluate how regional factors, oropharyngeal crowding secondary to fat deposition, and maxillomandibular encroachment impact the severity of OSA. A total of 703 Japanese men were enrolled and were divided into obese (BMI ≥30 kg/m²; n=158) and nonobese (BMI <30 kg/m²; n=545) groups. Lateral cephalometric analysis was used to measure tongue size (TG), lower face cage (LFC), and TG/LFC ratio (that is, oropharyngeal crowding) to evaluate the state of upper airway (upper airway) crowding. Correlations among these cephalometric measurements and BMI, age, and AHI were examined. In obese individuals, the TG-to-LFC ratio, BMI, and TG all positively correlated with AHI; in nonobese participants, age, BMI, and TG-to-LFC ratio significantly correlated with AHI. Stepwise multiple linear regression analysis revealed that the variables associated with AHI differed between the 2 groups, although BMI and TG-to-LFC ratio were significantly associated with AHI in both groups. Specifically, the contribution of TG/LFC to AHI was larger than that
of BMI in the obese cohort. The authors concluded that oropharyngeal crowding is a local anatomic factor that independently relates to OSA severity in both obese and nonobese patients. The more crowded the upper airway, the more severe the OSA.

Another study sought to determine whether arousal intensity was mediated by the strength of the preceding respiratory stimulus and to examine other factors mediating arousal intensity and its role in post-arousal ventilatory and pharyngeal muscle responses.367 Seventy-one adult participants (17 controls; 54 OSA patients) underwent PSG plus genioglossus and tensor palatini EMG, a nasal mask and pneumotachograph, and an epiglottic pressure sensor. Transient reductions in CPAP were delivered during sleep to induce respiration-related arousals. Intensity of arousals was measured using a validated 10-point scale. Average arousal intensity was not related to the magnitude of the preceding respiratory stimuli but was positively associated with arousal duration, time to arousal, rate of change in epiglottic pressure and negatively with BMI (R²=0.10, P≤.006). High-intensity (>5) arousals led to greater ventilatory responses than low-intensity (≤5) arousals (10.9 [6.8-14.5] versus 4.7-12.9) L/min; P=.036) and greater increases in tensor palatini EMG (10 [3-17] versus 6 [2-11])%max; P=.031), with less pronounced increases in genioglossus EMG. The authors concluded that average arousal intensity is independent of the preceding respiratory stimulus, which is consistent with arousal intensity being a distinct trait. Respiratory and pharyngeal control muscle responses elevated with arousal intensity. Therefore, patients with higher arousal intensities may be more prone to respiratory control instability. The authors claim these results are important for OSA pathogenesis.

Another project focused on the effects of OSA severity, sex, and race on oropharyngeal airway dimensions.367 Forty patients with mild to moderate OSA (46.9 ±9 years of age; BMI, 30.4 ±5.4 kg/m²; AHI, 32.8 ±22.5; 28 men) and 54 control participants (47 ±9 years of age; BMI, 24.7 ±3.8 kg/m²; 32 men) underwent a study using a 3-T MRI scanner to collect 2 high-resolution, T-weighted image series. White, Asian, African-American, and other ethnic designations constituted the cohort participants. Both image series were realigned and averaged, and reoriented to a common space. Epiglottis cross-sectional area and oropharyngeal airway length (OPAL) were measured, normalized for participant height, and compared between sex and disease severity levels in OSA patients and controls. Significantly decreased epiglottis cross-sectional area appeared only in severe OSA versus controls (P=.009). Oropharyngeal airway length increased significantly with OSA severity compared with controls (mild, P=.027; moderate, P<.001; severe, P<.001). Men with OSA demonstrated increased cross-sectional area and larger OPAL than OSA women, which may underlie the increased proportion of affected men with higher AHI scores. No significant differences were found between cross-sectional area and OPAL dimensions for male and female controls, suggesting that airway morphology may not be the sole contributor for airway collapse. No ethnic differences appeared for cross-sectional area or OPAL dimensions. The authors concluded that sex-based reductions in epiglottis cross-sectional area and increased OPAL in patients with OSA may enhance airway-collapse vulnerability, more so with greater disease severity, and partially underlie sex susceptibility to OSA.

A separate study investigated whether local and systemic inflammatory biomarkers are related in patients with OSA; an uncontrolled extension to the study assessed the response to effective treatment.368 Eighty-nine individuals with OSA (AHI ≥5 events/hour), 28 snorers, and 26 healthy controls participated. Pharyngeal lavage (PHAL) and plasma samples were collected at baseline and after a 1-year follow-up. Inflammatory cells were evaluated by flow cytometry; IL-6, IL-8, and TNF-α levels were evaluated by immunoassay. In PHAL, CD4+, IL-6, and IL-8 levels were elevated in OSA patients compared with those in snorers or controls (P<.05). The AHI correlated with CD4+, IL-6, and IL-8 in PHAL (all P<.05). No differences were found in the inflammatory biomarkers in plasma among the study groups, and no relationship between plasma and PHAL biomarkers were found. After 1 year of treatment with CPAP, biomarkers decreased significantly in PHAL but not in plasma. The authors concluded that increased levels of inflammatory biomarkers were detected in patients with OSA and decreased with effective treatment. No simultaneous increase in plasma inflammatory biomarkers was found.

Sleep bruxism and temporomandibular disorders
One group investigated whether the presence of both nasal septal deviation (NSD) and habitual prone sleeping posture (HPSP) predisposes to TMD.369 Two hundred participants were divided into 4 groups: group I consisted of NSD−, HPSP−/control group; group II consisted of NSD+, HPSP−; group III consisted of NSD−, HPSP+; and group IV consisted of NSD+, HPSP+. All patients were examined according to research diagnostic criteria to determine the presence of TMD. Group IV had the largest value for TMD incidence (44%). The authors found that the presence of both NSD and HPSP increased the incidence of TMD in group IV compared with that in the controls (P<.001). Also, group IV demonstrated significantly higher values than group II (P=.012) and group III (P=.039). For group III (NSD−, HPSP+), incidence of TMD was determined to be higher than that in the control group (P=.009). A statistically higher value of presence of TMD was determined in group II (NSD+, HPSP−) than in the control group.
(P=.029). The incidence of TMD was significantly higher in women than in men (P=.020). The authors concluded that, in individuals with a unilateral obstructive nasal septal deviation and a habit of sleeping in prone position, awareness for potential TMD is warranted.

Another study sought to assess the prevalence and perceived need for treatment of TMD pain and its association with socioeconomic factors and sex in adolescents in Xi’an Shaanxi Province, PR China, and compared the prevalence and association with sex of TMD pain in Xi’an with an age-matched Swedish population. Chinese teenagers 15 to 19 years of age in Xi’an (n=5524) were surveyed using a questionnaire with 2-stage stratified sampling and the school as the sampling unit; they included second year students at selected high schools. An age-matched Swedish population (n=17 015) was surveyed using the same diagnostic criteria for TMD pain as that used in the Chinese cohort. Temporomandibular dysfunction pain occurred in 14.8% (n=871) of the Chinese sample and 5.1% (n=871) of the Swedish group (P<.001). Women had significantly more TMD pain than men in both the Chinese (P<.05) and the Swedish (P<.001) samples. Pain from TMD increased with age in the Chinese population. Of the Chinese teenagers with TMD pain, 47% reported that they felt the need for treatment. Rural schools, low levels of parental education, poverty, living outside the home, poor general and oral health, and dissatisfaction with teeth all demonstrated significant positive correlations with TMD pain. Prevalence of TMD pain in Chinese adolescents was significantly higher than in the Swedish sample.

No definitive associations or causal relationships have been established between OSAH and sleep bruxism (SB). A sleep laboratory study investigated the associations between specific breathing and jaw muscle events. Polysomnography and audio-video data from 59 patients with concomitant history of OSAH and SB were analyzed. Masseteric bursts after sleep onset were scored and placed into 3 categories: (1) sleep rhythmic masticatory muscle activity with SB (RMMA/SB); (2) sleep oromotor activity other than RMMA/SB (sleep-OMA); and (3) wake oromotor activity after sleep onset (wake-OMA). Spearman rank correlation coefficient analyses were performed. Dependent variables were the number of RMMA/SB episodes, RMMA/SB bursts, sleep-OMA, and wake-OMA. Independent variables included AHI, arousal index (AI), BMI, sex, and age. All individuals had a history of both SB and OSAH; however, PSG results confirmed that these conditions were concomitant in only 50.8% of participants. Moderate correlations were found in the following combinations (P<.05): RMMA/SB episode with AI; RMMA/SB burst with AI and age; sleep-OMA burst with AHI; and wake-OMA burst with BMI. The authors reported that the results suggested that, first, sleep arousals in patients with both SB and OSAH are not strongly associated with onset of RMMA/SB and that, second, apnea-hypopnea events appear to be related to higher occurrence of other types of sleep oromotor activity and not SB activity. The authors concluded that OSAH activity and SB genesis during sleep are probably influenced by different mechanisms.

A systematic review sought to answer the focused question, “In adults, is there any association between SB and alcohol, caffeine, tobacco, or drug abuse?” Reviewed studies included those in which the investigators assessed SB diagnosis by using questionnaires, clinical assessment, or PSG and evaluated the association with alcohol, caffeine, tobacco, or illicit drug use. The authors graded SB as possible, probable, or definitive. Databases included Latin American and Caribbean Health Sciences Literature, PsycINFO, PubMed, Science Direct, Web of Science, Google Scholar, and ProQuest. The methodological quality of the included studies was assessed using the Meta-Analysis of Statistics Assessment and Review Instrument. Of 818 studies, 7 were selected for inclusion in which sample sizes ranged from 51 through 10 229. Sleep bruxism was highly associated with alcohol and tobacco use. In 1 study, the investigators noted a positive and weak association for heavy coffee drinkers. The odds for SB appear to increase nearly twice for those who consumed alcohol, almost 1.5 times for those who consumed more than 8 cups of coffee per day, and more than 2 times for those who were current smokers. Association between 3,4-methylenedioxy-methamphetamine (MDMA, aka, “ecstasy” or “E”) abuse and SB lacked sufficient evidence. The review concluded that, on the basis of limited evidence, SB was associated positively with alcohol, caffeine, and tobacco. The association between the studied drugs could not be discredited. However, stronger evidence based studies are warranted with greater methodological rigor.

Another project set out, first, to revisit the prevalence and characteristics of SB in a large cross-sectional survey and assess familial aggregation of SB; second, to assess comorbidity such as pain and insomnia; and third (3) to compare survey data in a subset of individuals with SB diagnosed using PSG research criteria. A sample of 6357 individuals from the general public in Quebec, Canada, was surveyed online to assess the prevalence of SB, comorbidities, and familial aggregation. Data for familial aggregation were compared with 111 participants diagnosed with SB using PSG. Regularly occurring SB was reported by 8.6% of the general population and decreased with age, without any sex differences. Sleep bruxism awareness is concomitant with complaints of difficulties maintaining sleep in 47.6% of the individuals. One-third of SB-positive probands reported pain. A 2.5 risk ratio (RR) of having a first-degree family member with SB was found in SB-positive probands. The risk of
reporting SB in first-degree family ranged from 1.4 to 2.9 with elevating severity of reported SB. Polysomnography data demonstrated that 37% of SB participants had at least 1 first-degree family member with reported SB with a relative RR of 4.625. The authors concluded that the study results support the heritability of SB tooth grinding and that sleep quality and pain are concomitant in a significant number of SB participants.

A different study sought to characterize self-reported sleep quality in individuals with TMD and to compare their results with those of healthy controls. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality in a convenience sample of 609 individuals with TMD and 88 controls. The RDC/TMD Axis I diagnostic nomenclature was used, but Axis I diagnoses are based on the consensus of 2 reliable criterion examiners and not the RDC/TMD algorithms. The PSQI scores for individuals with TMD were calculated also for the RDC/TMD Axis II measurements assessing chronic pain and disability, depression, and nonspecific physical symptoms. The PSQI scores of the patients with TMD were compared with those from controls. Individuals with TMD with 1-5 TMD diagnoses (n=609) had a mean PSQI score of 7.0 (95% CI, 6.7-7.4). In comparison, the mean score was 5.2 (95% CI, 4.6-5.9) for controls. For the subset of individuals with TMD with pain-free diagnoses (n=113), the PSQI score was similar to that of controls with 5.1 (95% CI, 4.5-5.6), whereas it was significantly different for individuals with pain-related diagnoses 7.5 (95% CI, 6.6-8.3; n=87). Although the number of TMD diagnoses and participant age had some bearing on sleep quality, psychosocial status, and pain-related impairment assessed with RDC/TMD Axis II measurements had the strongest association with sleep quality, in particular, dysfunctional chronic pain. The authors concluded that sleep quality is impaired in TMD patients with pain-related diagnoses and even more so in those with dysfunctional pain. This relationship suggests that sleep quality should be assessed in patients with TMD pain, especially in those with substantial Axis II involvement.

**IMPLANT DENTISTRY**

The scientific studies related to implant dentistry continued to grow rapidly in 2016. Reviews of implant studies are included in Periodontology and Prosthodontics. Some areas of interest are peri-implantitis, splinting versus nonsplinting, internal versus external connections, abutment materials, and immediate versus delayed loading.

Nobre et al. evaluated the 5-year outcome of implants placed in diabetic patients with or without cardiovascular diseases. Seventy patients were divided into 2 groups of 38 patients with cardiovascular disease (CVD) and 32 without CVD. Only 10% of patients were lost to follow-up, and the respective prosthetic survival rates at 5 years for the CVD patients and the others were 100% and 97.4%, respectively, without statistically significant differences. Implant survival rates were 86.7% in the CVD group versus 93.8% in the noncardiovascular group. These differences were not significantly different. Marginal bone loss at 5 years was 1.52 mm in the CVD group and 1.54 mm in the nondiseased group. The authors concluded that treating patients with diabetes with or without cardiovascular diseases can provide acceptable results without influence from the cardiovascular aspect.

Park et al. used a retrospective OHRQoL questionnaire with 71 patients. Thirty-five patients had received single-tooth implant restorations, whereas 36 patients were restored with a 3-unit fixed partial denture. Both of the procedures significantly improved the OHRQoL scores, but neither approach was better than the other.

Derks et al. have evaluated the prevalence of peri-implantitis from a study of the effectiveness of implant therapy in a large population data base. At 9 years, 427 patients presented with baseline radiographs and were clinically examined. Twenty-three percent of these patients presented with healthy peri-implant mucosa, whereas 32% had peri-implant mucositis (bleeding on probing and no bone loss). Peri-implantitis was diagnosed with bleeding on probing and more than 0.5-mm bone loss in 45% of patients. With regard to the severity of the bone loss, 26.9% of patients had more than 1 mm of bone loss, 14.5% more than 2 mm, 10.1% more than 3 mm, and 5.9% more than 4 mm.

Gherlon et al. attempted to compare the usability of digital versus conventional impressions for all-on-4 restorations in a clinical setting. Thirty prostheses in 30 patients were fabricated and divided into 2 groups: the control group with pick-up impression copings and a polyether impression and the test group with a digital impression using the Trios system. The authors used digital radiographs at the time of placement to evaluate discrepancies between the bar and the implants and found only 1 prosthetic bar to be inaccurate in the control group and none in the test group. However, the digital impression group proved more efficient than the conventional one when treatment times were compared. Bone loss and other variables did not show differences. This study demonstrates that a digital technique can be used with success and better time efficiency than a conventional impression technique for all-on-4 implant-supported restorations.

Ma et al. evaluated the 10-year prosthetic outcomes of 40 edentulous patients with maxillary overdentures supported by 3 implants in splinted versus nonsplinted modes. The overdenture nonsplinted attachments were ball attachments. Twenty-three of the original 40 patients were available for recall. No significant differences could
be found between the 2 groups in terms of success and maintenance.

Esposito et al\textsuperscript{139} compared the outcome at 5 years of a nonplatform switching external connection and a platform switched internal connection with implants of the same brand (EZ Plus; MegaGen Implant). The study included 120 patients divided into 2 equal groups with 96 implants with external connections and 107 with internal connections. No differences could be found for any of the variables tested: implant failures, prosthetic complications, or marginal bone level at the end of the study period. Marginal bone levels for both implant types were 1.13 mm for the external connection and 1.21 mm for the internal connection without statistical significance.

Zygogiannis et al\textsuperscript{380} reviewed 14 studies with a mean follow-up of 3 years and relating to the outcome of immediately loaded implant-supported overdentures opposed by complete dentures. Because of variations in clinical protocols and the reported outcomes of implant survivals and prosthetic complications, it was difficult to find differences between procedures, and the authors mentioned that “immediate loading protocols seem to be a viable alternative to conventional loading.”

Monje et al\textsuperscript{120} performed a meta-analysis to evaluate the influence of peri-implant maintenance therapy on the prevention of peri-implant diseases. The authors selected 13 clinical trials specifically performed to assess this issue. The authors found significantly less peri-implant mucositis and peri-implantitis on patients with peri-implant maintenance therapy at both implant and patient levels. Note that a history of periodontal disease increases the levels of peri-implant mucositis and peri-implantitis.

Moraschini et al\textsuperscript{1310} reviewed 5 studies with a mean of 30 months of follow-up and comparing immediate versus conventionally loaded single implants in the posterior mandible and could not find any statistically significant differences for all outcome variables. Their review shows that immediate loading protocols may be implemented with success in the posterior mandible. Readers of this review should understand that the RCTs in this review were conducted under ideal conditions in highly controlled settings. The findings correlate well with those of a previous consensus report by Galluci et al.\textsuperscript{382}

An example of a different type of study is that of Derks et al.\textsuperscript{377} This study evaluated the large-scale implementation of procedures in order to observe of what happens in daily practice.

Moraschini et al\textsuperscript{1310} evaluated 15 articles pertaining to the influence of smoking on marginal bone levels. The authors found that smokers had significantly more marginal bone loss than nonsmokers and that, in smokers, implants in the maxilla demonstrated more bone loss.

Vechiato-Filho et al\textsuperscript{385} evaluated 6 clinical trials to compare the 5-year success rate of zirconia abutments to that of Ti abutments. The respective success rates showed no significant differences in these trials. The authors proposed that the use of zirconia abutments in posterior areas should be implemented with caution until longer-term studies are provided.

### ORAL MEDICINE AND ORAL AND MAXILLOFACIAL SURGERY

The following aspects from the field of oral medicine and oral surgery with implications for prosthodontists have been identified in the review of the pertinent published studies of 2016: the interrelationship between prosthodontic treatment (complete removable, partial removable, and fixed prosthodontics) and oral mucosal health and the nutritional status of geriatric patients; implant dentistry and oral surgery in patients receiving anti-resorptive drugs (such as, BPs and denosumab); and the clinical application of platelet-rich fibrin (PRF).

Oral mucosal alterations are a common problem for patients with dentures. The prevalence of inflammatory papillary hyperplasia and that of denture stomatitis were examined in a systematic review by Gual Vaqués et al,\textsuperscript{384} who analyzed 190 articles published between 2005 and 2015, of which 16 original papers met inclusion criteria. The authors reported that denture stomatitis affected approximately 30% of the patients and was associated with long-term denture use and poor oral hygiene. Inflammatory papillary hyperplasia can be expected in approximately 5% of the patients treated with removable dentures and is extremely rare in the absence of dentures.

Denture stomatitis is often associated with Candida colonization.\textsuperscript{385,386} Candida-related denture stomatitis may be promoted by a low saliva pH-value and an increased carbohydrate intake as revealed by a Spanish group of researchers.\textsuperscript{385} In the cross-sectional study by Matori et al,\textsuperscript{385} 84 patients were questioned and examined clinically with regard to the quality of their prosthodontic treatment (retention, stability, occlusion, hygiene, wear), their mucosal health status, their salivary pH, and the presence of oral yeasts. Most of the examined prostheses were in a “good” state with respect to stability, integrity, and retention. Candida spp. was found on 85% on the dentures. Damage to the denture base, frequent (daily/weekly) sugar consumption, and low salivary pH were independently associated with Candida colonization. Interestingly, these findings seemed to be limited to patients with dentures of acrylic resin, whereas orthodontic appliances in young, healthy patients could not be identified to act as Candida carriers in a study by Yitschaky et al.\textsuperscript{387}

Yarborough et al\textsuperscript{386} conducted a systematic review to identify effective treatment modalities for denture
stomatitis. Of the 2360 primarily identified articles, only 67 qualified for final review. Although no gold standard for the treatment of denture stomatitis was suggested, the authors concluded that the following 4 measures proved to be effective: topical or systemic use of antifungal agents (that is, azoles, nystatin, amphotericin B), hard or resilient reline of the denture base, improvement of oral and denture hygiene (also with the use of alternative agents, such as propolis, pomegranate, and garlic extract), and laser treatment of the affected mucosal areas. Interestingly, no differences in clinical effectiveness between antifungal agents and alternative agents was found upon topical application in comparative studies (5 of 67 studies). However, another systematic review examining the application of aloe vera extracts in the treatment of denture stomatitis and other oral mucosal diseases concluded that its clinical effectiveness cannot be evaluated at the present time because of a lack of RCTs in this field.388

As suggested in studies conducted previously, the importance of high-quality prosthodontic treatment for the nutrition and improvement of the general health of geriatric patients has been confirmed in several studies. Aneja et al389 showed in a study cohort of 250 patients treated with different types of prostheses (complete denture, partial denture, fixed prosthesis) that complete dentures are a risk factor for impaired nutrition in the elderly, nondentate patients (parameters included body mass index, protein, iron, and carbohydrate values) compared with dentate patients. However, Han et al390 and Goel et al391 published concurring prospective, long-term findings that elderly patients with dentures (complete, partial) have improved nutritional status compared with patients with edentulism, which highlights the importance of prosthetic rehabilitation regardless of the age group.

Implant dentistry and oral surgery in patients receiving antiresorptive drugs remained a challenge for clinicians in 2016. However, evidence is emerging that dental implants can be placed safely in patients receiving low-dose antiresorptive drugs for benign conditions. A systematic review392 was designed to clarify whether oral rehabilitation protocols including dental implants have a similar or reduced risk of causing MRONJ compared with restorations without dental implants. The primary review yielded 606 articles, 50 of which met inclusion criteria. The authors stated that the overall quality of evidence was moderate and the studies were heterogeneous. Insufficient evidence is available to assess the risk of MRONJ development in patients receiving antiresorptive drugs (most studies of bisphosphonates) in high oncological doses. The included studies examining the success rates of dental implants in patients treated with antiresorptive drugs (bisphosphonates and denosumab) for benign conditions (such as, osteoporosis) reported implant-related MRONJ to be an extremely rare event. MRONJ in association with ill-fitting dentures is estimated to appear at a rate of about 30%. Despite the limited amount of evidence currently published on the effects of dental implants on the quality of life of patients receiving antiresorptive drugs, a significant benefit of implant prosthodontics solutions was inferred. The systematic review concluded that implant surgery is possible in patients treated with antiresorptive drugs given the adequate informed consent of the patient. Another systematic review on the same topic reviewing almost the identical studies was more conservative in its conclusions and failed to provide clinical recommendations because of the limited quality of the reviewed articles and their heterogeneity.393

Several papers published in 2015 suggested a significant reduction of MRONJ (caused by bisphosphonates) in the wake of oral surgical procedures when perioperative antibiotics are prescribed and tension-free primary wound closure is achieved.394 In a retrospective study, these results have now been proven valid for patients also receiving denosumab.395 In a retrospective study, this protocol after exodontia in patients under treatment with denosumab led to a complication-free healing rate of 92.5%. The study cohort included 19 patients and 40 surgical sites.

The review of studies published in 2015 included several studies discussing the application of PRF in periodontics.396 The positive findings were confirmed in scientific investigations of 2016. The beneficial effects of PRF on soft-tissue healing seems to be undeniable according to a systematic literature review by Miron et al.397 The systematic review included 48 studies, of which 8 were RCTs, and another 5 studies reported adequate controls. All studies unanimously supported the hypothesis that PRF positively influences soft-tissue wound healing. The evidence regarding bone healing is still less convincing. However, a systematic review by Castro et al398 identified 14 articles dealing with the effects of PRF on sinus elevation results, alveolar ridge preservation, and implant surgery. Platelet-rich fibrin accelerated bone healing in sinus elevation procedures reduced the buccal plate resorption in alveolar socket healing and improved primary and secondary implant stability in implant surgery compared with controls. The systematic review included only RCTs. The authors deemed the overall quality of evidence limited because of the rather low number of probands in the RCTs and concluded that more RCTs will be necessary in this field to provide satisfactory recommendations.

**DENTAL CARIES**

In 2016, the trend showing increasing publications on the subject of dental caries was once again confirmed.
Despite the quantity of papers on this subject, the research that is most relevant to the understanding, prevention, and treatment of this so widely diffused disease is only a small part of the whole. It is fairly common, while reading scientific papers, that, in the Discussion section, the authors conclude their article stating that “...however, more randomized controlled clinical studies should be performed to validate the data…” Therefore, the review will start by looking at some of the RCTs published in 2016. Many biomolecular studies were published ranging from new approaches in the treatment and prevention of caries, as with the use of nanotechnologies, to adding new knowledge about the mechanism of the formation of dental caries. In addition, silver diamine fluoride (SDF) was recently introduced for the first time in the United States and will soon be introduced in some European countries. Silver diamine fluoride is a method that has been proven effective to arrest dental caries. Therefore, some articles published on this subject also deserve mention.

**Randomized controlled trials**

Orthodontic acrylic resin retainers with their relatively rough surface provide a favorable environment for plaque accumulation leading to enamel demineralization. Farhadian et al prospecively evaluated 66 orthodontic patients comparing Streptococcus mutans counts on the acrylic resin retainers versus acrylic resin retainers with added silver nanoparticles as an antimicrobial agent. Adding silver nanoparticles to the acrylic resin base of retainers had a strong and statistically significant antimicrobial effect against S mutans.

A second study, although performed in only 24 patients but with a statistically powerful approach because of the split-mouth design, evaluated the protective effect against white spots and dental caries given by periodic application of fluoride varnish on orthodontic patients. The prevalence of white spots can be as frequent as 38% in 4 months and up to 47% in 12 months during orthodontic treatment with fixed appliances because of the increased plaque accumulation caused by the orthodontic brackets and the increased difficulty in hygiene maintenance by the patients. The patients were monitored for 12 months, and each of them had 2 quadrants (1 in the maxillary and 1 in the mandibular arch) treated with fluoride varnish and 2 quadrants used as control. The study concluded that, statistically, the application of fluoride varnish tends to protect against onset of white spots (checked with laser fluorescence) but not in patients with excellent oral hygiene. The application of the varnish can be performed every 6 months (no need for shorter interval application) and is mainly effective on anterior teeth. Therefore, especially in less cooperative patients, it is reasonable to adopt this straightforward and safe clinical strategy during orthodontic treatment. In contrast, Guglu et al reported that the application of 5% sodium fluoride varnish did not offer any clinical advantage when used as a supplement in casein phosphopeptide and amorphous calcium phosphate (CPP-ACP)-enhanced oral hygiene regimens. Probably, with CPP-ACP, the protective and remineralizing effect is so successful that the addition of fluoride varnish does not alter the clinical outcome.

An interesting study from Hong Kong looked at the efficacy of fluoride varnish versus SDF in preventing and arresting dental caries. For ethical reasons, this study did not have a negative control because all the children found with caries deserved some sort of treatment. Therefore, the comparison was among 3 different treatment approaches: group 1 had applications of a 30% SDF solution at baseline and every 12 months; group 2 had 3 applications of a 30% SDF solution at weekly intervals at baseline, whereas group 3 had 3 applications of a 5% NaF varnish at weekly intervals at baseline. The study concluded that the annual or 3 consecutive weekly applications of SDF solution was more effective in arresting dentin caries in primary teeth than 3 consecutive weekly applications of NaF varnish. Another RCT looked at the ability of SDF to arrest dental root caries and assessed the color of arrested carious lesions. Potassium iodide (KI) was tested in addition to SDF as a possible chemical agent able to counteract the darkening effect produced by SDF. The 30-month results revealed the elders in the control group had the lowest caries arrest rate which was approximately one-third of that of the elders who received annual applications of SDF or SDF plus KI solution. This shows that direct application of 38% SDF solution is effective in arresting active root caries in the teeth of community-dwelling elders in a water fluoridated area.

The mechanism of action of probiotics has not been fully understood. However, in past years, several researchers have reported the beneficial effect they offer in caries prevention. One cluster randomized 261 patients to triple-blind, placebo-controlled, 2-arm trial with a short observation period of only 10 months; the study reported that regular long-term intake of milk supplemented with probiotics may reduce caries development in high–caries preschool children. Once again, as reported by all the studies on probiotics, the beneficial effects of probiotics are strictly transient at the time of consumption. Interrupting the administration of probiotics quickly eliminates the benefits they provide.

The atraumatic restorative technique (ART) is an alternative method in which the softened tissue of the carious lesion is removed with a hand instrument and is sealed with an adhesive material, generally a glass ionomer cement. Usually this procedure is used in primary teeth and has been demonstrated to be effective on permanent molars, especially with class I lesions. At the University of Bogotá, Colombia, 75 elderly patients were
divided into 2 groups and treated with ART on root caries.404 The results showed a significantly higher rate of success (92.9%) using the conventional technique with rotary instruments. However, the authors concluded that ART may have been the preferred technique in the study population (elders who live in geriatric institutions) because 81% of those restorations survived or were successful during the observation period. Nineteen percent failures in 6 months does not seem to be a clinically acceptable result; therefore, it is difficult to accept the authors conclusion, regardless of the type of population at which the treatment is aimed. If we consider, however, that often in geriatric institutions, patients cannot be moved and rotary instruments cannot be used, ART could be a valuable alternative for treating class V root lesions compared with no treatment at all.

Genetic and biomolecular studies
A very interesting study of a small peptide called GH12 conducted in the Republic of China405 was published. Peptide GH12 is made from only 12 amino acids and was created to selectively adhere to the membrane of several species of streptococci and cause cellular death. The purpose of this study was to assess the stability of GH12 and measure its antibacterial and antifilm activity against oral streptococci. The various strains of oral streptococci tested in the study presented variable sensitivity to GH12 under the same experimental settings. According to the authors, GH12 is thought to act on bacterial membranes in a nonspecific manner based on polarity and electrostatics. Strain-specific differences in sensitivity may reflect differences in cell wall and membrane composition. This can affect the surface negative charge or create differences in molecules that interact with GH12 before membrane permeation. GH12 remains stable in human saliva and provides rapid, efficient bactericidal activity against oral streptococci associated with dental caries in vitro. These results suggest that GH12 deserves further testing in preclinical and clinical trials as an antimicrobial agent to prevent and treat dental caries.

Biomolecular studies in the past years, not only in dentistry but generally, have produced a great amount of scientific data for the effect of natural products derived from herbs and plants. Studies from Asia are particularly frequent. In a paper from India,406 the effect of a plant derivative called betulin was tested as an antimicrobial agent against S mutans and its biofilm. The effect was very promising in that it reduced biofilm formation by 93%. Also, by interfering with glucan synthesis, betulin reduced the adherence capacity of S mutans by 71%. The results obtained in this in vitro study imply that betulin presents clear antivirulence and antibiofilm potential against S mutans. Considering its nontoxic and antiinfective nature, betulin could be a promising compound to target S mutans as it will not affect the viability of the pathogen but rather disrupt its virulence. The authors concluded that incorporating it into toothpaste, mouthwash, and chewing gum could be a better strategy to prevent and treat dental plaque.

Similarly, Sakaue et al.407 demonstrated that magnolol (50 μg/mL) had greater bactericidal activity against S mutans biofilm than chlorhexidine (500 μg/mL) at 5 minutes after exposure. Furthermore, chlorhexidine (0.5-500 μg/mL) exhibited high cellular toxicity for the gingival epithelial cell line Ca9-22 at 1 hour, whereas magnolol (50 μg/mL) did not. Magnolol may therefore be a good candidate for the prevention and management of dental caries.

A unique study of the S mutans genome was published by Liu et al.408 Because of its small size, the S mutans genome is considered a poor source of natural products (proteins). However, by studying the available genomic information from 169 publicly accessible data from S mutans strains, many gene clusters that can synthesize natural products were identified. Recent human microbiome research has emphasized the importance of the human microbiome to health but has also discovered a new scientific frontier of interpreting the chemical language of communication among and between microbes and the human host. The authors emphasize that “because secondary metabolites frequently exhibit antimicrobial and signaling activities, characterization of compounds from human commensal or pathogenic microbes can enlighten our understanding of the host-microbe relationship.”408 Therefore, comprehension of the S mutans secondary metabolism can help us understand the biology of dental caries and provide therapeutic targets for future preventive treatments. Some of the discovered gene clusters produce compounds that are already active against gram positive pathogenic bacteria (such as, mutacin 1140) and eukaryotic pathogens (such as mutanobactins). The copiousness of natural product gene clusters in S mutans genomes predicts that many more fascinating compounds will be discovered and opens a totally new approach for researchers, such as direct intervention on the mechanism of interaction between bacteria of the biofilm. Perhaps the solution for caries treatment may reside in the genome of the main etiological agent itself.

Nanotechnologies today represent a new, fast developing research field in biology and science generally. A study from the University of Pennsylvania409 investigated the use of nanotechnologies to promote biofilm matrix degradation and kill bacteria to suppress dental caries. Catalytic iron oxide nanoparticles (CAT-NP) were synthesized, and their effect on biofilm was tested. The first challenge was to develop a product that could be retained within the depth of the biofilm structure. CAT-NP does that efficiently and catalyzes the H2O2...
formation in situ that produces rapid bacterial killing and EPS degradation, amplifying antibiofilm efficacy. After verifying all these useful effects in vitro, the test was performed in vivo in a rodent model. Although the model verifying all these useful effects in vitro formation in situ that produces rapid bacterial killing and bacterial morphology. The total biomass was significantly decreased after exposure of both 1% and 10% NAC. Furthermore, 16S rRNA amplicon sequencing analysis suggested that 1% NAC reduced biofilm adherence while maintaining biofilm ecology. Therefore, a NAC-based therapeutic approach formulated with taste improving additives such as xylitol may reduce dental plaque build-up by decreasing both biofilm matrix formation and bacterial growth, while keeping intact the overall biofilm ecology.

Nitric oxide (NO) is an endogenous, diatomic radical that serves a crucial role in wound healing, neurotransmission, and immune response to pathogens. Nitric oxide’s antimicrobial activity derives from its reaction with superoxide to form per-oxynitrite and oxygen to form dinitrogen trioxide. In research performed at the University of North Carolina, Backlund et al.\textsuperscript{110} reported the bacterial and biofilm activities of NO-releasing alkyl-modified dendrimers poly(amidoamine) (PAMAM) dendrimers were modified with alkyl epoxides to generate propyl-, butyl-, hexyl-, octyl-, and dodecyl-functionalized dendrimers against cariogenic \textit{S. mutans} as a function of alkyl chain length, pH, and NO-release kinetics. In addition to physiological pH (7.4) conditions, NO release from alkyl-modified dendrimers was characterized at pH 6.4 to more accurately simulate the in vivo environment associated with caries. The conclusion of the research was that bactericidal and antibiofilm activity of NO-releasing PAMAM dendrimers was amplified with better exterior hydrophobicity at both pH 7.4 and 6.4. More effective bactericidal capability was detected at lower pH (6.4) as a consequence of improved dendrimer-bacteria association and faster NO-release kinetics. The most active antibiofilm capability was found on the long alkyl chain (such as, octyl and dodecyl) modified dendrimers. The NO release from these dendrimer scaffolds somewhat diminished the cytotoxicity of the dendrimer to mammalian cells. In summary, collectively, these outcomes demonstrate the hypothetical utility of NO-releasing long alkyl chain-modified dendrimers as antibiofilm agents for the treatment of dental caries and studies involving polymicrobial biofilms that resemble dental plaque more accurately are needed to verify actual clinical utility.

Modern therapies for the treatment of dental caries must consider the importance of preserving bacterial ecology while reducing biofilm adherence to teeth. For this purpose a multispecies plaque-derived biofilm model was used by Rasmussen et al.\textsuperscript{111} to determine how concentrations of N-acetyl-l-cysteine (NAC) ranging from 0% to 10% influenced the growth of complex oral biofilms. Biofilms were cultivated for 24 hours on hydroxyapatite disks in culturing medium with 0.5% sucrose. Bacterial viability and biomass development was assessed on each disk using a microtiter plate reader. Fluorescence microscopy and scanning electron microscopy were used to qualitatively observe the effect of NAC on bacterial biofilm accumulation, extracellular components, and bacterial morphology. The total biomass was significantly decreased after exposure of both 1% and 10% NAC. Furthermore, 16S rRNA amplicon sequencing analysis suggested that 1% NAC reduced biofilm adherence while maintaining biofilm ecology. Therefore, a NAC-based therapeutic approach formulated with taste improving additives such as xylitol may reduce dental plaque build-up by decreasing both biofilm matrix formation and bacterial growth, while keeping intact the overall biofilm ecology.

Finally, interested readers are advised to look into an elegant, almost philosophical review of the acid-adaptive mechanisms of \textit{S. mutans}.\textsuperscript{412} In order to effectively compete with other bacteria of the dental plaque biofilm, \textit{S. mutans} produces acid to lower the local pH to a level it can tolerate, whereas competing microorganisms cannot. This mechanism includes an equilibrium of acid production with mechanisms to tolerate acid which inhibit \textit{S. mutans} from becoming a target of its own metabolism. When the extracellular environment becomes acidic, \textit{S. mutans} protects its acid-sensitive intracellular machinery by maintaining a $\Delta$ pH of approximately 1 pH unit. Extrusion of protons, influx of other cations, and generation of intracellular basic molecular species all directly contribute to the upkeep of this $\Delta$ pH. Other contributors to the $\Delta$ pH and acid tolerance response (ATR) include modification of the plasma membrane and extracellular matrix, as well as management of sugar import and output of fermentation end-products. \textit{S. mutans} also encodes a large repertoire of enzymes to repair acid damage to proteins and DNA that may occur. While knowledge of the activation and regulation of the ATR has increased significantly in recent years, the pathways of its regulation are intensely complex, and much additional research will be needed to bring sufficient clarity to the field. In a detailed and simple style, the authors summarize the ATR pathways discussed in this review and their associated knowledge gaps.

**Silver diamine fluoride**

Silver diamine fluoride is a colorless alkaline topical fluoride solution containing fluoride and silver ions. The silver salts act as antimicrobial agents and have been used for many years in medicine and dentistry. The fluoride has proven to be effective in dental caries prevention and promotes remineralization. Ammonia stabilizes the solution, therefore, the combination of silver and fluoride has the hypothetical capability to stop the caries process and simultaneously inhibit new caries formation.
Dental caries is an intricate sequence of events involving dietary sugars, bacterial metabolism, demineralization, and degradation of organic components. The collagenous organic matrix is exposed if the dentin substrate is demineralized and damaged by endogenous and bacterial proteases to enable a lesion to progress. Following application of SDF to a carious surface, a squamous layer of silver-protein aggregate develops, increasing resistance to acid dissolution and enzymatic digestion. Both hydroxyapatite and fluorapatite form on the exposed organic matrix, along with the presence of silver chloride and metallic silver. The area of the carious lesion becomes harder and increases in mineral density, while the lesion depth decreases. Meanwhile, SDF selectively inhibits the proteins that break down the exposed dentin organic matrix which are matrix metalloproteinases, cathepsins, and bacterial collagenases.

Silver ions kill bacteria in lesions by causing membrane disruption, by denaturing proteins, and also by inhibiting DNA replication. Ionic silver is actually capable of deactivating virtually any macromolecule. Silver diamine fluoride is superior to any other anticaries medicaments in killing cariogenic bacteria inside the dentinal tubules. Silver and fluoride ions penetrate up to 25 μm into enamel and 50 to 200 μm into the dentin substrate. The most important feature in this mechanism is probably that lesions treated with SDF are resistant to biofilm formation and further cavity formation, probably because of the residue of ionic silver. When bacteria killed by silver ions are added to living bacteria, the silver may be reactivated so that the dead bacteria kill the living bacteria in a so called “zombie effect.”

In August 2014, the FDA cleared the first SDF product for market, and as of April 2015, that product is available. For this reason, interest and papers investigating SDF are constantly increasing both in the academic environments and among clinicians. The University of California, San Francisco School of Dentistry assembled a committee and published a paper with the following goals: first, to develop a list of clinical indications for SDF; second, to delineate a protocol that maximizes safety and efficacy; and third, to build an informed-consent document to be used by clinicians in explaining to patients the new potentials and drawbacks of this fascinating new tool. Readers are encouraged to thoroughly read this article as well as the shorter overview of the clinical applications of SDF published by the University of Hong Kong. A third overview, focusing primarily on elderly patients, was published by Deutsch and involved 243 residents from 19 Melbourne residential aged care facilities. In that population, a prevalence of 67.9% untreated coronal caries and 77.4% untreated root caries were found. The author suggested helpful clinical guidelines subdividing the treatment into open, closed, and subgingival lesions.

Gao et al published the results of a systematic review of studies aimed at evaluating the effectiveness of professionally applied topical fluoride in remineralizing and arresting dental caries in children. Results of 2 meta-analyses to evaluate the remineralizing effects of 5% sodium fluoride varnish and use of 38% SDF in arresting dentin caries were also described in this paper. Meta-analysis is an overview of a combination of several individual studies to increase the statistical power of the results and the conclusions; for this reason, trials must have comparable and uniform outcome measurements. As the studies included in this review were conducted by different researchers using different treatments, studies with larger sample sizes were weighed more in the analysis and thus had a greater influence on the overall result. Results of meta-analyses of 4 studies showed that 5% NaF varnish remineralized approximately two-thirds of early enamel carious lesions in children. Five studies were selected in this systematic review of SDF. The authors all agreed that SDF is more efficient than fluoride varnish in caries prevention. In this review, 38% SDF was concluded to be effective in blocking dentin caries in children for both primary and permanent teeth. In addition, researchers discovered that 38% SDF treatment is better than NaF varnish in arresting dentin caries. Clinicians will be interested to know that eliminating the soft, infected dentin before SDF application is not necessary. The frequency of application of SDF varied from 1 time only (with the lowest success rate among all the studies in percentage of arrested caries) to twice a year. Black staining of caries lesions after SDF application is a critical drawback which may disappoint the children and their parents. A study used nanosilver fluoride as a new product and found it was effective in arresting dentin caries without causing dark staining. Finally, because of the protective effect that SDF provides, it has been suggested to apply a coat of this material beneath composite resin or glass ionomer restorations to prevent secondary lesions. With all the limitation of an in vitro study, the results of this study showed that the restorations with SDF conditioning were more resistant to development of secondary caries during a cariogenic challenge.

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