Novel Anticaries and Remineralizing Agents : Prospects for the Future

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ABSTRACT

Although the use of fluorides has been successful in reducing dental caries, the need remains to develop and evaluate new approaches and promising products for caries prevention. Comprehensive caries-prevention protocols should encompass fluoride and other agents affecting the de-/remineralization balance but also antimicrobial strategies. Different from the traditional restorative approach, the current opinion is that caries should be detected and monitored in its earliest stages, when a nonsurgical reversal can still be achieved. This paradigm shift has implications for methods of caries diagnosis, the choice of preventative materials and the design of randomized clinical trials. This article summarizes the highlights of a special conference dedicated to the topic of novel anticaries and remineralizing agents (ICNARA 2), and identifies the current consensus and remaining questions on pivotal issues in this field.

KEY WORDS: caries, new technologies, biofilms, antimicrobials, sugar substitutes, fluoride.

In recent decades, significant improvements have taken place in oral health in many countries. But even in such countries, from 10 to 20% of the population is still heavily affected by dental caries. An additional concern is that epidemiological surveys have shown that tooth decay may be increasing again (Bagramian *et al.*, 2009). In many developing countries, millions of patients would benefit from 'merely' improving the availability, accessibility, and affordability of basic dental care, such as proven fluoride products for caries prevention. To address the global caries burden, a comprehensive research agenda has recently been compiled (Pitts *et al.*, 2011).

Medicine and dentistry have gone through major paradigm shifts, partly due to the emergence of DNA-based technologies. The oral cavity is acknowledged as a part of the body where physiological processes and emerging pathology can be studied with relevance to organs and tissues elsewhere in the body. The effects of oral health on general health are now generally recognized, and a burst of amazing new data is appearing (*e.g.*, Söder *et al.*, 2012). As a consequence, the need to focus more on the prevention of oral diseases is now widely advocated (*Lancet* Editorial, 2009).

As a spin-off from fundamental research, new or revised oral care products and concepts continue to be developed, also reflecting the changes in our understanding of the disease. To encourage this process, it was believed that a dedicated, intense conference would help to identify and thoroughly evaluate the most promising new caries-preventive technologies. For this, the International Conference on Novel Anti-caries and Remineralization Agents (ICNARA) was convened in 2008 (for details, please see ten Cate, 2008). Based on the success of this first meeting, a second ICNARA conference was held in January, 2012 (ten Cate, 2012). An overview of the themes discussed is given below.

CARIES RISK ASSESSMENT AND CLINICAL TRIALS

Different from the traditional restorative approach, the current consensus is that caries should be detected and monitored in its earliest stages, when a nonsurgical reversal can still be achieved. The need to identify caries early makes the identification of patients at risk increasingly important (Featherstone and Doméjean, 2012). Consequently, Randomized Clinical Trials (RCT) should not necessarily have cavity levels as the end measure, but rather should use new methods for the early detection of caries, with the added benefit that shorter study times are required (Ellwood *et al*., 2012).

While fluoride is still the most effective caries-preventive agent, the search continues for compounds with additional or synergistic effects. Typically, these are based on other factors of caries etiology: A new functionalized

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β-tricalcium phosphate (β-TCP) shows promise by increasing remineralization when used together with fluoride (Karlinsey and Pfarrer, 2012). To this end, a more established calcium source is casein phosphate peptide-amorphous calcium phosphate (CPP-ACP), for which new modes of action and clinical efficacy data have become available (Cochrane and Reynolds, 2012). This is just one of the nanotechnological developments for the remineralization of incipient caries lesions. Nanotechnology is also used in the biomimetic strategies for enamel synthesis (Hannig and Hannig, 2012). To improve toothpastes further, various calcium additives have been shown to be efficacious, and their inclusion is definitely more than 'just marketing hype' (Lynch and Smith, 2012). Toothpastes and rinses are very effective for fluoride delivery, but caries-preventive agents can also be administered through alternative vehicles, such as chewing gums (Dodds *et al*., 2012). Their combined use is advocated, since an increased frequency of use and prolonged contact times enhance the efficacy of agents/products.

EROSION

Dental erosion can be a serious problem for both the patient and the dentist, particularly when diagnosed at an advanced stage (Schlüter *et al*., 2012). Considering the increased prevalence of dental erosion, the population should be informed about the risk of regular acid impact. While the efficacy of fluoride is limited in preventing erosion, other modalities have shown promise, such as the use of inhibitors of matrix metalloproteases (MMP) (Buzalaf *et al.*, 2012).

BIOFILMS, ANTIMICROBIALS

The paradigm shifts in caries etiology and their implications for the development of therapeutic agents have probably been the most significant change in the past decade. DNA-based assessments have identified numerous unknown bacterial species and caused a revolution in bacterial taxonomy. It is anticipated that the focus will now move to overall functionality of the oral microbiota rather than biofilm composition (Zaura, 2012), so identifying specific pathogens is perhaps no longer that important. Full genome sequencing of specific strains is important to obtain generic information about species, but essential genes and therefore functions may be missing in other strains, and clinical isolates might show very different virulence properties (Burne *et al.*, 2012). Our increasing understanding of bacterial interactions, such as signals involved in quorum-sensing and mutacins, opens new avenues to the development of antimicrobial agents (ten Cate and Zaura, 2012). A consensus is that antimicrobial agents should be more subtle in their mode of action than traditional chemotherapeutic agents. For example, concepts are now evaluated based on selectively targeted antimicrobial peptides (STAMP). These comprise a specific targeting moiety chemically coupled to a non-specific antimicrobial peptide which, when delivered to the targeted pathogen, kills the selected bacterium (Eckert *et al*., 2012). A similar, selective approach concerns targeting for virulence-involved bacterial proteins by compounds that will, based on stereochemical considerations, firmly bind and thereby inactivate their function (Horst *et al.*, 2012)

Antimicrobials generally have a limited capacity to eradicate bacteria deep into biofilms, partly due to binding of agents in the outer layers of the biofilm. In contrast, light of various wavelengths penetrates biofilms more deeply and may be antibacterial, particularly when combined with compounds that are broken down to antimicrobials (such as oxygen radicals) upon irradiation (Feuerstein, 2012).

PROBIOTICS

Considerably less novel is the idea of exploiting 'good' bacteria, probiotics, to promote health. This was first presented by Metchnikoff (1907) for maintaining a healthy gut flora. The concept to enrich the oral microbiota with health-associated species follows the paradigm that maintaining a healthy flora might be more successful than eliminating pathogenic microbiota. More comprehensive RCTs are still needed to confirm promising findings for oral health (Twetman and Keller, 2012).

SUGAR ALCOHOLS

The effectiveness of replacing sugars by xylitol and sugar alcohols in caries prevention was convincingly shown in the 'Turku studies' over 50 years ago. Xylitol is a safe dental caries-preventive incorporated into chewing gum or confections. Many health organizations worldwide already support the habitual use of sucrose-free xylitol or polyol combinations in chewing gum or lozenges for at-risk populations (Fontana and González-Cabezas, 2012). In spite of the available evidence, experts agree on the need for additional placebo-controlled RCTs, focusing on optimal dosage, vehicle, and possibly synergism with other preventive strategies (Milgrom *et al.*, 2012). New modes of xylitol delivery, such as xylitol wipes, have been found to reduce the development of new caries in very young children (Zhan *et al.*, 2012).

Moving from the very young to elderly patients: It has been advocated that multiple strategies for prevention are needed to preserve the dentition in this segment of the population (Walls and Meurman, 2012). The increasing group of patients desiring to keep their dentition functional warrants leveraging our research efforts for elderly patients.

CONCLUSIONS

In the past, dental caries research was rather strictly divided into 'hard tissue' and 'microbiological' topics. However, comprehensive caries-prevention protocols should encompass fluoride and other agents affecting the de-/remineralization balance as well as antimicrobial strategies. Although still being studied in their respective niches, there is an increasing overlap, since many agents positively affect the dental hard tissues and biofilms.

Considerable progress has been made in dental caries research, and several new technologies show promise. Many questions and issues remain, pertaining to both caries de-/remineralization (Cochrane *et al.*, 2012) and to biofilm/antimicrobial properties (Maltz and Beighton, 2012).

Based on our improved understanding of the caries process, the testing profiles for caries-preventive agents should also be

updated, from *in vitro* to *in vivo*. In line with that, the procedures used by regulatory bodies for accepting new products should be revised, since the acceptance criteria have generally not followed the changed paradigms of caries etiology and caries prevention.

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REFERENCES

Bagramian RA, Garcia-Godoy F, Volpe AR (2009). The global increase in dental caries. A pending public health crisis. *Am J Dent* 22:3-8.

Burne RA, Zeng L, Ahn S-J, Palmer S, Liu Y, Lefebure T, *et al*. (2012). Progress dissecting the oral microbiome in caries and health. *Adv Dent Res* 24:77-80.

Buzalaf MAR, Kato MT, Hannasa AR (2012). The role of matrix metalloproteinases in erosion. *Adv Dent Res* 24:72-76

Cochrane NJ, Reynolds EC (2012). Calcium Phosphopeptides — Mechanisms of Action and Evidence for Clinical Efficacy. *Adv Dent Res* 24:41-47.

Cochrane NJ, Zero DT, Reynolds EC (2012). Remineralization models. *Adv Dent Res* 24:129-132.

Dodds MW, Chidichimo D, Haas D (2012). Delivery of active agents from chewing gum for improved remineralization. *Adv Dent Res* 24:58-62.

Eckert R, Sullivan R, Shi W (2012). Targeted antimicrobial treatment to re-establish a healthy microbial flora for long-term protection. *Adv Dent Res* 24:94-97.

Ellwood RJ, Gomez Bulla J, Pretty I (2012). Caries clinical trial methods for the assessment of oral care products in the 21st century. *Adv Dent Res* 24:32-35.

Featherstone JD, Doméjean S (2012). The role of remineralizing and anticaries agents in caries management. *Adv Dent Res* 24:28-31.

Feuerstein O (2012). Light therapy: complementary antibacterial treatment of oral biofilm. *Adv Dent Res* 24:103-107.

Fontana M, González-Cabezas C (2012). Are we ready for definitive clinical guidelines on xylitol/polyol use? *Adv Dent Res* 24:123-128.

Hannig M, Hannig C (2012). Nanotechnology and its role in caries therapy *Adv Dent Res* 24:53-57.

Horst JA, Pieper U, Sali A, Zhan L, Chopra G, Samudrala R, *et al*. (2012). Strategic protein target analysis for developing drugs to stop dental caries. *Adv Dent Res* 24:86-93.

Karlinsey RL, Pfarrer AM (2012). Fluoride plus functionalized β-TCP: a promising combination for robust remineralization. *Adv Dent Res* 24:48-52.

Lynch RJ, Smith SR (2012). Remineralization agents – new and effective or just marketing hype? *Adv Dent Res* 24:63-67.

Maltz M, Beighton D (2012). Multidisciplinary research agenda for novel antimicrobial agents for caries prevention and treatment. *Adv Dent Res* 24:133-136.

Metchnikoff E (1907). "Essais optimistes: Paris," in *The prolongation of life: optimistic studies*, trans. and ed. PC Mitchell. London, UK: Heinemann.

Milgrom P, Eva M. Söderling EM, Nelson S, Chi DL, Nakai Y (2012). Clinical evidence for polyol efficacy. *Adv Dent Res* 24:112-116.

No Authors Listed (2009). Oral health: prevention is key. *Lancet* 373(9657):1.

Pitts N, Amaechi B, Niederman R, Acevedo AM, Vianna R, Ganss C, *et al*. (2011). Global oral health inequalities: dental caries task group—research agenda. *Adv Dent Res* 23:211-220.

Schlüter N, Jaeggi T, Lussi A (2012). Is dental erosion really a problem? *Adv Dent Res* 24:68-71.

Söder B, Yakob M, Meurman JH, Andersson LC, Söder PÖ (2012). The association of dental plaque with cancer mortality in Sweden. A longitudinal study. *BMJ Open* 2(3). pii: e001083.

ten Cate JM (2008). International Conference on Novel Anti-caries and Remineralizing Agents. *Adv Dent Res* 21:3.

ten Cate JM (2012). New agents for caries prevention: introduction to ICNARA 2. *Adv Dent Res* 24:27.

ten Cate JM, Zaura E (2012). The numerous microbial species in oral biofilms: how could antibacterial therapy be effective? *Adv Dent Res* 24:108-111.

Twetman S, Keller MK (2012). Probiotics for caries prevention and control. *Adv Dent Res* 24:98-102.

Walls AWG, Meurman JH (2012). Approaches to caries prevention and therapy in the elderly. *Adv Dent Res* 24:36-40.

Zaura E (2012). Next-generation sequencing approaches to understanding the oral microbiome. *Adv Dent Res* 24:81-85.

Zhan L, Featherstone JD, Lo J, Krupansky C, Hoang N, DenBesten P, *et al*. (2012). Clinical efficacy and effects of xylitol wipes on bacterial virulence. *Adv Dent Res* 24:28-31.