Novel Anticaries and Remineralization Agents: Future Research Needs

Journal of Dental Research
2018, Vol. 97(2) 125–127
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for Dental Research 2018
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DOI: 10.1177/0022034517746371
journals.sagepub.com/home/jdr

J.D. Featherstone¹, M. Fontana², and M. Wolff³

Keywords: dental caries, caries risk, fluoride, antimicrobials, microbial ecology, behavior

Introduction

More than 60 y have passed since the widespread introduction of fluoride use and 50 y since the introduction of sealant therapy. Yet, dental caries remains a significant disease, particularly in underserved and aging communities. An international conference dedicated to the topic of novel anticaries and remineralizing agents (ICNARA 3) was held in May 2017. The ICNARA 3 conference was the third in a series of ICNARA conferences (ICNARA 1 held in January 2008 and ICNARA 2 January 2012; ten Cate 2008, 2012). These conferences brought together scientists who could summarize the current status of caries management and highlight exciting new therapeutic possibilities, as well as research needs for the future. ICNARA 3 recognized that the new frontier in reducing caries experience and helping maintain health may not solely depend on developing cost-effective products or devices to target the biofilm and/or the tooth, but may rest in a series of behavioral modification and/or targeted approaches, such as efforts to reduce sugar consumption, for ultimate success, based on individual or community risks for dental caries.

Dental caries is a microbial disease resulting from a dysbiosis in the oral microbiome. Ecological pressures, such as frequent intake of sugar and/or reductions in saliva flow, can result in extended period of low pH in the biofilm and change the proportions of the normal resident species. This in turn results in the selection of species with an acid-producing/acid-tolerating phenotype, thereby increasing the risk of dental caries (Marsh 2018).

The progression of dental caries lesions to cavitation is dependent on the balance between demineralization, caused by biofilm dysbiosis, and remineralization, which is dependent on calcium, phosphate, and fluoride. Despite the significant reduction in caries prevalence in many parts of the world, dental caries remains a major public health problem affecting people of all ages, and remains one of the most common unmet health care needs of economically disadvantaged populations. Furthermore, the disease is not equally distributed, with multiple population groups at increased risk. Existing caries management strategies include, for example, the promotion of a healthy diet, including a low frequency and amount of exposure to fermentable carbohydrates/sugars, and frequent oral hygiene with fluoride-containing toothpaste. However, even with regular fluoride use, caries lesions can still develop if

other caries risk factors are present. Thus, together with strategies to reduce sugar consumption, strategies to prevent demineralization and/or promote remineralization of caries lesions need to be enhanced and promoted to reach those at risk.

Caries Management, Clinical Trials, and Behavioral Issues

There is a need for continued research into cost-effective strategies for caries prevention and management that could work as a supplement or as an alternative to fluoride. Modern caries management stresses a philosophy involving targeted risk assessment and disease management, accurate and early detection of caries lesions, and efforts to remineralize or arrest non-cavitated lesions to preserve tooth structure and maintain health. As discussed during the ICNARA 3 conference, this can be achieved in private-practice dental settings (Rechmann et al. 2018); although, more refinement and research is needed to enhance the implementation and dissemination of modern caries management not only in dental settings but in medical health care settings, schools, among others (Fontana et al. 2018). In addition, although research is being conducted to validate the utility of caries risk assessment forms (Featherstone 2018), it was agreed that more research is needed to identify better methods of biofilm modification and remineralization across individuals of different ages and of varying risk. Furthermore, although randomized clinical trials offer a robust methodology for testing such treatments, there has been a call for better coordination between researchers and funders, and attention needs to be paid during the design stage of such caries trials to ensure the results will be appropriate for clinical use (Innes 2018). Finally, even with the availability of chemical

¹Preventive and Restorative Dental Sciences, School of Dentistry, University of California San Francisco, San Francisco, CA, USA

²Cariology, Restorative Sciences and Endodontics, School of Dentistry, University of Michigan, Ann Arbor, MI, USA

³Cariology and Comprehensive Care, College of Dentistry, New York University, New York, NY, USA

Corresponding Author:

M. Fontana, Department of Cariology, Restorative Sciences and Endodontics, School of Dentistry, University of Michigan, 1011 North University, Room 2393, Ann Arbor, MI 48109, USA.
Email: mfontan@umich.edu

and biological therapies to modify the biofilm or enhance remineralization, none of this is useful if individuals will not modify their behavior to reduce their exposure to risk factors (e.g., sugars) and adopt and utilize effective therapies (Heyman et al. 2018). Thus, efforts should continue to expand research into the adoption of proven behavioral interventions to reduce dental caries in multidisciplinary settings.

Antimicrobial Agents and Biofilm Modifiers

In caries research, there is currently a major emphasis on opportunities and challenges associated with strategies to shift the dental biofilm from a state of dysbiosis to a state of symbiosis with the tooth (Marsh 2018; Tanner et al. 2018; Mira 2018; Liu et al. 2018; Burne 2018; Zhan 2018; Nascimento 2018; De Cock 2018; Wolff and Schenkel 2018), as reflected in the conference. The study of the microbiome suggests a clinical role in assaying selected putative cariogenic species particularly in aggressive caries disease phenotypes. However, for many populations with caries progression, assaying multiple species will likely continue to be warranted to determine the caries-profile of the population and/or individuals under study (Tanner et al., 2018).

Among the therapeutic approaches discussed were those that modulate the oral microbiome, manipulating the oral environment to selectively favor the growth of beneficial organisms at the expense of cariogenic organisms that cause dysbiosis, with pre- and probiotics emerging as promising new approaches to prevent caries lesions (Mira 2018). In addition, strategies that disrupt the extracellular polysaccharide matrix of oral biofilms, and those with enhanced bioactive drug-delivery components that are triggered in low pH environments, are being explored for their potential to interfere with the caries process with high efficacy, minimal toxicity, and long-term therapeutic effects (Liu et al. 2018).

It was agreed that future research must continue to focus on understanding three key aspects. 1) There is a need to understand the drivers of oral biofilms in health and disease, including the role of sugars and diet, healthy microbiome profiles, dysbiotic microbiome profiles, the role of transmission, and the acquisition of microbiome profiles throughout the lifespan. 2) It is important to identify ways to manage the oral microbiome associated with dental caries, including strategies to (a) boost beneficial species and alter their balance in the biofilm, (b) inhibit the key functions of detrimental species (rather than killing them), (c) design and test beneficial probiotic phenotypes, (d) adopt strategies that intervene when disease occurs with enhanced duration, (e) identify strategies to boost host defenses against pathogenic microbial profiles, and (f) identify strategies to enhance salivary function to promote symbiosis among others. And, finally, 3) there is a need to improve diagnostics, including markers of dysbiosis, and explore their role in enhancing caries risk assessment tools. It is also relevant to design markers that can detect biofilm changes over time for both health and disease.

Remineralization and Biomimetics

As highlighted above, there is no doubt that, for individuals at increased caries risk, fluoride therapy on its own may be insufficient when the biofilm is in a state of dysbiosis and acid production prevails following carbohydrate consumption. Continuing efforts are being made to reduce sugar consumption, enhance remineralization, supplement fluoride and find other strategies that have preventive or reparative effects on noncavitated and cavitated caries lesions (González-Cabezas and Fernández, 2018). There was an extensive discussion around the use of silver-containing strategies for caries control, focusing on the role of silver either alone (nanoparticles) or in combination with fluoride (e.g., silver diamine fluoride) as antibacterial and remineralizing agents (Schwass et al. 2018; Horst and Seto 2018; Burgess and Vaghela 2018). In addition, several clinical studies were reviewed that highlighted the combined effect of arginine and fluoride (Wolff and Schwartz 2018), and stannous fluoride delivery technologies (Shi et al. 2018) to provide anti-carries and remineralization therapy. In addition, the discussion brought to light several novel remineralization methods that are progressing toward clinical use and show great promise for the future; for example, a novel peptide that clinically can enhance a deeper remineralization (Alkilzy et al. 2018), and the use of electrically assisted enhanced remineralization (Pitts 2018). Laboratory and clinical studies on such novel agents and many others are in progress.

Challenges for the Future

Although the science of cariology with respect to microbiome dysbiosis, caries lesion remineralization, and caries risk assessment is well advanced, one of the biggest challenges is translating all of this information into practical, evidence-based treatment recommendations for practice and home care. The challenging process of translating mechanistic research into clinical practice includes the cost and difficulties associated with conducting clinical trials and obtaining regulatory approvals. There is also the ongoing issue of how much evidence is necessary before we can proceed with using a product or procedure to manage caries lesions when fluoride is not sufficient. Interventions that are to be used on a population basis need to be cost-effective, affordable, acceptable and easily delivered. Implementation and dissemination science needs to be brought to bear on the problems of translating discoveries into reality, and enhancing the adoption of evidence-based strategies into practice. How can we have third-party payers, and other health funding agencies, pay for nonsurgical interventions and risk-based care, rather than primarily surgical intervention? Many countries face similar issues but there are issues related to specific countries, regions and cultures as well as their regulatory and health care agencies that need to be continuously addressed if progress is to be made.

Social media offers a new avenue that should continue to be explored to manage the above problems. The dental profession and the public of all ages can be educated using social media with creative videos, messages, crowd sourcing, smart phones,

electronic tracking devices, games, among others. We need to continue to enlist health care providers, other than dentists, to deliver a simple unified caries preventive message and effective interventions, and we must assess cost-effective implementation efforts to enhance effective interprofessional care. Patient engagement is also crucial for success, which involves careful attention to issues associated with literacy and understanding that dental caries is a manageable disease that may require different interventions throughout their lifespan. Financial incentives need to be put in place to move the dental profession toward prevention and minimal intervention dentistry. Electronic record systems need to be modified to match these needs.

Conclusions

The dental caries disease process is a balance of biofilm dysbiosis, fueled by increased access to frequent sugars/carbohydrates, and the prevention or reversal of noncavitated lesions by enhanced remineralization. Caries risk assessment tools are available and will be improved further in the future. Novel approaches to biofilm modulation, remineralization therapies, and caries management are in progress and well advanced, and many more promising strategies will be available as research continues. The extension of knowledge and appropriate skills to other health care providers, together with enhanced electronic health records and registries to improve interprofessional care, will be essential to reduce the large disparities in dental caries around the world. Some of the barriers to success include difficulties associated with behavioral change, the ease of access to cheap sugars and carbohydrates, the cost of clinical trials for testing interventions, the need for a major change in the way caries management is approached by the dental profession (away from restoration of the consequences of the disease to management of the disease throughout the lifespan), and the financial support for this paradigm shift.

In conclusion, dental caries remains a significant problem throughout the world for individuals throughout their lifetime. It is important for dentistry to recognize that the historic approach to the prevention and management of the disease has reduced prevalence, but not eliminated disparities, and has certainly not eliminated the progression of the disease over the course of an individual's lifetime. This conference highlighted innovative technologies and techniques that could be used by a variety of health care providers and educators to address the ongoing caries disease pandemic. We must continue to explore these innovative methodologies if we are to improve the oral health for those in need.

Acknowledgments

The articles discussed in this editorial were presented at the ICNARA 3 conference (May 2017).

The ICNARA 3 conference was financially supported by the Colgate Palmolive company, C3 Jian Inc., The Procter and Gamble Company, DentaQuest Foundation, Elevate Oral Care, 3M Oral Care, Ultradent, Wrigley, Cargill, with in-kind support from New York University College of Dentistry, the University of Michigan School of Dentistry and the University of California- San Francisco School of Dentistry. The authors declare no other potential conflicts of interest with respect to the authorship and/or publication of this article.

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