OREC PANORAMA 2/2024

Special Issue Periodontology - Bacteriophages in oral applications & Bidirectional relationship diabetes - periodontitis

In this issue, we would like to focus on various topics within the field of periodontology. This time, we have selected two topics from the range of current Master's theses at the IMC that are rarely the focus of articles on periodontal treatment and we hope that these otherwise less frequently considered topics will be an exciting addition to the usual specialist reading.

The first topic is dedicated to the use of bacteriophages - both in the oral cavity and for broader clinical application. The respective thesis was already written in 2019. Our student from Russia was already at that time very interested in this topic, as the use of bacteriophages has a long history in Eastern Europe. The discussion about the use of bacteriophages has gained new momentum in recent years, firstly because antibiotic-resistant bacteria are on the rise and thus the need to look for new treatment options is much more urgent and secondly because several countries are now intensifying research activities in this field, among the Western European countries particularly Belgium. The Coordination Group for Bacteriophage Therapy Leuven (CBL) was founded in 2018 and received financial support through a grant from the KU Leuven. Finally, the Belgian Society for Microbial Viruses (BSVoM) was founded in 2022 to further capture and promote the spirit of collaboration between the growing community of microbial virus researchers in Belgium bringing together fourteen different research institutions from academia, industry and government.

As usual in our previous Panorama issues we present the summary of a master's thesis focusing on phage application in the clinical field (page 2), including links to the evaluated studies, as well as additional scientific background on phage therapy in general (starting on page 1) and an update on the current study situation. In particular, we highly recommend a recently published open access review, which specifically addresses phage therapy for oral diseases. The key findings from this review and the current state of research or need for research, respectively, are presented on page 3 of this issue.

The other topic dedicated to the field of periodontology deals with two different aspects of the bidirectional relationship between diabetes mellitus type 2 and the presence of periodontal disease. While one thesis was specifically focused on the occurence of a variety of diabetes complications in presence of periodontitis, the other thesis summarized the potential benefit of periodontal therapy on glycemic control in diabetic patients. The content of both theses, both only recently finished, and related background is shown starting on page 4.

Last but not least, please have a look on the new developments on our OREC platform, the announcements for the 5th Sino-German Symposium and other actual conferences summarized on last page.

Prof. Dr. Joos (Editor)

Scientific Background I - Bacteriophages

Introduction: Since their discovery in 1928, antibiotics have been used to treat a wide range of serious infections, saving millions of lives. However, as a result of the overuse and misuse of antibiotics, bacteria have managed to develop multiple resistance mechanisms to antibiotics and our former wonder weapon is almost powerless. We are now facing a post-antibiotic era in which common infections or minor injuries can be fatal (WHO 2014). If nothing is done, the World Health Organization estimates that around 10 million people a year could die from drug-resistant infections by 2050. The search for and development of new antibacterial agents is urgently needed to avoid such a threatening future, and (bacterio)phages could play an important role in addressing this global crisis.

While the use of phages in human therapy began over a century ago, their use in clinical practice in Western countries was quickly overshadowed by the introduction of antibiotics. However, in countries such as Georgia and Poland, phage therapy has continued to be actively used to this day, mainly through two large

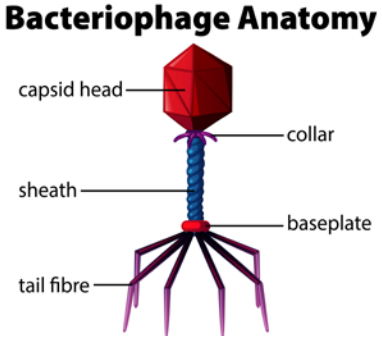

Fig. 1: Structure of bacteriophages (designed by Freepik - free use CC-BY)

phage therapy centers: the Eliava Institute of Bacteriophages, Microbiology and Virology (Tbilisi, Georgia) and the Ludwik Hirszfeld Institute of Immunology and Experimental Therapy (Wroclaw, Poland).

In particular patients with antibiotic-resistant infections often travel to these research facilities from all over the world to receive individualized phage therapy as a last hope.

Despite all the successful cases documented so far and almost no undesirable side effects, the introduction of phage therapy in Western countries still faces major obstacles, particularly regulatory issues.

Master thesis I

Application of bacteriophages in the oral cavity - Evaluation of potential efficacy vs. risks

Master of Science in Implantology and Dental Surgery - 2019

Objectives: The objective was to assess the efficacy and safety of bacteriophages for application in the oral cavity.
Material & methods: The electronic database MEDLINE (Pubmed) was used to find studies and articles with comparable data from ex vivo studies, in vitro studies, animal studies, as well as clinical trials related to the clinical application of bacteriophages. In summary, from a total of 5624 sources 166 articles were selected by title. After full text screening and inclusion of 6 studies from hand search, 26 studies were retained for complete analysis; from which 5 were related directly with application inside the oral cavity while 21 studies were selected for a more general analysis of efficacy and safety aspects in the application of bacteriophages.
Results: All studies showed the introduction of bacteriophages at an average concentration of 10^7 - 10^8 PFU/mL showed a remarkable reduction in bacterial biofilm. At an average of 24 hours, the majority of bacteria were eliminated. Safety testing indicates that there are no major side effects noted at this time. Minor side effects could include mild gastrointestinal irritation. No signs of bacteriophage resistance or harmful consequences are a concern at present. With respect to administering bacteriophages, studies indicate that application per os or by injection has proven to be more successful than by topical means.
Conclusion: Bacteriophages are a safe and effective alternative to antibiotic treatment. Due to the limited number of clinical trials and lack of approval in several geographic regions, this poses a challenge for most clinicians who wish to turn to alternative care for their patients. Further research and awareness may help overcome this obstacle in time.
Key words: Bacteriophages, Biofilm, Antibiotics, Efficacy, Safety.

Basic mechanism of action: Bacteriophages can influence bacteria because they can replicate through four different mechanisms: the lytic, lysogenic, chronic, or pseudolysogenic cycles (Fig. 2). The virion-productive life cycle of all tailed phages ends in lysis of the host bacterium, initiating a new cycle of extracellular search for new bacteria (Fig. 3). This lysis breaches the bacterial cell envelope, thereby destroying the infected bacterium. Alternatively, many phages can display so called lysogenic cycles, which are not virion productive but during which the phage genom (prophage) nevertheless replicates along with its bacterial host. Lysogenic cycles can eventually also give rise to lytic infections, but to a much lower extent than for lytic phages. Much more important - such phages also called „temperate" phages - carry the risk to propagate bacterial resistance genes to new hosts. It is indeed observed that people in close contact with others exhibit a high extent of analogous antibiotic resistances.

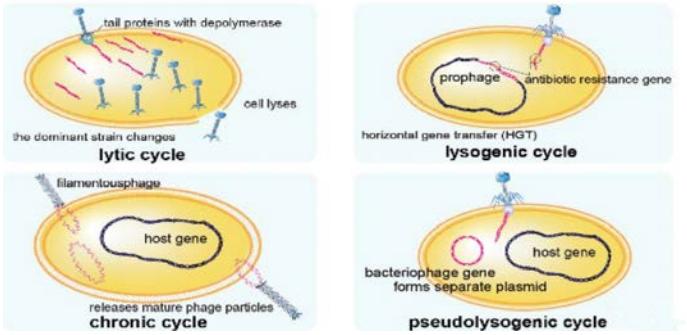

Fig. 2: Replication cycles of bacteriophages
(copied from Guo et al. 2024 - free use CC-BY)

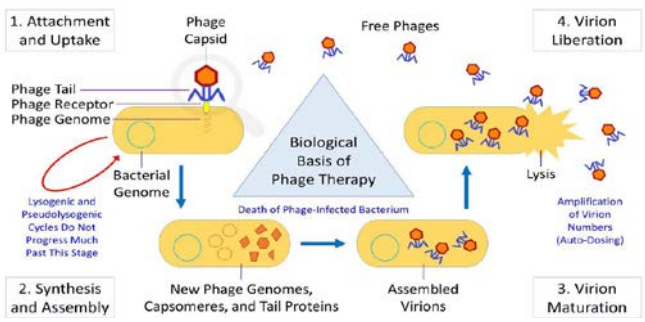

Fig. 3: Lytic infection cycle of bacteriophages
(copied from Fabijan et al. 2023 - free use CC-BY)

List of included studies

ex vivo:
Dalmasso, M. et al. 2015. Isolation of a novel phage with activity against Streptococcus mutans biofilms. PLoS One, 10(9), e0138651.
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Paisano, A. F. et al. (2004). In vitro antimicrobial effect of bacteriophages on human dentin infected with Enterococcus faecalis ATCC 29212. Oral microbiology and immunology, 19(5), 327-330.
Phee, A. et al. (2013). Efficacy of bacteriophage treatment on Pseudomonas aeruginosa biofilms. Journal of endodontics, 39(3), 364-369.
Pires, D. P. et al. (2016). Genetically engineered phages: a review of advances over the last decade. Microbiology and Molecular Biology Reviews, 80(3), 523-543.

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animal studies
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Yilmaz, C. et al. (2013). Bacteriophage therapy in implant-related infections: an experimental study. JBJS, 95(2), 117-125.

clinical studies:
Briusov, P. G. (2011). Phagoprophylaxis and bacteriophage treatment of surgical infections. Voenno-meditsinskii zhurnal, 332(4), 34-39.
Fadlallah, A. et al. (2015). Corneal infection therapy with topical bacteriophage administration. The open ophthalmology journal, 9, 167.
Rhoads, D. D. et al. (2009). Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial. Journal of wound care, 18(6), 237-243.
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New perspectives on oral bacteriophages

This page summarizes the most important facts for the potential use of bacteriophages in the oral cavity from a highly recommended review by Guo et al. (2024). This article is freely available and the interested reader is referred to this article for further background. (Accordingly, the original articles cited are not listed separately here.) Three different disease types might be targeted - periodontal disease, caries or endodontitis (Fig. 4).

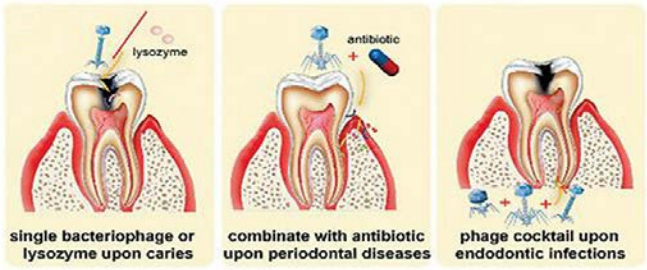

Fig. 4 Potential application of bacteriophages in the oral cavity (from Guo et al. 2024 - free use CC-BY)

Periodontal disease

As a chronic infectious disease, periodontal disease is associated with microbial plaque dysbiosis and an imbalance in the host's immune defenses. However, **bacteria alone do not seem to fully explain the reasons** for the devastating progression of periodontal disease. The contribution of eukaryotic viruses such as herpesviruses, Epstein-Barr virus and cytomegalovirus to periodontal disease was investigated early on. Some authors found an increased activity of herpesviruses and bacteriophages, others a significantly higher proportion of mycoviruses in subgingival biofilms of patients with periodontal disease compared to healthy individuals, suggesting that periodontal disease already favors the growth of lysogenic bacteriophages in those patients.

Interestingly, in contrast to most other periodontal pathogens, so far no lytic bacteriophages have been identified and/or isolated against *P. gingivalis*, the most important member of the red microbial complex and a driver of inflammation. In contrast, other members of the red complex, namely *Tannerella forsythia, Treponema denticola, Prevotella intermedia/Prevotella nigrescens* and *T. denticola* were found to harbor lytic bacteriophages. As an "adherent" bacterium, *F. nucleatum* forms a bridge between commensal early colonizers and pathogenic late colonizers in the subgingival plaque. Various phages have also been identified for this bacterium, which are present in the subgingival plaque, while for *Aggregatibacter actinomycetemcomitans*, known for its strong association with localized aggressive periodontitis, mainly temperate phages were found. A new finding in this field is that lysogenic bacteriophages influence bacterial physiology and may therefore be **even involved in the progression of periodontal disease.** A significantly higher detection rate of certain phages was found in patients with chronic periodontitis than in healthy individuals. Bacteriophages could regulate the growth, adhesion and mutual competition of the red complex.

P. gingivalis has been shown to strongly upregulate CRISPR-associated genes for defense against viral infections during the progression of periodontal disease, which may support its dominance in periodontal pocket biofilms. Also prophages of *A. actinomycetemcomitans* can regulate pathogenic processes and thus help to evade the immune response. Despite the obvious presence of bacteriophages in periodontal disease, particularly the joint application of bacteriophages, lysozymes, and antimicrobial agents might be a powerful option, considering that CRISPR-associated DNA nucleases of the temperate phages could reverse antibiotic resistance.

Strategies of phage therapy to combat caries

It is encouraging that *in vitro* and *in vivo* studies have shown the efficacy of the aforementioned bacteriophages and their derivatives in the prevention and treatment of dental caries. Antimicrobial peptides produced by bacteriophages are excellent candidates for caries treatment. ClyR-lysine, a known chimeric lysozyme, could act selectively on cariogenic *S. mutans* and *S. sobrinus* without affecting other harmless commensal oral bacteria. Alternatively, continuous application of ClyR significantly reduced caries rates in rat models with single or mixed infections, suggesting that ClyR may be a promising agent or additive for the treatment of dental caries. Further research is needed to fully understand the anti-caries effects and functions in micro-ecological regulation to ensure safe and efficient application of these compounds in human healthcare.

Phage therapy for endodontic infections encounters both hurdles and opportunities

Endodontic infections are caused by pathogenic bacteria, of which *F. nucleatum* is most common in primary infections, while *Enterococcus faecalis* is more common in secondary infections. Antibiotics have traditionally been used in endodontic treatment, but there is growing concern about antibiotic resistance, particularly with vancomycin-resistant *Enterococcus faecium* (VREfm). Isolated anti-*E. faecalis* phages have been identified with efficacy against *E. faecalis* in biofilms, particularly against VRE strains. The isolated *E. faecalis* phages offer a wide range of therapeutic options due to their different morphology, host range and potential functions. In addition, the safety of these bacteriophages has been demonstrated as they do not exhibit cytotoxicity to mammalian epithelial cells.

Unfortunately, rapidly evolving bacteriophages pose new challenges for clinical applications, e.g. phage resistance. Combinations of active bacteriophages in a cocktail therapy are very valuable to prevent the rapid emergence of phage resistance. Mixtures of two or more different bacteriophages have been found to be effective in reducing the number of phage resistance mutants, whereas a greater diversity of mixtures could increase the chances of antagonistic phage interactions. The co-evolutionary arms race between bacteriophages and hosts generally leads to bacterial resistance, which decreases phage infectivity over time. To obtain longer-lasting therapies, comprehensive characterize of the bacteriophages and careful selection of combinationswoudl be required. The combination of antibiotics and bacteriophages can not only combat phage resistance but also reverse antibiotic resistance. Finally, endolysins offer an option for phage therapy. Although some phages have a limited host range and are therefore unsuitable for clinical therapy, their endolysins, such as LysEFm5, have a broader bactericidal spectrum that includes seven strains of vancomycin-resistant *E. faecalis*. However, it remains a mystery how endolysins could acquire a broader host range than their parental bacteriophages.

However, bacteriophages also suffer from shortcomings such as instability and short maintenance time. Future research can refer to phage encapsulation to achieve an intelligent release of phages.

And additional hurdles for phage therapy include the inability of isolated phages to cope with all the complex and individualized clinical cases, the evolution of clinical bacterial strains, the variability and unpredictable of immune responses, the rapid emergence of phage resistance. Nonetheless, it is a promising treatment option.

Topic II - Diabetis & Periodontology

Master thesis IIa

Does periodontitis have a negative influence on complications in diabetes patients?

Master of Science in Periodontology - 2024

Objectives: The aim of this literature review is to investigate the impact of periodontitis on diabetic complications, specifically nephropathy, neuropathy and retinopathy. Additionally, it examines the influence of other factors on the risk of diabetic complications.
Material & methods: A comprehensive search was conducted through the PubMed database, supplemented by a manual search for relevant articles, from February 2024 to April 2024. The search strategy employed terms adhering to the PICO (Population, Intervention, Comparison, Outcome) framework. A total of 521 articles were initially screened using the Covidence application. Of these, 49 studies were assessed for eligibility, and ultimately, 23 articles were selected for inclusion in the analysis of this review.
Results: In terms of crude odds ratio (OR), there is a statistically significant effect of periodontitis on diabetic complications, with a detectable dose-response relationship. The most pronounced effect was observed on nephropathy. However, if adjustments were performed in the individual studies, the effect size diminished as more confounders were adjusted for in the analysis.
Conclusion: Within the limitations of this review, it is highly advisable for diabetic patients to receive periodontal treatment as part of their comprehensive diabetes management plan. This integrated approach can facilitate better control of both conditions and reduce the risk of associated complications. However, caution must be exercised in not overestimating the effect of periodontal treatment on diabetes management until further robust studies are conducted.
Key words: Periodontitis, Diabetes type 2, Neuropathy, Nephropathy, Retinopathy.

List of included studies

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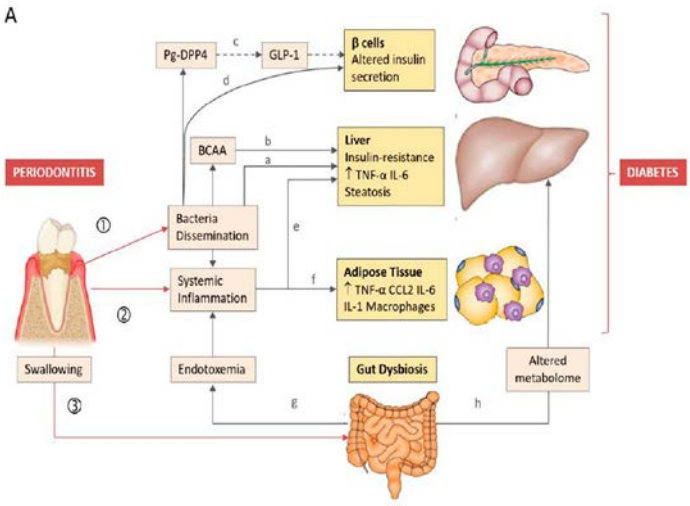

Fig. 5A: Bidirectional relationship - 1. Periodontitis to Diabetes: periodontitis favors development/worsening of type 2 diabetes by three major mechanisms:
(1) Dissemination of periodontal bacteria/bacterial products into the bloodstream. Bacteria/ bacterial products can induce insulin resistance (a) by inhibiting hepatic glycogen synthesis, increasing hepatic gluconeogenesis, and (b) blocking the insulin receptor substrate via production of branched-chain amino acids (BCAA). (c) Dipeptidyl peptidase-4 (DPP4) produced by *P. gingivalis* (Pg-DPP4) can reduce glucose-induced insulin production by enhancing glucagon-like peptide 1 (GLP-1) degradation (d) *P. gingivalis* may alter insulin production by inducing cell dedifferentiation.
(2) Induction/magnification of systemic inflammation, favoring both (e) hepatic and (f) adipose tissue insulin resistance.
(3) Gut dysbiosis induced by swallowed periodontal bacteria, favoring both (g) endotoxemia and (h) changes in the blood metabolome.
(from Barutta et al. 2022)

Scientific Background II

Periodontitis (PD) is a chronic inflammatory disease that affects the periodontium, which includes the gingiva, the periodontal ligament, and the alveolar bone. Despite it's negative consequences for oral health, PD is also associated with several chronic diseases, including obesity, metabolic syndrome, diabetes mellitus (DM), and cardiovascular diseases. Here, we will summarize the most interesting data on the bidirectional association between PD and DM, only recently published by Barutta et al. (2022).

Hyperglycemia caused by either absolute or relative insulin deficiency is the hallmark of DM. In type 1 DM destruction of β cells in the pancreatic islets is due to an autoimmune process, while type 2 DM is caused by both peripheral insulin resistance and relative deficiency of β-cell insulin secretion.

Bidirectional Relationship between Periodontitis and DM

A bidirectional relationship between PD and DM exists independently of associated risk factors and the two diseases additionally affect each other. The increased risk of PD in DM was first described by Löe in 1993, and PD was found as the sixth complication of DM. Moreover, the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) added DM among the risk factors for the progression of PD.

Mechanism

Studies in animals have partially clarified the mechanisms behind.

Periodontitis—Type 2 DM Direction (see Fig. 5A)

(1) Dissemination of periodontal bacteria and bacterial products from the periodontal tissues to the bloodstream:

Periodontal bacteria and/or bacterial components were found in various extraoral locations. *P. gingivalis* can evade circulating phagocytes by adhering to erythrocytes and can also enter the circulation using monocytes and DC cells as Trojan horses.

P. gingivalis can enhance hepatic glucose output and circulating blood glucose levels by reducing the inhibitory effect of insulin on hepatic gluconeogenesis. Periodontal pathogens might also act through their metabolic activities. Specifically, branched-chain amino acids (BCAA) have been proposed as a factor contributing to the development of insulin resistance. *P. gingivalis* was found to express an enzyme (Pg-DPP4), degrading gut incretin hormones (which would normally increase insulin production). Bacteria can also affect insulin production by epigenetic changes in the nuclei of β-cells, which alter their identity by inducing dedifferentiation (seen as changes in the islet architecture).

(2) Induction of systemic inflammation via spill over of inflammatory cytokines and host response to the dissemination of bacteria

The systemic increase of pro-inflammatory cytokines initiated by periodontal bacteria may promote insulin resistance. LPS from *P. gingivalis* is a possible mechanism leading to low-grade systemic inflammation, resulting in the adipose tissue in overexpression of proinflammatory genes and downregulation of genes that enhance insulin sensitivity. In the liver, accumulation of triglycerides, overexpression of genes promoting inflammation, lipid droplet formation, fatty acid synthesis and gluconeogenesis was observed in response to *P. gingivalis.*

(3) Abnormalities in the gut microbiota and increased gut permeability

Swallowed periodontal bacteria can induce gut dysbiosis, resulting in downregulation of tight junction proteins likely leading to enhanced gut permeability (favoring endotoxemia). Interestingly, *P. gingivalis* induced changes in the gut microbiota prior to the development of systemic inflammation, suggesting that this dysbiosis may lead to the systemic inflammation and only finally to the insulin resistance. Gut dysbiosis may also alter the products of gut bacterial metabolism and after absorption such metabolites can affect the serum metabolome.

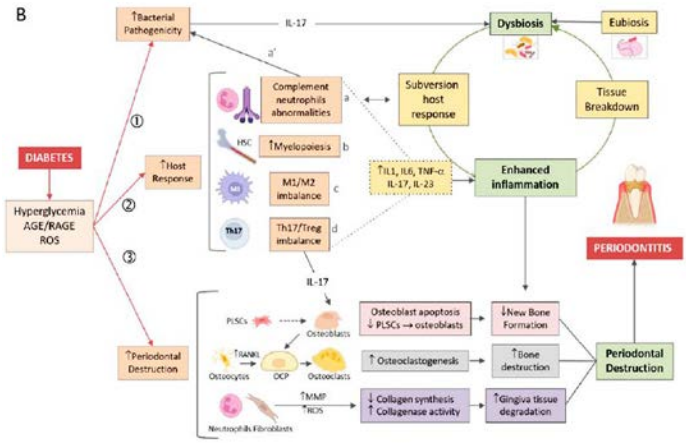

Fig. 5B: Bidirectional relationship: 2. Diabetes to Periodontitis: Dysbiosis, inflammation, and destruction of the periodontium (green boxes) are characteristic features of periodontitis. Dysbiotic bacteria reduce the efficacy of the host immune response, while fuelling inflammation (open green arrow). In turn, inflammation-induced tissue breakdown favors dysbiosis (closed green arrow) closing the vicious cycle. Mechanisms linking DB to PD are shown on the left hand side. Diabetes favors development/worsening of periodontitis by 3 major mechanisms:
(1) Increasing periodontal dysbiosis and bacterial pathogenicity via IL-17.
(2) Enhancing the host response to the bacteria. Diabetes (a) alters complement and neutrophil function (which also affects susceptibility to infection a'), (b) increases myelopoiesis, enhances (c) the M1/M2 macrophage ratio, (d) the Th17/Treg lymphocyte ratio, thus raising inflammatory cytokines levels (dotted lines) and fueling inflammation.
(3) Increasing periodontal destruction. Diabetes reduces new bone formation by enhancing apoptosis of bone-forming cells and by lowering periodontal ligament stem cells (PLSCs) proliferation and differentiation in osteoblasts (pink boxes). Diabetes enhances osteoclastogenesis by increasing RANKL release by osteocytes/osteoblasts, leading to osteoclast precursor (OCP) differentiation in osteoclasts (grey boxes). Diabetes augments gingiva tissue degradation by increasing release of metalloproteinases (MMP) and reactive oxygen species (ROS) by neutrophils and fibroblasts (violet boxes). (Barutta et al. 2022)

Type 2 DM - Periodontitis Direction (see Fig. 5B)

(1) Changes in the Microbiota

Data on the effect of DM on the oral microbiota are often inconsistent, likely because of a large number of confounders. On the other hand, recent studies suggest that DM can increase the pathogenicity of the periodontal microbiota as well as reduce oral microbial diversity. Further data indicate that DM causes an increase in IL-17, which alters the periodontal microbiome, favoring the pro-inflammatory response.

(2) Host Response

DM can increase the susceptibility to PD by enhancing the inflammatory response to oral bacteria (increased IL-1, IL-6, and TNF-α levels). A reduction in both anti-inflammatory cytokines (IL-4, IL-10, TGF-b1) and resolvins may also contribute to enhanced inflammation. Finally, DM can also induce epigenetic changes (DNA methylation changes in more than one thousand genes). Among them, TNF-α and IL-6 genes were hypomethylated and thus more likely to be expressed.

Hyperglycemia-induced nonenzymatic glycation reduces complement activation via the lectin pathway. Moreover, DM-induced epigenetic changes have been shown to inhibit both the classical and lectin complement pathways, while the alternative pathway remains active.

Studies reported enhanced numbers, but reduced function (chemotaxis, phagocytosis) of neutrophils in DM patients. Macrophages are increased in the DM periodontal tissue and polarized towards the M1 proinflammatory phenotype, while the number of anti-inflammatory M2 macrophages is reduced probably by changes in systemic metabolism. Changes are usually induced by inflammatory cytokines; however, elevated extracellular glucose levels also enhance glycolysis in macrophages and this may itself promote a shift from an anti-inflammatory to a proinflammatory status. (See more on page 7.)

Master thesis IIb

Effect of periodontal treatment on glycaemic control and other complications in diabetic patients

Master of Science in Periodontology - 2024

Objectives: This systematic review aims to evaluate the impact of initial periodontal intervention on the glycaemic control in patients diagnosed with type II diabetes. Further it also shows how non-surgical periodontal therapy helps improve the overall periodontal health in diabetic patients.

Material & methods: A comprehensive literature search was conducted, consisting of an electronic (using PubMed) and manual search to identify relevant studies published between 2010 and 2024 assessing the effect of non-surgical periodontal therapy on the glycaemic control of patients with type II diabetes. In total, 554 articles were found out of which 51 were shortlisted for screening, from which 14 studies were included in the review. Randomized Controlled Trials and Clinical Trials were included. In this review data on glycaemic control of various patients in different studies were collected and the effects of periodontal intervention on the glycaemic control were studied. Surgical periodontal interventions were disregarded.

Results: This systematic review revealed an improvement or change in the HbA1c levels as well as the periodontal parameters, among patients with type II diabetes mellitus following initial periodontal therapy, in the majority of included studies. Non-surgical periodontal therapy (NSPT) demonstrated efficacy in reducing HbA1c levels, suggesting a potential beneficial effect of addressing periodontal health in the management of type II diabetes mellitus.

Conclusion: This review establishes the significance of initial periodontal treatment to improve HbA1c levels in patients suffering from type II diabetes mellitus. It also proves that non-surgical periodontal therapy helps to improve the overall periodontal health of diabetic patients.

Key words: Initial periodontal therapy, type II diabetes mellitus, HbA1c levels, glycaemic control, non-surgical periodontal therapy

List of included studies

Studies with control group

El-Makaky, Y. & Shalaby, H. K. 2020. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: A randomized controlled trial. Oral diseases, 26(4), 822-829.

Engebretson, S. P. et al. 2013. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. Jama, 310(23), 2523-2532.

Gay, I. C. 2014. The effect of periodontal therapy on glycaemic control in a H ispanic population with type 2 diabetes: a randomized controlled trial. Journal of clinical periodontology, 41(7), 673-680.

Kanduluru, A. & Naganandini, S. 2014. Effect of nonsurgical periodontal treatment on clinical response and glycemic control in type 2 diabetic patients with periodontitis: . Journal of Indian Association of Public Health Dentistry, 12(4), 261-267.

Kaur, P. K. et al. 2015. Periodontal and glycemic effects of nonsurgical periodontal therapy in patients with type 2 diabetes stratified by baseline HbA1c. Journal of oral science, 57(3), 201-211.

Koromantzos, P. A. 2011. A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control. Journal of clinical periodontology, 38(2), 142-147.

Kumar, M. et al. 2015. Effect of periodontal therapy on glycemic control and circulating TNF-α in type 2 diabetic patients. International Journal of Diabetes in Developing Countries, 35, 96-102.

Moeintaghavi, A. 2012. Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial. Australian dental journal, 57(1), 31-37.

Qureshi, A. et al. 2021. Clinical efficacy of scaling and root planing with and without metronidazole on glycemic control: three-arm randomized controlled trial. BMC Oral Health, 21(1), 253.

Raman, R. P. C. et al. 2014. Effect of nonsurgical periodontal therapy verses oral hygiene instructions on type 2 diabetes subjects with chronic periodontitis: a randomised clinical trial. BMC Oral Health, 14, 1-10.

Telgi, R. L. 2013. Efficacy of nonsurgical periodontal therapy on glycaemic control in type II diabetic patients: a randomized controlled clinical trial. Journal of periodontal & implant science, 43(4), 177-182.

Tsobgny-Tsague, N. F. 2018. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. BMC oral health, 18, 1-8.

Studies without control group

Gaikwad, S. P. 2013. Effect of scaling and root planing combined with systemic doxycycline therapy on glycemic control in diabetes mellitus subjects with chronic generalized periodontitis: a clinical study. Journal of periodontal & implant science, 43(2), 79-86.

Sundaram, S. G. et al. 2023. Effect of Non-Surgical Periodontal Therapy on Systemic Inflammatory Markers, Glycemic Status and Levels of Proteinuria in Type 2 Diabetic and Non-Diabetic Patients With Chronic Periodontitis. Cureus, 15(9).

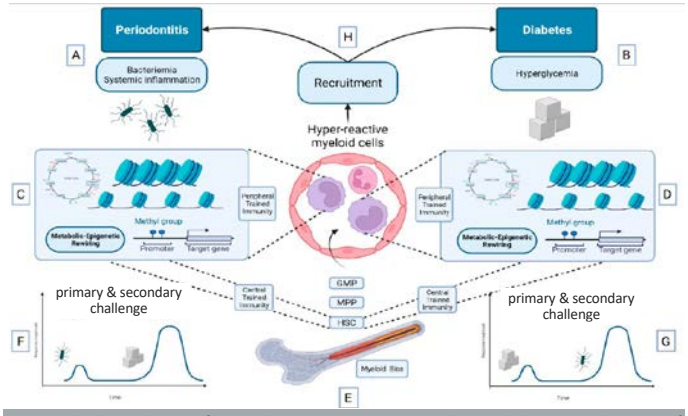

Fig. 6: The hypothesis of trained innate immunity as the underlying mechanism of the bidirectional relationship between diabetes and periodontitis (Barutta et al. 2022): (A) Periodontitis-induced release of bacterial products and inflammatory cytokines (B) diabetes-induced hyperglycemia inducing epigenetic rewiring of peripheral myeloid cells (C,D) and bone-marrow precursors (central trained immunity) (E). This generates hyper-active myeloid cells responding more effectively. (F) Myeloid cells epigenetically trained by an exposure to periodontitis-related bacterial products display an enhanced response to hyperglycemia and thus exacerbate diabetes-related inflammation. (G) myeloid cells epigenetically trained by an exposure to hyperglycemia display an enhanced response to bacterial products and thus exacerbate periodontitis-related inflammation. (H) Regardless of whether hyperactive myeloid cells are first affected by either periodontitis or diabetes, trained immunity can have a deleterious effect on both conditions. HSC (hematopoietic stem cells), MMP (multipotent progenitors), GMP (granulocyte/macrophage progenitors).

Background on mechanism - continued from page 5

DM also enhances myelopoiesis. Particularly intermittent hyperglycemia induces both proliferation and expansion of bone marrow myeloid progenitors, resulting in an increased release of monocytes in the circulation. In DM the proinflammatory environment created by macrophages and inflammatory cytokines favors differentiation of naive $CD4^+$ T cells in proinflammatory Th17 rather than in regulatory Treg. In turn, Th17/Treg imbalance can further fuel inflammation.

(3) Periodontal Tissue Destruction

Potential pathogenic mechanisms for enhanced periodontal tissue destruction in DM include: Diminished generation of collagen, exaggerated collagenolytic activity, enhanced RANKL-mediated osteoclastogenesis, and reduced new bone formation.

Neutrophils are the main cellular source of the increased collagenase activity with MMP-8 being the predominant host-cell-derived collagenase that leads to periodontal tissue destruction. In addition, advanced glycation end products (AGEs) can modify collagen structure, making the periodontal tissues more susceptible to periodontal breakdown.

DM enhances RANKL expression in osteocytes resulting in an increased RANKL/OPG ratio. Interestingly, inflammation is important, but periodontal bone loss does not occur in the absence of RANKL overproduction. Moreover, enhanced both RANKL production and osteoclast formation in DM could be diminished by a TNF-α-antagonist. Finally, DM reduces bone formation by apoptosis of bone lining cells, osteoblasts, and periodontal ligament fibroblasts.

Another interesting finding is, that inflammatory factors can elicit a form of memory also in innate immune cells, enabling them to respond more effectively to a second challenge, also called "trained immunity". This suggests that myeloid cells from patients with periodontitis or diabetis are in a trained state, which enables them to have an enhanced response to a second (inflammatory) challenge (see Fig. 6).

Consensus report and guidelines of the joint workshop

The following excerpts and summaries are based on the Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology published by Sanz et al. 2018 copublished also by Journal of Clinical Periodontology.

Clinical Relevance

Scientific rationale for the study: Periodontitis and diabetes are chronic non-communicable diseases that impact upon the course and outcome of each other and also appear to interact in a manner that increases the risk of all-cause and cardiovascular mortality. This joint workshop between the European Federation of Periodontology (EFP) and the International Diabetes Federation (IDF) updated the evidence from the international EFP/AAP workshop in 2012 and developed consensus statements about the relationship between these two important diseases.

Principal findings: Poor glycaemic control in diabetes is associated with poorer periodontal status and outcomes. Periodontitis is associated with dysglycaemia and increased insulin resistance in people with diabetes, as well as increased risk for incident diabetes and diabetes complications, including mortality. Periodontal therapy improves serum HbA1C levels and is safe to perform, although there is limited evidence for adjunctive therapies.

As this issue is directed mainly to oral health professionals the *recommendations for physicians and other medical heath related professions* as well as all related *guidelines for the patients* are not shown here due to limited space. The interested reader is referred to the respective full text of the reference.

Guidelines for oral health professionals for use in dental practice/office for people with diabetes mellitus

- People with diabetes should be advised that they have an increased risk for gingivitis and periodontitis. They should also be told that if they suffer from periodontitis, their glycaemic control may be more difficult to achieve, and they are at higher risk of other complications such as eye, kidney and cardiovascular diseases.
- Collect a careful history to highlight the type of diabetes, duration of the disease, the presence of any complications, diabetes therapy and concomitant therapies, remembering that most people with diabetes are also being treated with anticoagulant/antiplatelet drugs, antihypertensive drugs or lipid-lowering medications.
- Ask the patient how well controlled their diabetes is and when they last had their blood glucose levels checked. Request that patients bring a copy of their last HbA1C result, or that they report their latest results.
- Oral health education should be provided to all patients with diabetes. This should include individualized advice on relevant risk factors, and a tailored oral hygiene regime, including twice-daily brushing, inter-dental cleaning and in some cases the use of adjunctive chemical plaque control, may be appropriate.
- People presenting with a diagnosis of any form of diabetes mellitus should receive a thorough oral examination, which includes a comprehensive periodontal evaluation, to include full-mouth pocket chart and bleeding scores if indicated by periodontal screening.
- If no periodontitis is diagnosed initially, patients with diabetes should be placed on a preventive care regime and monitored regularly for periodontal changes.
- People with diabetes presenting with any acute oral/periodontal infections require prompt oral/periodontal care. If periodontitis is diagnosed, it should be managed without delay.

Guidelines (continued)

- Irrespective of the level of diabetes control, non-surgical periodontal therapy should be provided, as this may help to improve glycaemic control.
- Surgical periodontal and implant therapy is not indicated in patients who do not have acceptable diabetes control. In well-controlled patients, the results of surgical interventions are equivalent to patients without diabetes. However, attention should be paid to:
  – people with poorly controlled diabetes, who have an increased risk of postoperative infections;
  – patients managed with insulin or sulfonyl ureas, when the physician should be consulted about the timing of the planned procedure and a possible change in dosage of therapy to reduce the risk of intraoperative hypoglycaemia.
- People with diabetes who have extensive tooth loss should be encouraged to pursue dental rehabilitation to restore adequate mastication for proper nutrition.
- People with diabetes should also be evaluated for other potential oral complications, including dry mouth, burning mouth, candida infections and dental caries.
- For children and adolescents diagnosed with diabetes, an annual oral screening for early signs of periodontal involvement and dental caries is recommended starting as early as possible.
- Patients who present in the dental surgery/office without a diagnosis of diabetes, but with risk factors for type 2 diabetes should be informed about their risk for having diabetes and referred to a physician for appropriate diagnostic testing and follow-up care.
  – Patients' risk may be screened for using a validated questionnaire (e.g. in a Caucasian population, FindRisk Questionnaire; http://www.idf.org/webdata/docs/FINDRISC_English.pdf)
  – For oral health professionals with a special interest in diabetes, they may wish to consider screening based upon the recommendations of the American Diabetes Association (Diabetes Care 2017, see Table 1)
  – If symptomatic (polydipsia, polyuria, polyphagia, unexplained weight loss), refer directly to a physician.

Table 1 – Criteria for testing for diabetes or prediabetes in asymptomatic adults (from Diabetes Care 2017)

1. Testing should be considered in overweight or obese (BMI 25 kg/m^2 or 23 kg/m^2 in Asian American) adults who have one or more of the following risk factors: - AIC 5.7% (39 mmol/mol), IGT, IFG on previous testing - First degree relative with diabetes - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander) - Women who were diagnosed with GDM - History of CVD - Hypertension (140/90 mmHg or on therapy for hypertension) - HDL colesterol level <35 mg/dL) and/or a triglyceride level >250 mg/dL (2.82 mmol/L) - Women with polycystic ovary syndrome - Physical inactivity - Other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)
2. For all patients, disease testing should begin at age 45 years
3. If results are normal, testing should be repeated at a mınimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

Practical implications: The oral healthcare team have a role to play in identifying both prediabetes and undiagnosed diabetes mellitus, and physicians need to be aware of periodontal diseases and their implications for glycaemic control and complications in people with diabetes.

Save the date

The OREC platform would like to announce the **5th Sino-German Symposium** - this year focusing on **TMJ and Related Skeleton Treatment**. This event which will be held in a hybrid format for the first time. Registration for online participation is still possible: For more details and registration please visit our website at imc-orec.de.

Conference

Topics	Chairs
Monday 14th October	
Session I: Anterior Disc Displacement and Condylar Resorption	Prof. Günter Lauer, Prof. Dongmei He
Session 2: Condylar Fracture and Ankylosis	Prof. Jozsef Piffko, Prof. Minjie Chen
Tuesday 15th October	
Session 3: TMJ Reconstruction	Pd. Fillies, Prof Songsong Zhu
Session 4: TMJ-Cranio-Jaw Related Clinical Concerns	Prof. Andew Sidebottom, Prof Shanyong Zhang

More international congresses:

- XXIV. **Dental World**: October 10-12, Budapest, Hungary
- 29th **American World Dentistry Congress**: October 24-25, Toronto, Canada
- 27th **China International Exhibition on Dental Equipment Technology & Products**: October 24-27, Shanghai, China
- 42nd Conference on **Dentistry and Dental Marketing**: November 13-14, San Francisco, USA
- 29th **AEEDC Conference**: February 4-6, 2025 | Dubai, UAE

Continuing dental education

News on OREC platform

Only recently we have added a new option on our OREC platform. Having started in the summer semester 2024 it is now possible to attend various specially designed curricula or courses in the field of implantology, orthodontics, surgery and general dentistry with the primary aim to learn foundational and advanced knowledge in these specialisation areas.

All these curricula are focused primarily on theoretical and practical skills. If participants later wish to upgrade later their certificates into a Master's degree, the successful completion of the curriculum may contribute credits towards the respective Master Courses issued by the International Medical College (IMC) of the University of Duisburg-Essen. Next curricula in Implantology start on 1st of October 2024, the Curriculum on Orthognatic Surgery on 1st of April 2025. If you are interested in any of those curricula or courses - please visit our website for more information on the respective content and organizational details.

New dental journal

A new Open Access journal in the field of dentistry was founded this year in cooperation of the University of Münster with the International Medical College of the University Duisburg-Essen - the **Archive of Orofacial Data Science**. It is possible to publish original research or literature reviews such as condensed Master theses. This is a peer-reviewed, international open access journal with the aim to make research freely accessible to all, regardless of their financial status or institutional affiliation. This ensures that knowledge is accessible to a global audience, which promotes equality and inclusion. The journal can as of now be found on Google Scholar, and in the future will also be listed on PubMed. For more details please visit the journal's website.

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