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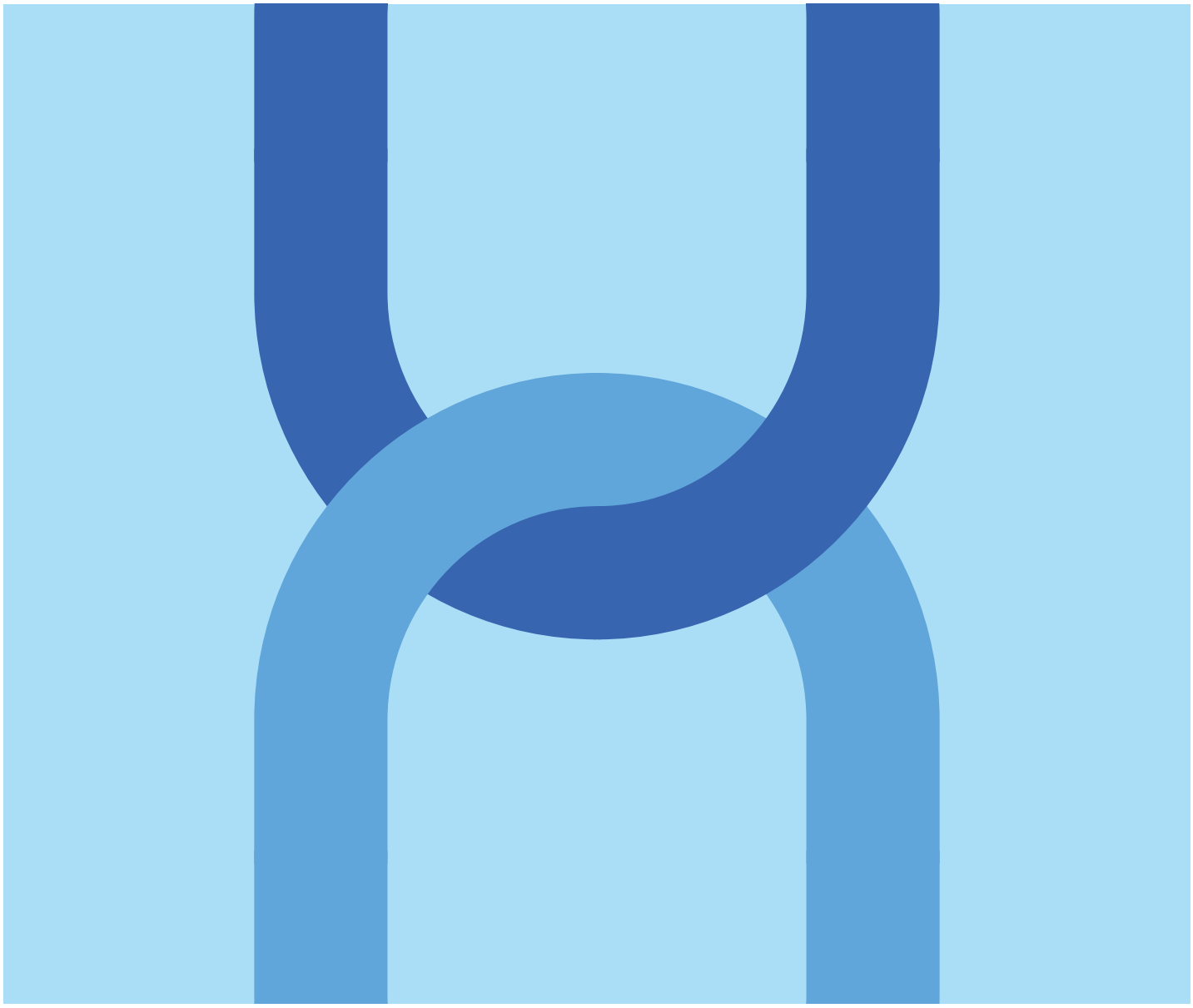
Summary of the evidence for **pathogenic mechanisms linking periodontitis** and **diabetes mellitus**

(based on the systematic review by Polak & Shapira 2018)

Written by **Prof Henrik Dommisch**



Perio & Diabetes

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Summary of the evidence for **pathogenic mechanisms linking periodontitis** and **diabetes mellitus**

Part I

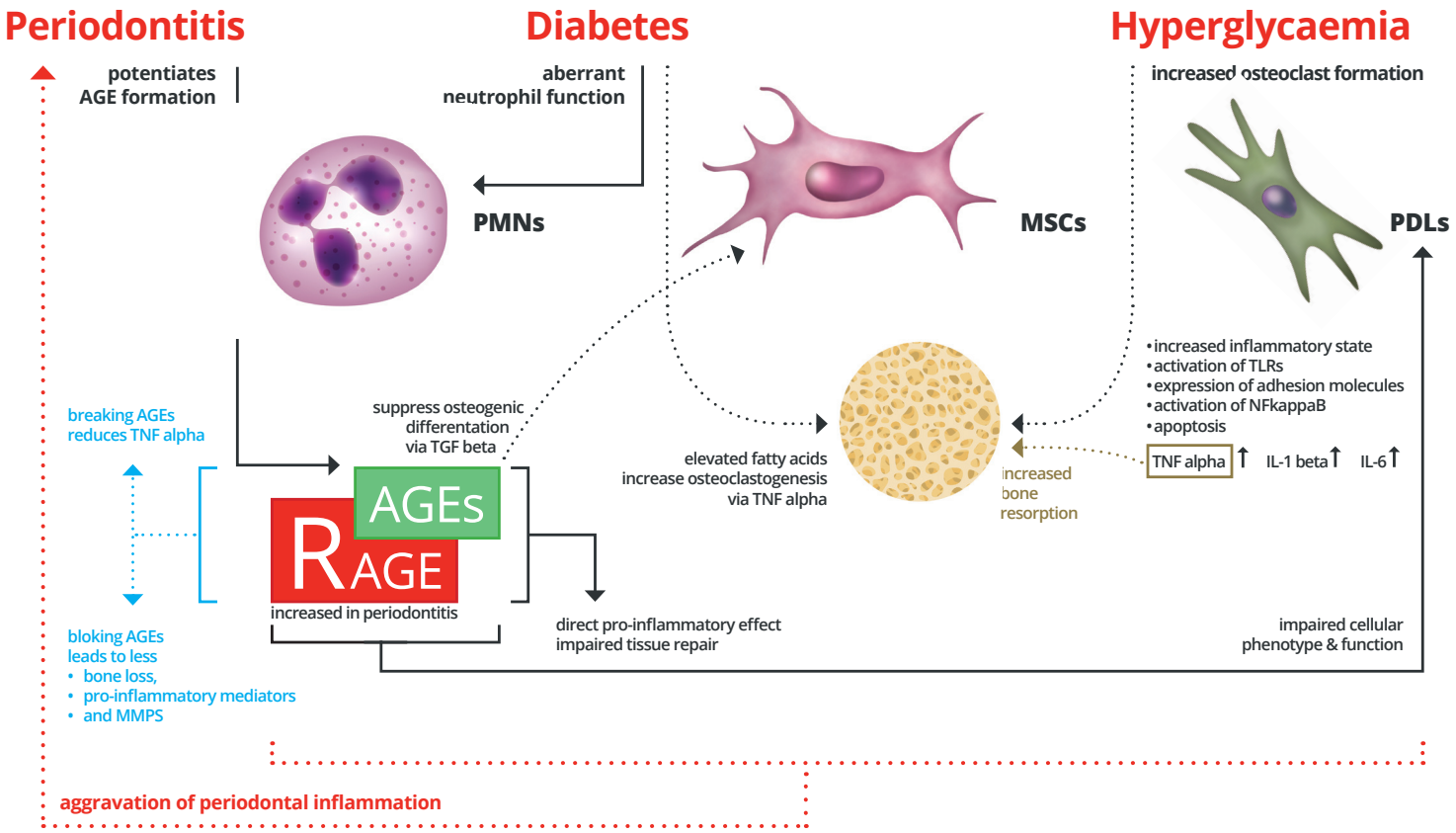
Summary of the evidence for pathogenic mechanisms linking periodontitis and diabetes mellitus

(based on the systematic review by Polak & Shapira 2018)

The relationship between diabetes mellitus and periodontitis was first described 25 years ago (Löe 1993). Diabetes mellitus is a metabolic disease that is characterised by chronic hyperglycaemia and, once this condition is present, patients are required to take appropriate medications for the rest of their lives. As diabetes mellitus is not a transient condition, patients may develop various complications. Diabetic complications result mainly from microvascular and macrovascular alterations that affect important structures such as the heart, the brain, the kidneys, and the eyes. In 1993, Löe described periodontitis as the sixth complication of diabetes mellitus, and this subsequently became generally accepted within the scientific community.

As knowledge about the interaction between diabetes mellitus and periodontitis grew, a bidirectional relationship in which each condition affects the other, was revealed. In this context, it has been shown that patients with diabetes mellitus exhibit more severe and rapidly progressive forms of periodontitis when compared to patients without diabetes. Furthermore, patients with periodontitis tend to demonstrate elevated glycaemic blood levels and may thus be prone to developing diabetes mellitus.

Figure 1



One the major remaining questions is: What are the pathogenic connections and mechanisms that link periodontitis and diabetes mellitus?

There are several levels of potential pathogenic mechanisms (see figure 1), and these may be classified as: (i) microbial factors, (ii) pro-inflammatory mediators, (iii) immune cells, (iv) hyperglycaemia, (v) advanced glycation end-products (AGEs) and their corresponding receptor (RAGE), and (vi) homeostasis of the alveolar bone in conjunction with hyperglycaemia.

Pathogenic mechanisms linking periodontitis and diabetes

1. There is no strong evidence that the **microbial biofilm** of patients with periodontitis is affected when diabetes mellitus is present. Recent data, however, indicate that diabetic patients show differences in the microbial composition of the dental-plaque biofilm, but there is not yet any explanation of causality.

2. Patients with periodontitis and diabetes mellitus exhibit elevated levels of the

pro-inflammatory mediators interleukin (IL)-1 beta and IL-6, and the RANKL/OPG (receptor activator of nuclear factor kappa B [NFkappaB] ligand/osteoprotegerin) ratio when compared to patients with periodontitis alone, and these cytokine levels demonstrate a quantitative relationship with the glycaemic control. In patients with diabetes, this hyper-inflammatory state is supported by the evidence for increased levels of IL-1 beta, IL-6, and tumour necrosis factor alpha (TNF alpha) measured in the gingival crevicular fluid (GCF). These mediators and the acute-phase protein C-reactive protein (CRP) are part of the pathogenic mechanisms that explain insulin resistance.

In addition to the previously mentioned pro-inflammatory mediators, adipokines – such as resistin, substance P, and receptors of the innate immune response (toll-like receptors, TLR2 and TLR4) – are also associated with diabetes.

The decrease of the inflammatory burden (TNF alpha and CRP) influences metabolic control, and this may therefore provide a partial explanation for improved HbA1c levels after periodontal therapy.

3. The evidence regarding an altered **immune-cell function** (neutrophils, T-cells) is limited. However, there are other cells, such as periodontal ligament (PDL) fibroblasts, that also fulfil immune-cell function by secretion of pro-inflammatory mediators, expression of adhesion molecules, and activation of TLRs and NFkappaB in response to advanced glycation end-products (AGEs).

4. In the presence of high blood sugar, the non-enzymatic glycation of proteins, lipids, and nucleic acids (Maillard reaction) leads to so-called **AGEs**, which exhibit direct pro-inflammatory and pro-oxidant effects on cells. On multiple cells, the receptor for AGEs – named **RAGE** – is expressed. Activation of this receptor impacts the cellular phenotype and function, including tissue-repair mechanisms. The impact of AGEs and RAGE on the aggravation of periodontitis is underpinned by their elevated levels in diabetic patients with periodontitis.

5. **Hyperglycaemia** is associated with an impaired **bone homeostasis** through the negative influence of AGEs and fatty acids on osteogenesis. In this context, the pro-inflammatory mediator TNF alpha seems to play an important role by elevating chemokine expression, which leads to an increased osteoclast activity.

Part II

Editorial / expert opinion and additional points to consider

1. In patients with diabetes mellitus and periodontitis, the microbial composition of the dental-plaque biofilm may be different when compared to patients with periodontitis alone. The causal relationship, however, is still under investigation.

   Recent technical developments, such as the introduction of 16s rRNA sequencing, allow more precise data generation. Studies that utilise comparable techniques in terms of whole-microbiome analysis on larger-sized populations are necessary to provide more detailed information.

2. The inflammatory state is an important aspect in the etiopathogenesis of both conditions, periodontitis and diabetes mellitus. Inflammatory mediators in the blood stream may impair glycaemic control by influencing the insulin resistance. In turn, increased blood sugar leads to elevated levels of advanced glycation end-products (AGEs), which then trigger inflammation and aggravate periodontitis.

   This is a vicious circle, which can be interrupted only by a systematic treatment concept that addresses both glycaemic control and periodontitis. The exact pathogenic mechanisms of how the periodontal inflammatory burden influences metabolic control are still being investigated.

   As pro-inflammatory mediators are precisely regulated, knowledge regarding the pro-inflammatory state opens new avenues for diagnostic tests to detect pre-diabetes, for innovative anti-inflammatory treatment concepts, and – most importantly – for prevention.

3. The identification of functional changes in immune cells – such as neutrophils and T-cells – as the result of hyperglycaemia and/or diabetes mellitus is extremely difficult because these cells are responsible for multiple functions and for regulating pathways involved in innate and adaptive immune responses. It is important to observe that not only “classic” immune cells but also any other cell – e.g. epithelial cells, fibroblasts, and osteoblasts – can synthesise both cell surface receptors such as TLRs and molecules with pro-inflammatory and antimicrobial functions as part of their innate immune response.

4. The formation of AGEs and/or the interaction with RAGE are the major pathogenic mechanisms that explain the aggravated periodontal destruction in patients with diabetes. The level of glycated haemoglobin (HbA1c) mirrors the formation of AGEs in the body. Thus, in patients with diabetes mellitus, it is of the utmost importance to monitor HbA1C levels, not only as part of diabetic control but also in the treatment of inflammatory diseases, such as periodontitis.

Communication and collaboration between physicians and dental professionals are the prerequisites for successful patient management.

Understanding the pathogenic mechanisms that link diabetes mellitus and periodontitis is essential for an optimal therapeutic concept based on precision medicine. Thus, both clinical and basic science research are enormously important in order to gain knowledge from different perspectives. With a sound knowledge of the pathogenic mechanisms, it will be possible to develop new diagnostic tools that will eventually lead to new therapeutic and preventive strategies for both conditions, periodontitis and diabetes mellitus.

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