A cross-link between diabetes mellitus type 2 and periodontal disease

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ABSTRACT

Diabetes mellitus is a frequently occurring disease and its prevalence is dramatically rising worldwide. Diabetic patients are commonly encountered in the dental office. Extensive research has been conducted to explore the impact of diabetes on oral health. Among oral diseases examined for a possible relationship to diabetes, the association of periodontal disease with diabetes mellitus type 2 is well established and is based on high quality evidence.
Periodontitis and diabetes mellitus are both inflammation-based diseases, and host inflammatory response is considered as the main mechanism underlying most of the modifiable risk factors in both conditions. A two-way relationship is proposed. A dysbiotic biofilm on the tooth surface in the gingival area may induce an inflammatory response in the surrounding periodontal tissue, which in a susceptible host can accelerate and eventually result in loss of attachment. In a diabetes patient hyperglycemia can aggravate the periodontal inflammation and contribute to reduced repair of inflamed tissue. The increased risk of periodontal and peri-implant inflammation and impaired tissue healing in patients with hyperglycemia are among the issues elaborated in this review, in addition to discussing the biological background. The need for a careful supportive periodontal therapy is underscored.

EMNEORD Diabetes | periodontitis | hyperglycemia | systemic disease

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DIABETES MELLITUS is a chronic metabolic disease characterized by increased glucose levels in blood, hyperglycemia. Type 1 (T1DM) and type 2 (T2DM) diabetes mellitus are the most prevalent types, amounting to about 10% and 90%, respectively (1). Whereas T1DM is the consequence of autoimmune destruction of pancreatic β-cells resulting in deficient insulin production, T2DM results from an incapacity of β-cells to produce sufficient insulin to maintain normoglycemia and/or increased cell resistance to endogenous insulin. Hyperglycemia is harmful for many of the body's systems, and is associated with direct and indirect complications.

The degree to which diabetes is controlled has mostly been assessed by measuring the percentage of glycated hemoglobin, HbA1c, in blood. Glucose is irreversibly bound to hemoglobin in the red blood cells over their lifetime, which is approximately 120 days. HbA1c, "long-term blood sugar", reflects the average blood sugar during the last 2-3 months. Recently there has been a change in the reporting units for HbA1c from percentage to mmol glycated hemoglobin per mol hemoglobin (mmol/mol). HbA1c ≥ 48 mmol/mol (≥ 6.5%) on two separate tests indicates T2DM.

EPIDEMIOLOGY

Prevalence of diabetes and periodontitis

Diabetes and periodontitis are common chronic inflammatory conditions and prevalence varies across populations, genders and age groups, and with disease definitions and methods for data collection. In 2010, severe periodontitis was the sixth most prevalent health condition in the world, affecting approximately 11% of the global adult population (1). The incidence is expected to rise due to longer life span and better tooth retention. Worldwide, diabetes affects more than 425 million people aged 20–79 years, and each year an estimated 9 million new cases of diabetes will be diagnosed (2). Although the prevalence of diabetes is increasing, a recent study reported decreasing incidence of T2DM in Norway from 2009-2014, with an annual reduction of 10.1% (3).

Periodontitis related to diabetes and vice versa

A two-way relationship between diabetes and periodontitis is proposed, meaning diabetes increases the risk for periodontitis and vice versa. Epidemiological studies have shown diabetes to be a risk factor for periodontitis, and periodontitis has been called the 'sixth complication of diabetes' (4). Periodontitis is more prevalent in diabetic individuals. Numbers from US adults 65 years or older indicate that 83% of diabetic patients and 73% of non-diabetic individuals have periodontitis (5). Others found the risk of periodontitis to be increased by approximately threefold in diabetics compared with non-diabetics (6).

Poorly controlled diabetes is stronger associated with periodontitis than well controlled diabetes, and increases the risk for onset or progression of periodontitis with 86% (7). Subjects with diabetes have more marginal bone loss than non-diabetics (8). Individuals with an HbA1c level of 42 – 47 mmol/mol (6.0 – 6.4 %) (prediabetes), having blood glucose levels above normal but below diabetes thresholds, are at risk of developing diabetes. Prediabetic subjects exhibit periodontal attachment loss in a state between diabetes patients and normoglycemic individuals (9).

Diabetics have more severe periodontitis than non-diabetics (5), but the impact of periodontitis on diabetes condition is not that clear. It seems that diabetes is more prevalent in periodontitis patients than in periodontally healthy individuals. A recent study calculated the prevalence of diabetes according to periodontal health and disease to be 9.6% and 13.1%, respectively (10). Furthermore, periodontitis patients needing periodontal surgery have 19% higher risk to get diabetes within 2 years compared with periodontitis patients not in need for surgery (11). Periodontitis is associated with elevated levels of HbA1c and fasting blood glucose, and worsening of glycemic control (12), by which periodontal destruction and outcomes of periodontal therapy seem to deteriorate (13).

Missing teeth or periodontitis have been associated with increased hazards for incident diabetes (14-16). In a large study with over two decades of follow-up of nondiabetic males and females aged 25-74 years, periodontitits was found to be an independent predictor of incident diabetes (16). This was confirmed in a recent prospective cohort study, where moderate to severe periodontitis was an independent risk predictor of incident T2DM in a group of 58-72 year-old-men (15).

To conclude, substantial evidence demonstrates an independent association between diabetes and periodontitis. However, most of the studies reporting an association between diabetes and periodontitis have cross sectional designs, and there is a need for more prospective longitudinal studies to strengthen the scientific evidence for a causal relationship (17). Also, one should be aware of that almost none of the studies have taken into account the presence of other oral inflammatory pathologies, such as periapical pathology of endodontic origin.

Peri-implant disease related to diabetes

Meta-analyses have identified diabetes mellitus as a risk factor for peri-implantitis, but poor glycemic control has not been found associated with peri-implant mucositis (18). The prevalence of peri-implantitis increases in a dose-response relationship with HbA1c. Patients with hyperglycemia were two to three times more prone to develop peri-implantitis compared to non-diabetic individuals (18-20). However, there are studies where diabetes mellitus was not reported as a risk factor for peri-implantitis (21,22). Because of few studies and a previous lack of a globally accepted case definition of peri-implant diseases, the scientific evidence is limited.

PATHOGENESIS

Diabetes is strongly associated with microvascular (diabetic nephropathy, neuropathy and retinopathy) as well as macrovascular (cardiovascular diseases, stroke) complications (23). Over time, hyperglycemia has an injurious effect on the endothelial cells causing thicker microvascular basal membranes, impaired vessel wall elasticity and reduced lumen with circulatory consequences. Slower fibroblast proliferation and reduced collagen synthesis combined with increased collagenase activity incur enhanced collagen degradation. Inflammatory response may be weakened by neutrophil dysfunction, impaired chemotaxis, phagocytosis and adherence with increased risk of infection (Fig. 1). The central pathological mechanism in macrovascular disease is the process of atherosclerosis thought to result from chronic inflammation.

What biological mechanisms link diabetes to periodontal disease?

Periodontitis and diabetes mellitus are chronic inflammation-based diseases, and host inflammatory response is considered the main mechanism underlying most of the modifiable risk factors in both conditions.

Periodontitis is characterized by destruction of connective tissue, loss of periodontal attachment and resorption of alveolar bone (Fig. 2). The disease is initiated by dysbiotic microbiota in the dental biofilm (24), which in a susceptible host, lead to destruction of the tooth-supporting structures. Thus, dental plaque is required, but not sufficient to induce periodontitis. It is the interplay between the pathogenic bacteria and the host inflammatory response which is decisive for the outcome (25). ▶

Fig. 1.
Molecular and cellular events in hyperglycemia

- Glycation of proteins and collagens to advanced glycation end products (AGEs)
- AGEs bind to receptors on monocytes, macrophages, endothelial cells
- Increased production of pro-inflammatory cytokines; IL-1b, IL-6, TNF-a, RANKL/OPG
- Activation of immune cells
- Neutrophil dysfunction
- Reduced chemotaxis
- Inhibited inflammatory response
- Vascular changes
- Slower fibroblast proliferation
- Reduced collagen synthesis
- Increased collagenase activity
  => Tissue destruction
  => Reduced regenerative ability
  => Reduced wound healing

The periodontal bacteria and/or their degradation products may penetrate host tissue and trigger a complex innate-adaptive immune interaction. A systemic inflammatory response to subgingival bacteria leads to systemically elevated levels of pro-inflammatory mediators such as interleukin (IL)-1β, IL-6, C-reactive protein (CRP), tumor necrosis factor alpha (TNFα), receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratio and oxygen metabolites (Fig. 2) (17,26). Increased levels of these cytokines and markers that facilitate insulin resistance are also present in uncontrolled diabetes, where a quantitative relationship with glycemic control has been shown. Patients with both periodontitis and diabetes have higher levels of pro-inflammatory mediators compared to those with periodontitis only. Elevated pro-inflammatory factors systemically and in the gingiva of patients with poorly controlled diabetes suggest a biological pathway that may aggravate periodontitis.

Animal and cell culture studies as well as human studies show clearly that hyperglycemia conditions augment the pro-inflammatory response in the periodontal environment (17). However, the level of evidence to support biological mechanisms mediating the effect of periodontitis on diabetes control is moderate.

Advanced glycation end products (AGEs)

An important chronic effect of hyperglycemia involves the irreversible non-enzymatic glycation of proteins and lipids to the formation of advanced glycation end products (AGEs). (5,17). Monosaccharides, such as glucose, fructose, and glyceraldehyde can react non-enzymatically with amino groups of proteins, lipids and nucleic acids to form senescent macromolecules termed AGE. AGE modification alters the structural integrity and function of various types of macromolecules, and have substantial effects on cell-cell, cell-matrix and matrix-matrix interactions (27). The receptor for AGEs, RAGEs, are found on the surface of many different cell types, such as monocytes, macrophages and endothelial cells, and interaction of AGE to RAGE has been shown to evoke oxidative stress, inflammatory, thrombotic and fibrotic reactions in numerous kinds of cells. It results in increased permeability of the blood vessels, increased production of pro-inflammatory cytokines, increased osteoclast activity, and reduced regenerative ability. AGE-modified macromolecules are hardly metabolized and eliminated from the body, and cause a hyper-reactive inflammatory condition. The binding of AGE to collagen may aggravate the periodontal inflammation and contribute to reduced repair of periodontal tissue, especially in diabetic patients with poor glycemic control.

Subgingival microbiome in diabetes

T2DM patients may have higher concentrations of glucose in gingival crevicular fluid (GCF). Consequently, a different bacterial population might be expected in such a glucose-rich environment. New sequencing technology and identification methods have revealed some difference in the subgingival microbial profile between chronic periodontal disease with and without T2DM (28). Molecular periodontal microbiome studies indicate a possible association between altered glycemic status in T2DM and changes in the periodontal microbiome, but with no evidence for causal relationships (17,29,30). Thus far, the data should be treated with some caution because the available studies suffer from a great variability of methodology, case definitions, diagnostic criteria and microbiological analyses, and are small-scale studies (28,31).

TREATMENT

Effect of periodontal treatment in diabetic patients

In recent years, the effect of periodontal treatment on the reduction of HbA1c in patients with diabetes has been debated. Reductions have been observed in a number of randomized controlled clinical studies, and the effect of periodontal treatment on hyperglycemia has been touted as equivalent to the addition of a second drug to a pharmacological diabetes treatment regimen (32).

A requirement for a causal effect of periodontal disease on diabetes would be that periodontal treatment reduces hyperglycemia and ultimately diabetes complications. A recent study reported mean reductions in HbA1c at 3-4 months following periodontal therapy ranging from -0.27% to -1.03% (33). Whether this effect remains at 6 months and beyond is not known, despite a recent study indicated small improvements in the long term (34). Although a reduction of HbA1c of 1.0 % or less may seem negligible, it may have significant clinical impact. Each 1% reduction of HbA1c has been estimated to reduce the risk for diabetes complication end points; 21% for diabetes-related deaths, 14% for myocardial infarction and 37% for microvascular complications (35). Importantly, studies investigating the effect of periodontal therapy on HbA1c levels in diabetic patients have not been unequivocal.

Collectively, reviews on the effect of periodontal intervention on hyperglycemia conclude that additional trials are needed to clarify the relationship. It seems that the worse the glycemic state and the worse the periodontitis, the more likely HbA1c reduction following periodontal therapy, due to greater potential for improvement in disease status (34,36).

In summary, the treatment of periodontitis in diabetic patients may improve hyperglycemia and potentially even prevent some of the complications described herein. Arguably the most important outcome of periodontal treatment in diabetes patients is improved oral health, retention of teeth, and prospects of dental rehabilitation in case of inadequate masticatory function, all of which improve quality of life and also may facilitate glycemic control. There is no evidence for a superior periodontal treatment modality in terms of glycemic reduction, and therefore treatment should be performed similar to the treatment in non-diabetics. Nevertheless, the need for careful supportive periodontal therapy performed on a regular basis must be emphasized.

clinical relevance

Treatment advice

- Ask the patients about their glycemic control
- Inform patients with diabetes and pre-diabetes about the increased risk for periodontitis and the importance of regular maintenance care
- Diabetes patients should be enrolled in a preventive care regime and monitored regularly for periodontal changes
- Careful supportive therapy is particularly critical for periodontitis patients with diabetes
- Peri-implantitis and lack of osseointegration seem to be more prevalent in poorly controlled diabetes patients than in non-diabetic subjects. This difference has not been seen between well maintained diabetic patients and non-diabetic subjects.

Poorly controlled diabetes and periodontitis

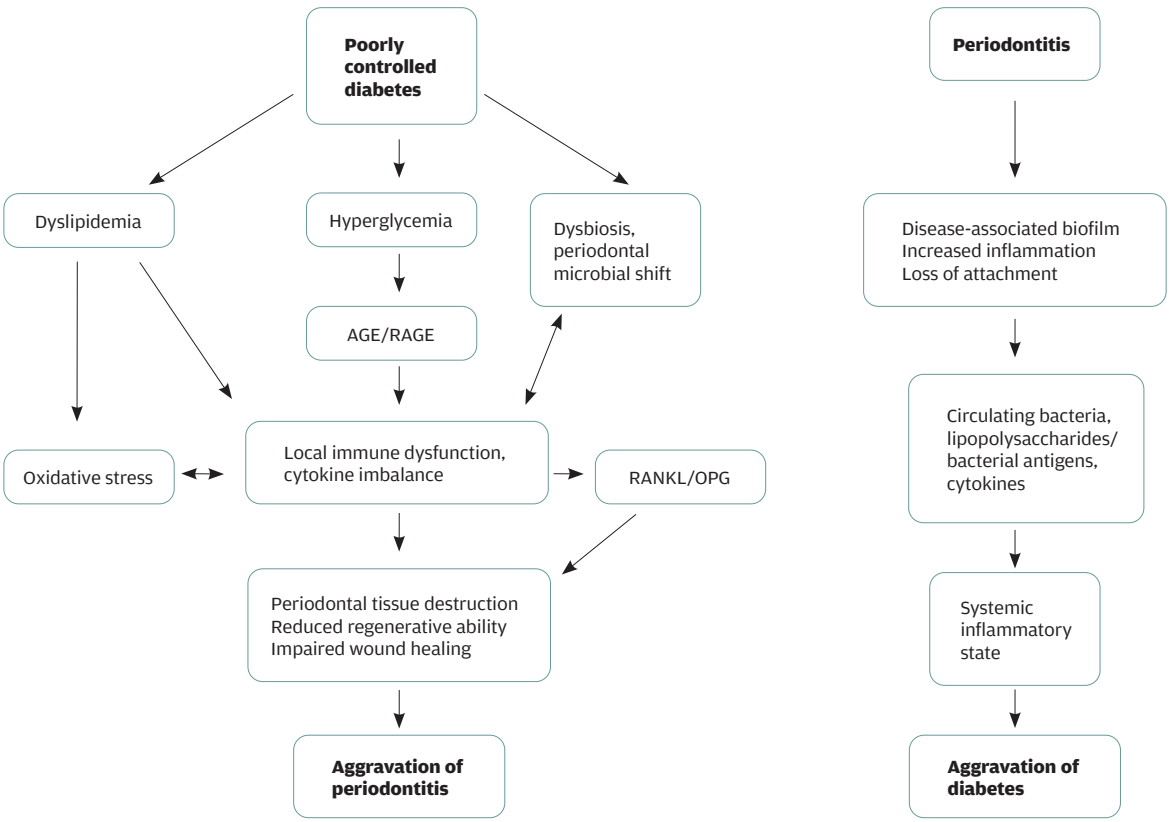

Fig. 2. The figure depicts possible consequences of hyperglycemia on periodontal condition with deterioration of periodontitis in a susceptible host, as well as a possible effect of periodontitis on diabetic control (Modified from Polak and Shapira, 2018 (17)).
Fig. 2. Illustrasjonen viser mulige konsekvenser av hyperglykemi på periodontale forhold med forverring av periodontitt hos disponerte individer, så vel som en mulig effekt av periodontitt på diabetes kontroll (Modifisert fra Polak og Shapira, 2018 (17)).

Effect of hyperglycemic treatment on patients with periodontitis

Periodontal disease has a negative impact on quality of life and may lead to tooth loss (37), and control of glycemic status is an important goal of a comprehensive periodontal treatment. The important role of glycemia in periodontal disease was recently highlighted following the latest World Workshop on the Classification of Periodontal Diseases as the glycemic state of patients is now a key part of the periodontitis diagnostic grading system (38). Although diabetes is an established risk factor for periodontal disease, there is a paucity of clinical studies demonstrating that control of diabetes may improve periodontal status. It is not biologically unreasonable that a systemic decrease of these inflammatory markers following diabetic treatment may lower periodontal inflammation, but clinical data is lacking. Such clinical study designs may have ethical challenges. There are, however, mechanistic evidence linking hyperglycemic status to periodontal status (39-41).

Hyperglycemia in subjects with dental implants

Diabetes mellitus has previously been considered to be a contradiction to oral implant treatment, and the level of glycemic control has been emphasized (42,43). Implant failure was reported to be more prevalent in subjects with T1DM than non-diabetics (44,45). Others could not confirm this (8). Today, there are several studies indicating that implant treatment is safe in subjects with diabetes, especially well-maintained patients (46).

CONCLUSION

Periodontitis and DM are highly prevalent chronic disorders, inflammation being an executive player in the association between them. Diabetes clearly increases the risk of periodontitis, whereas the impact of periodontitis on glycemic control is less clear. The importance of clinically preventive and therapeutic monitoring of DM and periodontitis is emphasized. ◆

ABSTRACT (NORSK)

EN KRYSSKOBLING MELLOM DIABETES TYPE 2 OG PERIODONTAL SYKDOM

Diabetes mellitus er en hyppig forekommende sykdom, og dens utbredelse øker dramatisk verden over. Mange av pasientene vi får til behandling i tannlegestolen, har diabetes. Effekten av diabetes på oral helse er gjenstand for omfattende forskning. Av orale sykdommer som er undersøkt for en eventuell assosiasjon til sykdommen, finner man periodontitt, og det foreligger nå solid dokumentasjon på at det er en assosiasjon mellom periodontitt og diabetes mellitus type 2. Periodontitt og diabetes mellitus er begge betennelsesrelaterte sykdommer. Vertens inflammasjonsrespons blir ansett som hovedmekanismen bak de fleste av de modifiserbare risikofaktorene ved begge tilstander. Relasjonen synes å være toveis. En dysbiotisk biofilm gingivalt kan indusere en inflammatorisk respons i periodontalt vev, som i en mottakelig vert kan akselerere og til slutt føre til tanntap. Hos en diabetespasient kan hyperglykemi forverre periodontal inflammasjon og bidra til redusert reparasjon av betent vev. Motsatt kan en effekt av periodontitt på diabeteskontroll heller ikke utelukkes.

Økt risiko for periodontal og peri-implantat inflammasjon og hemmet vevstilheling i pasienter med hyperglykemi er blant temaene som omtales i denne artikkelen. I tillegg diskuteres mulig biologisk bakgrunn for dette. Behov for nøye oppfølging av diabetespasienter understrekes.

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