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INTEGRATED STUDY MASTER'S THESIS

The Relationship Between Diabetes Mellitus and Periodontitis

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Abstract

Diabetes mellitus and Periodontitis are two of the most common chronic diseases worldwide. As they co-occur frequently in the same patient and exacerbate each other, a precise understanding of their pathogenesis is needed for their management and prevention. Many aspects in the association of their pathogenesis still remain unclear. Further, the awareness of the concomitant occurrence is low amongst patients and clinicians. The research question of this Master thesis is "How do Diabetes mellitus and Periodontitis interact with each other and why?". The research strategy was a research literature review of the available research literature. Key findings are that Diabetes mellitus induces chronic inflammation via its characteristic hyperglycemia, oxidative stress and immune cell stimulation. Periodontitis is a chronic inflammation of the periodontium and has systemic effects via inducing an oral dysbiosis and an altered systemic inflammatory response. Key findings of this thesis are that Diabetes mellitus exacerbates periodontitis by an altered and impaired immune response, oxidative stress and microvascular changes in the periodontal tissues amongst other tissues. Periodontitis vice versa exacerbates Diabetes mellitus by an altered immunological Response and the formation of insulin resistance. The key Management is that both diseases can be easily avoided by lifestyle Management, sports, proper oral hygiene and smoking cessation.

Key words: Diabetes, Periodontitis, Diabetes and periodontitis relations, dysbiotic shift, hyperglycemia, chronic inflammation, lifestyle modifications.

Outline

1.Introduction

This thesis is a narrative research literature review of the recent research literature about the interactions of diabetes mellitus and periodontitis. The objectives are to understand the pathogenesis, clinical presentation and the management of both Diabetes mellitus and Periodontitis and especially to understand the interactions between these two diseases as they are two of the most common inflammatory diseases worldwide, have an increasing prevalence and occur very frequently concomitant in the same patients (Bui et al, 2019; Graves et al, 2020). The research question is “How do Diabetes mellitus and Periodontitis interact with each other and why?”. For narrowing the research question, in Diabetes only type 1 and type 2 Diabetes mellitus were examined and studied as they are the most common types; in periodontitis, this research literature review focusses on the microbiology and immunology, excluding the classification of periodontal diseases and gingivitis; nevertheless, the 2018 classification of periodontitis is mentioned.

Regarding the interactions of Diabetes mellitus and Periodontitis, common factors in the pathogenesis and etiology are described to be able to explain why Diabetes mellitus and Periodontitis are associated with each other and occur often concomitantly in the same patients. The interactions between Periodontitis and Diabetes mellitus are the bestinvestigated bidirectional relationships to systemic diseases (Bui et al 2019; Sanz et al, 2018). Despite that, many aspects remain unclear (Jepsen et al, 2020). As well, the awareness of the bidirectional association of both diseases is relatively low (Shimpi et al, 2020; Panakhup et al 2021). Conclusions of this thesis are that Diabetes mellitus exacerbates periodontitis by an altered and impaired immune response, oxidative stress and microvascular changes in the periodontal tissues amongst other tissues, that Periodontitis vice versa exacerbates Diabetes mellitus by increased inflammation, impaired immunological responses and the formation of insulin resistance. Plaque control in Periodontitis may arrest the chronic inflammation and the progression of periodontitis, but not of Diabetes. Diabetes treatment by lifestyle changes and medication regimen improve the immune responses (also to periodontitis), but the lifestyle changes are usually multimodal and affect diet habits as well.

1.1. Material and Methods

The research literature search strategy was manual research in the PubMed database with the key words “periodontitis”, “diabetes mellitus” and “diabetes and periodontitis”. As this master thesis aims at reflecting the most recent knowledge, the filters “literature not older than five years”, “free available articles/ articles available via VU VPN on PubMed database” and “languages: English and German” are applied. Each article was screened according to their importance for this thesis especially regarding the pathogenesis of both diseases, to find out common factors of the etiology and to investigate the concomitant pathogenesis.

1.2. Importance

Periodontitis is a very common inflammatory disease in adults, causing speech impairment, low self-esteem, reduced quality of life and has the risk of causing or exacerbating systematic inflammations (Stöhr et al, 2021). Similar, Diabetes Mellitus is also a very common disease in adults based on hyperglycaemia, thus causing immune system dysfunction and it has a significantly increasing prevalence (Harreiter & Roden, 2019; Lovic et al, 2020). A common problem is that approximately half of the people with diabetes are unaware of their disease which is a feature similar for periodontitis (Kocher et al, 2018).

Many patients have both diseases because people with Diabetes are more prone to have periodontitis (Kocher et al, 2018) and other diseases (Reddy et al, 2022). Diabetes mellitus has frequent complications as microvascular dysfunction which causes the deterioration of periodontitis (Petersmann et al, 2019). Vice versa periodontitis causes a state of chronic inflammation which impairs the patient’s immune system (Cardoso et al, 2018).

2.Diabetes mellitus

2.1. Etiology and causes

Diabetes mellitus is a collective group of heterogenous diseases which all have hyperglycaemia (elevated blood sugar levels) in common (Harreiter et al, 2019; Ikegami et al, 2022; Petersmann et al, 2019; Harreiter et al, 2023). The disease name is combined of the terms diabetes (latin “pass through”) and mellitus (lat. sweet, sugar) (Demir et al, 2021).

Insulin insufficiency occurs either due to pancreatic beta cell dysfunction, impaired insulin secretion or both (Reddy et al, 2022; Petersmann et al, 2019). Another cause of hyperglycaemia is the absence of body's reaction to insulin (Ikegami et al, 2022), which impairs the glucose metabolism.

Regarding Diabetes mellitus (DM), we need to distinguish between type 1 and type 2 Diabetes. Especially in type 1 DM "Genetic predisposition of human leukocyte antigen (HLA) with class 2 genes" (Reddy et al, 2022) plays a significant role and restricts the amount of type 1 DM patients to approximately 10 % of all diabetic patients (Harreiter et al, 2019; Harreiter et al, 2021; Cloete 2022). A slowly decreasing pancreas function by aging also leads to diabetes type 1 (Ikegami et al, 2022; Petersmann et al, 2019). Vitamin D deficiency is another factor in the etiology of both type 1 and type 2 DM (Reddy et al, 2022). Other influencing factors in the progression of type 1 DM are environmental toxins and viruses which cause inflammation of the Langerhans islets, so called insulitis (Graves et al, 2019).

The insulin insufficiency can explained so that oxidative stress reactions are damaging pancreatic beta-cells and cause endothelial dysfunctions, thus continuously and progressively decreasing the pancreas function and impairing metabolic pathways as the glycolysis (Darenskaya& Kolesnikov, 2021). The oxidative stress reactions are caused by oxygen metabolism byproducts as superoxide, hydroperoxyl radical, hydroxyl radical and nitric oxide which stimulate inflammatory responses (Darenskaya& Kolesnikov, 2021).

Risk factors leading to manifested type 2 Diabetes mellitus are a hypercaloric diet, a lack of body activity, overweight (may be caused by the diet and missing body activity), Hyperlipidaemia and genetic predisposition with the presence of two or more specific autoantibodies which is typical for Dm type 1 (Harreiter et al, 2019; Petersmann et al, 2019). Also, age and smoking are factors which reduce the insulin receptor sensitivity (Graves et al, 2019).

2.2. Prevalence

Regarding the epidemiology of Diabetes mellitus more than 422 million people worldwide were having diabetes in 2014 with a rising prevalence (Kocher et al, 2018; Graves et al, 2019; Lovic et al, 2020; Stoehr et al, 2021). The perspective, which is also based and confirmed by more recent data shows an increase up to 629 million people in

2045 (Harreiter et al, 2019) or according to newer predictions 463 million people in 2019 (Demir et al, 2019) or 783 million people in 2022 (Harreiter et al, 2023). As well only around 50% of diabetic patients are diagnosed clinically (Graves et al, 2019). Nevertheless, U.S. population analyses predict that approximately one third of the population especially in highly industrialised countries has undiagnosed diabetes (Shimpi et al, 2020). In 2021 537 million people between 20 and 79 years old were diagnosed with diabetes mellitus (Harreiter et al, 2023). Diabetes mellitus occurs in 5% of the world population (Nguyen et al, 2020).

On the other hand, (Cicalau et al, 2021) reported that in 2021 415 million people were diagnosed with diabetes and there is an expected rise to 640 million patients in 2040. Regarding the age of the diagnosis of type 2 Diabetes mellitus the patients are mostly between 65 and 79 years old but had manifested DM in some cases almost ten years before the clinical diagnosis (Leroith et al, 2019).

Major factors affecting the prevalence of diabetes are income status and urbanization (Lovic et al, 2020; Harreiter et al, 2023). Moreover, "75% of people with diabetes live in low- and middle-income countries" (Harreiter et al, 2023, Kocher et al, 2018). Most hyperglycaemic diseases are type 2 diabetes (Kocher et al, 2018). A more differentiated perspective shows that in patients older than 65 years type 2 Diabetes mellitus makes up around 90 % of all cases, whereas the other 10% are made up by type 1 diabetes mellitus (Leroith et al, 2019). Also, Diabetes mellitus is classified as one of the most leading causes of mortality in recent times (Panakhup et al, 2021) and in the future (Cicalau et al, 2021). Nevertheless, hyperglycaemia can be also caused by cystic fibrosis and organ transplantation, hence a thorough diagnosis and differential diagnosis is essential (Harreiter et al, 2019).

2.3. Classification

2.3.1. Type 1 Diabetes

According the ICD-10 code type 1 Diabetes mellitus is classified as ICD-10 E10 (Jensen et al, 2018). In Type 1 Diabetes mellitus the insulin secretion is disturbed due to an autoimmune destruction of the pancreatic beta cells (Harreiter et al, 2019; Petersmann et al, 2019; Demir et al, 2021). The pancreatic beta cell destruction is mediated by diabetes-associated autoantibodies released by lymphocytes and other immune cells that cause a slow, but constant loss of the pancreatic beta cell function leading to an insulin deficiency (Harreiter et al, 2019; Graves et al, 2019; Cicalau et al,

2021; Cloethe, 2022). In cancer immunotherapy, “immune checkpoint inhibitors as antiprogrammed cell death 1, anti-cytotoxic T-lymphocyte associated protein 4 antibodies” are used; these also induce and accelerate auto-immune reactions as the development of Diabetes-associated auto-antibodies (Ikegami et al, 2022; Petersmann et al, 2019). Type 1 DM makes up only around ten percent of all diabetic patients and occurs more frequently in younger patients (age lower than 40 years old) (Demir et al, 2021). The patient’s bodyweight is usually normal, and the symptoms of hyperglycaemia (see 2.5) are occurring frequently (Harreiter et al, 2019). A strong genetic predisposition with more than 50 susceptible genes for type 1 Diabetes mellitus was found (Graves, et al
2019). Type 1 DM is known as “insulin-dependent” diabetes (Ikegami et al, 2022; Petersmann et al, 2019; Cicalau et al, 2021; Cloete, 2022).
Type 1 DM includes according to the pathogenesis also latent insulin-dependent diabetes (LADA) in adulthood which causes a slow loss of pancreatic beta cell function (Petersmann et al, 2019; Harreiter et al, 2023). The familiar predisposition is low, whereas the risk of occurring diabetic ketoacidosis is high (Harreiter et al, 2023). Diabetes Type 1 is also characterized by low or absent plasma C-peptide and and frequent evidence of diabetes-associated autoantibodies in the blood plasma (Harreiter et al, 2019; Ikegami et al, 2022). An insulin therapy should be started promptly to prevent ketoacidosis and the symptoms of hyperglycemia (Ikegami et al, 2022; Harreiter et al, 2019).

2.3.2. Type 2 Diabetes

According to the ICD-10 code type 2 Diabetes mellitus is classified as ICD-10 E11 (Jensen et al, 2018). In type 2 Diabetes mellitus, the Insulin secretion from pancreatic beta-cells is impaired and exacerbates, occurs either with or without insulin resistance (Darenskaya& Kolesnikov, 2021; Harreiter et al, 2019). Type 2 DM is also referred as insulin-dependent diabetes (Cicalau et al, 2021). The Insulin deficiency is usually relative at the beginning and the glucose-dependent Insulin-secretion decreases progressively (Harreiter et al, 2023; Cloete, 2022). Insulin resistance which occurs concomitantly with an insulin deficiency due to decreased insulin secretion is frequently associated with other diseases as the metabolic syndrome (Petersmann et al, 2019). A

key difference to type 1 Diabetes besides the pathogenesis is also that Type 2 Diabetes occurs later in life (Demir et al, 2021).

Type 2 DM has a heterogenous pathogenesis which is frequently linked to other systemic disorders as the metabolic syndrome and can be caused by either an insulin resistance due to a significant secretory defect or by an insulin resistance associated with a relative insulin deficiency (Petersmann et al, 2019; Cloete, 2022).

Laboratory parameters for screening are glycated hemoglobin levels (HbA1c), GAD autoantibodies (Petersmann et al, 2019) or increased C-peptide-levels which are in contrast missing in Diabetes type 1 (Harreiter et al, 2019). Diabetes type 2 makes up most of the diabetic patients (>90%) and occurs more in elderly patients older than 40 years but has a significantly increasing prevalence in younger patients (Harreiter et al, 2023). An important, macroscopically visible clinical feature is the overweight of type 2 Diabetes patients (Harreiter et al, 2019). The symptoms of hyperglycaemia are in contrast with Diabetes type 1 rarer and the risk of occurring diabetic ketoacidosis is very low or absent (Harreiter et al, 2019). The familiar association (first grade relatives) is high, whereas in DM type 1 it is very low; other differences towards DM type 1 are that the plasma-C-peptide levels are higher than normal and the absence of Diabetes-associated autoantibodies (Harreiter et al, 2019).

2.4. Pathogenesis

According to (Kocher et al, 2018) diabetes mellitus is “a serious, chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces”. Thus, Diabetes mellitus can be characterised as a metabolic disorder with hyperglycaemia due to inherited or acquired deficiency of insulin production by pancreatic ß-cells (type 1) (Bui et al, 2019) or action (type 2) (Liccardo et al, 2019) or both, (Demir et al, 2021; CLOETE, 2022). Besides Type 1 Diabetes mellitus and Type 2 Diabetes mellitus, there are other disorders causing a pancreas impairment: Exocrine pancreatic diseases as pancreatitis or hemochromatosis and endocrinopathies as acromegaly or Cushing’s syndrome (Petersmann et al, 2019). Another cause of non-diabetic hyperglycaemia and insulindependent diabetes is pancreatectomy leading to the total loss of pancreatic beta cells and subsequent insulin lack (Ikegami et al, 2022). Diabetes can also be medically

induced by glucocorticoids, neuroleptics, INF alpha or pentamidine (Petersmann et al, 2019).

The defined hyperglycaemia thresholds for glycated hemoglobin are for a prediabetic state 5.7% and 6.4%, diabetes occurs at a level of >6.5% (47.5mmol/mol) of glycated hemoglobin (HbA1c) and its measurement occurs according to the fasting plasma glucose levels (Kocher et al, 2018). Hyperglycaemia enhances reactive oxygen molecule production (Darenskaya& Kolesnikov, 2021; Harreiter et al, 2019). Long term hyperglycaemia causes micro- and macrovascular complications (Nguyen et al, 2020; Ceriello& Prattichizzo, 2021; Harreiter et al, 2019).

2.5. Clinical presentation

The clinical presentation of diabetes mellitus can be divided into biochemical markers and classic clinical symptoms. Diabetes mellitus is diagnosed by measuring the fasting plasma glucose levels, oral glucose tolerance test or by the levels of glycated hemoglobin (HbA1c) in the venous blood plasm (Harreiter et al, 2019; Petersmann et al, 2019).

For the definitive diagnosis at least two elevated blood glucose levels need to be measured at two or more different days; the normoglycemic values are <100 mg/dl (<5.6mmol/l in venous blood plasm, whereas prediabetic blood glucose levels are 100125 mg/dl blood and diabetic blood plasma levels are >125 (140) mg/dl (Cloete, 2022; Harreiter et al, 2019).

The measured plasma glucose levels in venous blood which are occasionally more than 200 mg/dl or more than 11.1 mmol/l (gold standard), fasting plasma glucose levels exceeding 126 mg/dl (7.0 mmol/dl) after a fasting period for eight to 12 hours are diagnostic features of Diabetes mellitus (Petersmann et al, 2019). In older patients HbA1c levels and fasting plasma glucose levels should be screened regularly to recognize the occurrence of Diabetes as soon as possible (Leroith et al, 2019). Predispositions and conditions to measure the blood glucose levels are that the patient is fasting at least eight hours before measuring the blood glucose, that the blood glucose level is measured in the venous blood and the absence of concurrent disorders as infections (Harreiter et al, 2023; Cloete 2022). Also, gastrointestinal diseases, infections, hemodialysis, pregnancy, dehydration, and the glucocorticoid medication

therapy should be excluded before measuring blood glucose levels (Harreiter et al, 2019; Harreiter et al, 2023).

Another method to measure is to screen the glycated hemoglobin levels (HbA1c) which are exceeding 6.5% (or more than 48 mmol/ mol Hb) in Diabetes mellitus (Petersmann et al, 2019; Harreiter et al, 2023). The HbA1c levels required to diagnose diabetes mellitus are for prediabetic stage 5.7%-6.4% and for the manifested diabetes mellitus >6.5 mmol on at least two different days; the ratio behind this is the increasing risk of occurring diabetic retinopathy which is a potentially occuring severe complication of Diabetes (Harreiter et al, 2019).
It is important to mention that diabetes mellitus can be diagnosed based on the HbA1c levels only in adult patients because there is still a lack of reference data for patients younger than 18 years old (Harreiter et al, 2019; Harreiter et al, 2023). The limitations of diagnosing DM according the HbA1c levels are that the clinician needs to exclude hemoglobinopathies, altered erythrocyte turnover time due to anemia caused by iron deficiency or lack of Vitamin B-12, pregnancy and high age (Harreiter et al, 2019). Therefor the diagnosis of manifested diabetes mellitus should be in doubt not based only on the HbA1c levels but also confirmed with the oral glucose tolerance test or fasting plasma glucose levels (Petersmann et al, 2019; Leroith et al, 2019). Additionally the clinician should always confirm the diagnosis of diabetes mellitus manifested by one testing method with another testing method except unequivocal results or clinical symptoms are present in the patient (Harreiter et al, 2023). Preanalytic interventions are needed to guarantee that the glycolysis is inhibited in the blood samples; here citrate combined with fluoride is used to inhibit the glycolysis (Petersmann et al, 2019).

The third way of diagnosing Diabetes mellitus is the oral glucose tolerance test (OGTT) which is especially indicated for patients which are very old, pregnant, or excluded by the above-mentioned other methods (Harreiter et al, 2019).

Oral manifestations of Diabetes mellitus are Xerostomia, Salivary gland enlargement, Lichen planus, oral candidiasis, gingivitis, periodontitis, and tooth loss (Reddy et al, 2022). The most significant clinical symptoms of hyperglycaemia are Polyuria, Polydipsia, tiredness, unexplainable weight loss, vision disturbances and ketoacidosis (Harreiter et al, 2023; Cloete, 2022). Also, a classic symptom (the first ever mentioned in the history by the ancient Egyptians ca 1550 BC) is sweet-smelling urine which led to

the name Diabetes mellitus (Demir et al, 2021). On the other hand, chronic hyperglycaemia disturbs the secretion and action of insulin and causes functional damages of the eyes (diabetic retinopathy), kidneys, nerves and the cardiac tissues and may cause more significant complications (Harreiter et al, 2019).

2.6. Influencing factors

Influencing factors regarding the course and progression of the diabetes pathogenesis are the efficacy of diabetes treatment, the patient's adherence to the treatment regimen and most importantly the patient's modification of the main influencing factors as nutrition, diet, body activity which may lead to first prediabetes and then to manifested diabetes (Ikegami et al, 2022). The Diabetes type 2 prevention is based mostly on changing the patient's lifestyle and medication regimen, whereas in the long-termperspective life-style modifications are significantly more effective than medications (Harreiter et al, 2019; Cloete, 2022). In contrast, the prevention of type 1 DM aims mainly at prolonging the pancreatic beta cell survival and function (Ikegami et al, 2022). Smoking, poor sleeping quality and lack of sleep are also significant factors influencing the diabetes mellitus risk and course (Harreiter et al, 2023).

The lifestyle modifications include nutrition and body activity. Regarding the diet, the nutrition should be changed by reducing the general amount of carbohydrates and reducing highly processed carbohydrates and sucrose-containing foods and drinks in the diet; instead, the source of carbohydrates should be vegetables, milk, lentils, wholegrain products (Harreiter et al, 2019). Also sports in patients at risk for diabetes, patients with prediabetes or patients with manifested Diabetes mellitus increases the insulin sensitivity and decreases the amount of abdominal fat (Cloete, 2022; Harreiter et al, 2023). In contrast, modifiable factors as poor glycaemic control, associated hypertension, dyslipidemia (increased LDL& total cholesterol), longer duration of having manifested diabetes, smoking and anemia increase the risk of occurrence of diabetes-associated complications (Crasto et al, 2021). Regarding lipids the uptake of saturated fatty acids should be replaced by consuming mono- or poly-unsaturated fatty acids (Harreiter et al, 2019).

The medication regimen to manage Diabetes mellitus includes metformin, orlistat, Thiazolidinedione and Glucagon-like peptide 1 receptor agonists and artificial Insulin; these medications are especially important in preventing the progression of prediabetes

to manifested Diabetes (Harreiter et al, 2023). Metformin medication for glycaemic control combined with lifestyle modifications is the first-line treatment for DM in elderly patients but should be avoided in cases of intolerance or significantly decreased glomerular filtration rate which represents impaired kidney function (Leroith et al, 2019). Patient factors of the success of insulin therapy in type 1 DM are age, impaired cognitive functions, impaired body functions due to frailty (Ikegami et al, 2022; Leroith et al, 2019) and amount and specificity of the autoantibodies (Harreiter et al 2023). Aging also accelerates the progression of diabetic complications (Leroith et al, 2019; Harreiter et al, 2023).

It is very important to mention at this point that diabetes management by prevention aims at modifying the above-mentioned risk factors if possible (Crasto et al, 2021; Harreiter et al, 2019; Leroith et al, 2019). Prevention of type 1 DM aims mainly at prolonging the pancreatic beta cell function (Ikegami et al, 2022; Harreiter et al, 2023).

2.7. Complications

Diabetes patients are more prone to infections and periodontitis (Liccardo et al, 2019; Stoehr et al, 2021) and usually present some significant dysfunctions of other organs in the body (Demir et al, 2021; Cloete, 2022). Microvascular complications as endothelial dysfunction, diabetic nephropathy, hypertension, retinopathy, cognitive dysfunction, liver or lung fibrosis and neuropathy occur in up to 20 per cent of all diabetic patients (Faselis et al, 2020; Darenskaya& Kolesnikov, 2021; Crasto et al, 2021; Demir et al, 2021; Stoehr et al, 2021).

The pathogenesis of microvascular complications is based mainly on disrupted microvascular structure (Crasto et al, 2021). Altered and impaired elements of the normal microvascular or capillary function are increased endothelial cell apoptosis, increased pericyte loss, thickening of the basement membrane and accumulation of advanced glycation end products, capillary closure and/ or vascular leakage (Crasto et al, 2021).

Macrovascular complications are mostly cardiovascular disorders (Darenskaya& Kolesnikov, 2021; Ceriello& Prattichizzo, 2021; Crasto et al, 2021; Harreiter et al, 2023). The macrovascular complications are influenced by the amount of lipids which leads to atherosclerosis (Ceriello& Prattichizzo, 2021; Crasto et al, 2021).

Hyperlipidemia forms plaque which causes atherosclerosis, whereas a low amount of high-density lipids promotes inflammation by monocyte activation and increasing the

amount of released tumor-necrosis-factor TNF-alpha which subsequently promotes atherosclerosis as well (Wu et al, 2021). Another diabetes-associated cardiovascular disorder is diabetes-associated cardiovascular autonomic neuropathy in which "autonomic nerve fibers which innervate the heart and blood vessels" are damaged and cause orthostasis, myocardial infarction, exercise intolerance or resting tachycardia due to hyperglycemia causing oxidative stress which is neurotoxic and subsequently causes vascular occlusion or endothelial dysfunction (Agashe& Petak, 2018).

Prediabetes which is characterised by elevated HbA1c and blood glucose levels near but below the threshold values for diabetes mellitus and it already increases the risk of cardiovascular diseases as coronary heart diseases or strokes (Harreiter et al, 2023). Risk factors for complications are blood pressure, heart rate, body weight and variable lipid parameters influenced by the patient's diet [LDL- and HDL-cholesterol, triglycerides) (Ceriello et Prattichizzo 2021). Also, hypertension, dyslipidemia, the duration of diabetes and smoking have synergistic, potentiating effects on the occurrence of micro- and macrovascular complications (Crasto et al, 2021). The lipid parameters can be influenced and deteriorated by removal of the exocrine pancreas which causes a lack of digestive enzymes as lipase (Ikegami et al, 2022). An altered lipid profile with a higher than normal amount of triglycerides (HDL-C) and increased HbA1c in type 2 DM patients also increases the risk of diabetic peripheral neuropathy by changing the blood viscosity and causing atherosclerosis which may ultimately lead to a thrombus interrupting the blood flow and leading to necrosis (Wu et al, 2021). Statin therapy improves the lipid levels, but non-adherence to statin therapy is an influencing factor leading to a higher risk of possible complications due to hyperlipidemia (Ceriello& Prattichizzo, 2021).

Variable blood pressure in diabetic patients predicts micro- and macrovascular complications as cardiovascular problems like myocardial infection or stroke or nephropathy which may occur either de novo or exacerbates; significant cardiovascular complications also include increased cardiovascular-related mortality and lower extremity amputation (Crasto et al, 2021; Ceriello& Prattichizzo, 2021). Lower extremity amputation usually follows the diabetic foot ulcer which is caused by reduced sensation due to polyneuropathy and microvascular changes as vascular compromise and functional changes in the microcirculation (Crasto et al, 2021; Leroith et al, 2019). In type 1 DM (insulin-dependent) the absence of insulin treatment can lead to

ketoacidosis with subsequent coma and death (Ikegami et al, 2022; Cloete, 2022). In Type 2 Diabetes Mellitus (insulin-independent) variable blood pressure decreases the glomerular filtration rate and predicts diabetic nephropathy (Ceriello& Prattichizzo 2021). Reducing and maintaining the blood pressure at a level of 140/90 mmHg reduces the risk of progressive diabetic nephropathy and also of strokes and cardiovascular complications (Leroith et al, 2019).

The diabetic nephropathy is caused by prolonged hyperglycaemia, hypertension and dyslipidemia and is manifested by inflammation, oxidative stress, fibrosis and endothelial dysfunction which leads to basement membrane thickening, glomerulosclerosis and reduced glomerular filtration surface density (Crasto et al, 2021). Conspicuously variable lipid levels (HDL, LDL, triglycerides) in the blood plasma especially in diabetic patients predict cardiovascular complications similar as the body mass index (BMI) the efficacy of diabetes therapy (Ceriello& Prattichizzo, 2021). The risk factors for complications in diabetic patients may potentiate each other and significantly increase the risk of complications (Cloete, 2022; Crasto et al, 2021; Ceriello& Prattichizzo, 2021).

2.8. Management

The glycaemic control by Insulin therapy is the essential way of diabetes management (Cloete, 2022); nevertheless, the difference between type 1 DM and type 2 DM is that in type 1 DM the insulin therapy should be started promptly after the diagnosis because it is insulin-dependent, whereas in type 2 DM it can be started a while after the diagnosis as it is insulin-independent (Harreiter et al, 2019). Insulin therapy to maintain the insulin levels and to prevent hypoglycaemia is used especially in type 1 DM (Ikegami et al, 2022; Harreiter et al, 2019); factors influencing the insulin therapy are the efficacy of the function of the remaining pancreatic beta-cells and chronic complications as tissue damages (Ikegami et al, 2022; Ceriello& Prattichizzo, 2021). It is important to note that in elderly patients the first-line treatment is not insulin (which should be used sparingly to avoid hypoglycaemia) and instead metformin combined with lifestyle modifications aiming at a glycemic control (Leroith et al, 2019). Smoking cessation is also included in lifestyle modifications (Harreiter et al, 2019) and decreases the risk of hypertension and macrovascular complications (Crasto et al, 2021; Leroith et al, 2019).

The glycaemic control aims at reducing the HbA1c levels to less than 7% or 53 mmol/mol which is the threshold value for manifested diabetes mellitus and the possibly co-occurring diabetes-associated complications (Crasto et al, 2021). Also, the glucose levels in the blood should be screened regularly additionally to measuring the HbA1c levels (Leroith et al, 2019; Cloete, 2022). Antioxidant therapy (Darenskaya& Kolesnikov, 2021) can also be used to restore insulin sensitivity and hence to improve glycaemic control.

Another attempt is to maintain risk factor parameters (as lipid concentration in the blood plasma, blood pressure, body weight) by for example Statin therapy which is used to decrease lipid levels in the blood plasma to prevent cardiovascular complications and to improve the renal function in order to prevent macrovascular complications (Crasto et al, 2021; Ceriello& Prattichizzo, 2021). The blood pressure control in case of hypertension is maintained by the usage of angiotensin-receptor blockers and ACE inhibitors (Crasto et al, 2021; Leroith et al, 2019).

A possible medication regimen for improved glycaemic control includes glucoselowering agents as Glucagon-like peptide 1 (GLP-2) receptor agonists or sodiumglucose co-transporter-2 inhibitors (CRASTO et al, 2021). Nevertheless, in diabetic patients older than 65 years, medication regimens should be kept as simple as possible due to potentially impaired cognitive abilities (LEROITH et al, 2019).

Weight loss attempts to improve heart rate and minimize heart rate variabilities which are a risk factor for macrovascular complications show to decrease the risk of macrovascular complications (Ceriello& Prattichizzo, 2021). Reducing the blood pressure my 10 mmHg reduces the occurrence of microvascular complications by already 11% (Crasto et al, 2021). Concomitantly, (Crasto et al, 2021) report a reduction of the risk of diabetic retinopathy by 48 %. If a diabetic patient has an associated cardiovascular disease as congestive heart failure (irrespective of developing as a complication of diabetes or occurring independently), oral hypoglycaemic medications as glinides, dipeptidyl-peptidase-4 inhibitors or glitazones should be used to avoid worsening of heart failure (Leroith et al, 2019).

The management of Diabetes mellitus also includes prevention which is based on improving all possible modifiable risk factors and the lifestyle and should be thus always multifactorial (Crasto et al, 2021; Harreiter et al, 2019; Leroith et al, 2019; Cloete, 2022). The lifestyle modification is the first-line treatment of hyperglycaemia in

elderly patients (Leroith et al, 2019). In long-term perspective lifestyle modifications appear to be more effective than the medication regimen alone (Harreiter et al, 2023).

2.9. Prognosis

An increasing number of diabetic patients with higher age occurs due to increasing life expectancy (Ikegami et al, 2022), and due to increased influence of aging on the metabolic regulation (Leroith et al, 2019). Lifestyle modifications as diet changes and more body activity can prevent the progression of prediabetes to manifested to diabetes and help to maintain the blood glucose levels stable below 7& HbA1c (Harreiter et al, 2019; Crasto et al, 2021). Therefor the diet should be rich in proteins and energy for elderly patients (Leroith et al, 2019).

Normoglycemia can be achieved by an effective insulin therapy or blood glucose level maintenance (Ikegami et al, 2022). On the other hand, especially older patients have a higher risk of developing diabetic complications as diabetic nephropathy, myocardial infarction, diabetic foot ulcer, and diabetic retinopathy (Leroith et al, 2019). In longterm perspective lifestyle modifications appear to be more effective than the medication regimen alone (Harreiter et al, 2023).

3. Periodontitis

3.1. Prevalence

“Periodontitis is one of the most common inflammatory diseases in adults. In 2010, 3.9 billion people worldwide were reported to have periodontitis” (Bui et al, 2019); In the United States >40% of all adults have periodontitis (Shimpi et al, 2020; Kwon et al, 2021). Other studies reported at least 743 million people worldwide in 2010 (Stoehr et al, 2021). The prevalence of mild periodontitis is around 35% and the prevalence of moderate and severe periodontitis was 11% (Bui et al, 2019). Among that, other authors reported that severe periodontitis affects 7.5-11.2% percent of patients, thus it is a very prevalent condition (Sanz et al, 2020; Kwon et al, 2021). Similar data estimated that 10% of the global population are suspected to have periodontitis (Nguyen et al, 2020); Severe periodontitis affects around 10% of the global human population (Kocher et al, 2018); according (Kwon et al, 2021) around 11 % worldwide. (Cicalau et al, 2021) reported on the other hand that the periodontitis prevalence is around 20 to 50% worldwide, so the available data for the prevalence of periodontitis is very

heterogenous. Another contributing factor for the variable data regarding periodontitis prevalence is the low awareness of the patient as periodontitis has a relatively asymptomatic or silent progression, especially in the initial stages which means that periodontitis is often only diagnosed after some progression (Shimpi et al, 2020).

3.2. Etiology and causes

Periodontitis is caused by a dysbiosis within the bacterial biofilm and dental plaque attached to the tooth (Rosier et al, 2018; Liccardo et al, 2019). Long-term bacterial deposits on the teeth and in the sulcus cause chronic inflammation and immune response (Nguyen et al, 2020) leading ultimately to periodontal tissue destruction (Kwon et al, 2021). The dysbiosis induces an altered interaction between certain subgingival microbes, host immune response, environmental exposure, and genetic factors (Liccardo et al, 2019). Regarding the periodontitis pathogenesis, an increased amount of gram-negative anaerobic bacteria is noted (Loos& Van Dyke 2020).The key microbes are Gram-positive and Gram-negative: *Treponema denticola, Tannerellea forsythia, Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Eubacterium timidum* and *Porphyromonas gingivalis* (Liccardo et al, 2019; Bui et al, 2019; Sedghi et al, 2021). Especially *T. denticola*, *T. forsythia* and *P. gingivalis* are considered as the "red triangle" in periodontitis pathogenesis (Zhang et al, 2021; Kwon et al, 2021). Other associated pathogenic bacteria are *Filifactor alocis, Synergistetes* and *Fusobacterium nucleatum* (Sedghi et al, 2021).

The shift in the four most abundant phyla is represented by a decrease of *Proteobacteria* and *Actinobacteria*, and the simultaneous increase in *Bacteroidetes* and *Firmicutes* provokes periodontal disease (Sedghi et al, 2021).

The virulence factors of the periodontal pathogens stimulate the host macrophages and other inflammatory cells to release pro-inflammatory cytokines which stimulate the production of matrix metalloproteinases (MMPs) (Kwon et al, 2021). The MMPs destroy the collagen fibers of the periodontal ligament and induce the differentiation of osteoclast precursors instead of osteoblasts into osteoclasts which destroy the alveolar bone (Kwon et al, 2021).

3.3. Classification

Periodontitis is classified in four stages. Additionally to each stage the extent and distribution are mentioned which can be described as localised extent (less than 30 % of all the involved teeth) generalised or molar-incisor pattern (Papapanou et al, 2018; Kwon et al, 2021).

Stage I has a clinical attachment loss (CAL) of 1 to 2 mm, a radiographic bone loss in the coronal third of the root (<15%), no teeth lost due to periodontitis and a maximal probing depth of 4 mm; the bone loss is mostly horizontal (Papapanou et al, 2018; Kwon et al, 2021).

Stage II is characterised by an interdental CAL of 3 to 4 mm, a radiographic bone loss in the coronal third up to one third of the root (15-33%), no tooth loss due to periodontitis, mostly horizontal bone loss and a maximum probing depth of up to 5 mm (Papapanou et al, 2018; Kwon et al, 2021).

In Stage III the CAL exceeds 5 mm, the radiographic bone loss reaches the middle or apical third of the root, there are up to 4 teeth lost due to periodontitis; additionally to stage II the probing depth is 6 mm or more, there is vertical bone loss which is 3 mm or more, a moderate ridge defect and a furcation involvement class II or III (Papapanou et al, 2018; Kwon et al, 2021).

Stage IV periodontitis is characterized by a CAL of 5 mm or more, a radiographic bone loss extending to the middle or apical third of the root, 5 or more teeth are lost due to periodontitis, additionally to stage III features there is the need of complete rehabilitation due to secondary occlusal trauma (mobility grade 2 or more), masticatory function, a severe ridge defect and impaired occlusal function. As well in Stage IV periodontitis there are less than 20 or 10 opposing pairs of remaining teeth (Papapanou et al, 2018; Kwon et al, 2021).

Additionally, to the 2018 classification periodontitis can be graded according to the progression, the case of progression, smoking, and diabetes. Grade A or slow progression has a progression up to 0.25% of bone loss/ age, heavy biofilm deposits with low levels of destruction, the patient is a non-smoker and no diabetes is diagnosed (Papapanou et al, 2018; Kwon et al, 2021). Grade B of progression indicates a progression of 0.25 to 1.0% bone loss per age, a destruction corresponding to the amount of the biofilm deposits, the patient is a smoker of 10 cigarettes per day and the

glycated hemoglobin levels are up to 7% thus the patient has diabetes (Papapanou et al, 2018; Kwon et al, 2021).

In Grade C progression indicates a bone loss of more than 2 mm in five years, or a bone loss in % divided by age of more than 1%, the destruction is faster than the expectation with the biofilm deposits, a lack of standard therapy response, an early onset, the patient is a heavy smoker of more than10 cigarettes per day and/ or he is diagnosed diabetes with HbA1c levels of 7% or more (Papapanou et al, 2018; Kwon et al, 2021).

3.4. Pathogenesis

Initially periodontitis is caused by plaque accumulation around the neck of the tooth which is referred as a dental biofilm around the tooth; this biofilm undergoes a dysbiotic shift as mentioned in the etiology (Kwon et al, 2021). *Especially T. denticola, T. forsythia* and *P. gingivalis* are very abundant and they are considered as the "red triangle" in the pathogenesis of periodontitis (Zhang et al, 2021; Kwon et al, 2021). Periodontitis is a multifactorial chronic Inflammation with an aberrant immune response and progressive destruction of the periodontium with loss of periodontal tissue support (Sanz et al, 2020; Stoehr et al, 2021; Loos& Van Dyke, 2020). The initial stage is biofilm-induced gingivitis which may gradually progress into periodontitis (Zhang et al, 2021).

On a cellular level periodontitis can be described as a "dysbiosis of oral microbiota and proinflammatory events involving both cells and mediators from innate and adaptive immunity" (Cardoso et al, 2017), also as dysbalance of pro-inflammatory and antiinflammatory mediators (Loos& Van Dyke, 2020). As well, the pathogenesis is an altered interaction between certain subgingival microbes, host immune response, environmental exposure and genetic factors (Liccardo et al, 2019). Additionally, the progression of periodontitis proceeds in a nonlinear, disproportional manner (Loos& Van Dyke, 2020).

The manifestations of proceeding periodontitis are clinical attachment loss, alveolar bone loss, periodontal pockets, gingival inflammation and bleeding, increased probing depth, tooth migration and eventually tooth loss due to periodontal tissue breakdown (Sanz et al, 2020; Stoehr et al, 2021; Kwon et al, 2021). One of the main problems which cause the patient to seek dental treatment for periodontitis are tooth loss, impaired chewing and aesthetics, masticatory dysfunction and moreover negative

influence on the overall general health (Sanz et al, 2020). The tooth loss significantly reduces masticatory efficacy which decreases the quality of life (Kwon et al, 2021). In the altered immune response bacteria surface molecules as lipopolysaccharides (LPS) cause release of inflammatory mediators and cytokines which subsequently activate the release of matrix metalloproteinases (MMPs) that break down the bone substance (Liccardo et al, 2019). Bone loss and tissue degradation occur due to the inflammation which induces the polymorphonuclear neutrophil action, especially if *Porphyromonas gingivalis* is abundant (Loos& Van Dyke, 2020). Initially, phagocyte (macrophages, neutrophils) migration to the lesion site and simultaneous mediator release by epithelium occurs (Liccardo et al, 2019). Released mediators are especially interleukins (ILs), prostaglandins (PGE2) and tumor necrosis factor alpha (Liccardo et al, 2019). The phagocytes normally have specific receptors as the Toll-like receptors (TLR) that bind to bacterial surface molecules in order to destroy the pathogens and clear the debris away by macrophages and monocytes, whereas in the altered immune response the leukocyte adhesion by the TLRs decreases (Loos& Van Dyke, 2020).

The keystones for the dysbiotic shift causing periodontitis are the overgrowth of pathogens, that the acute inflammation becomes chronic, subsequently more immune cells (T cells, monocytes) causing bone resorbtion by osteoclasts, periodontal ligament breakdown and granulation tissue formation (Liccardo et al, 2019). Dysbiosis with an overgrowth of biofilm and poor plaque control is associated with a shift from grampositive to predominantly Gram-negative anaerobic species (Bui et al, 2019). In the normal plaque microbiome gram-positive bacteria are abundant (Loos& Van Dyke, 2020).

In the normal plaque differentiation, the plaque periphery is nutrient-rich, oxygen-rich and colonized by *Haemophilus*, *Aggregatibacter* and *Neisseriae* (Sedghi et al, 2021). But their metabolic products create an anoxic central biofilm in which an anoxic environment develops and anaerobic species as *Leptotrichia*, *Fusobacterium*, *P. gingivalis* and others live and grow to bigger numbers (Zhang et al, 2021). In the inflammatory state, the plaque and biofilm environment develop to an anaerobic state and the overgrowth of the periodontal pathogens occurs (Loos& Van Dyke, 2020). The shift in the four most abundant phyla is represented by a decrease of *Proteobacteria* and *Actinobacteria*, and an increase in *Bacteroidetes* and *Firmicutes* which provoke periodontal disease (Sedghi et al, 2021).

Antagonistic and synergistic interactions of the pathogens, "for example *Fusobacterium nucleatum* increases survival of the […] periodontal pathogen *Porphyromonas gingivalis* in aerobic conditions" (Sedghi et al, 2021) cause an overgrowth of *P. gingivalis*. *Porphyromonas gingivalis* is considered as the key pathogen in periodontitis (Zhang et al, 2021). Despite that, other authors suggest that periodontitis is polymicrobial (Ng Hm et al, 2019). Both *Treponema denticola* and *P. gingivalis* are found to be abundant in deep periodontal pockets in chronic periodontitis (Ng HM, Slakeski N et al, 2019). Microbial changes in periodontitis are different cell motility, processing and signaling (Sedghi et al, 2021). The metabolism of cofactors, nucleotides and vitamins is changed and increased amount of bacterial motility proteins is formed (Sedghi et al, 2021). This is represented for example by *Porphyromonas gingivalis* to act more specifically by releasing outer membrane vesicles to the environment (Zhang et al, 2021).

In the pathogenesis, *Porphyromonas gingivalis* infection decreases the gingival vascularisation and increases insulin resistance in rats (Bui et al, 2019). Also, P. gingivalis impairs and decreases the host immune system reaction and increases the proinflammatory response and subsequently it promotes the dysbiotic shift of the oral microbiota, especially subgingivally (Zhang et al, 2021). Other changes in the altered immune response are impaired immune system and autophage pathways and oxidative stress (Portes et al, 2021).

The mutual action in the dysbiotic shift is the bilateral potentiation of *Trephonema denticola* and *Porphyromonas gingivalis* in which *T. denticola* metabolizes succinate produced by *P. gingivalis* so both colonies can multiplicate easier and have a synergistic relationship (Ng HM, Slakeski N et al, 2019; Sedghi et al, 2021). The synergistic relationship may be based on the circumstance that *T. denticola* releases chemotaxis which create pores in the biofilm matrix through which both *P. gingivalis* and *T. denticola* can move and increase the biofilm mass by enhanced metabolism (Ng Hm et al, 2019). *T. denticola* also transforms in the dental biofilm into two different *T. denticola* mutants of which one has no motility and the other one has genetic changes which enhance the motility (Ng Hm et al, 2019). Another interesting feature of *T. denticola* is that *T. denticola* alters the RASA4 transcription which deregulates cytoskeletal dysfunction and enhances actin depolymerization in periodontal ligament cells by increasing the matrix metalloproteinase-2 activity (Malone et al, 2021).

Another observation in the simultaneous occurrence is that the co-culture of *T. denticola* and *P. gingivalis* causes shifts in fatty acid and thiamine pyrophosphate synthesis in *P. gingivalis* which also alters glutamate and glycine catabolism by *T. denticola* due to altered gene expression (Sedghi et al, 2021). The gene alteration can be seen in transcripts of the ribosomal subunit biogenesis and carbohydrate utilization and stress response transcripts provoked by *P. gingivalis* (Sedghi et al, 2021; Malone et al, 2021). An experimental investigation showed that in rats, a *Porphyromonas gingivalis* infection decreases gingival vascularisation and increases insulin resistance (Bui et al, 2019).

Another feature of the dysbiosis in the biofilm is the mutual growth of *Filifactor alocis* and *Aggregatibacter actinomycetemcomitans* which causes a localized aggressive progression periodontitis which proceeds periodically (Sedghi et al, 2021; Loos& Van Dyke, 2020). The increased bone loss in periodontitis occurs due to co-infection of *Tannerella forsythia* and *Fusobacterium nucleatum* and due to the symbiont-pathogen interactions of *Streptococcus gordoni* and *Porphyromonas gingivalis* which cause periodontitis potentiation compared to an infection with only one species (Sedghi et al, 2021). There is a positive correlation of microbial interactions, meaning that a shift in one species causes simultaneous shift in the other species as well due to synergism and antagonism (Sedghi et al, 2021).

The second main feature of periodontitis is the altered immune response. Vice versa, an altered immune response causing periodontitis can cause a dysbiotic, self-exacerbating shift in the subgingival plaque (Loos& Van Dyke, 2020). The altered immune response and dysbiotic imbalance in the gingiva and periodontium, overgrowth of pathogens, inflammatory response induce a chronic inflammation state and irreversible proteolytic tissue destruction (Sedghi et al, 2021).
In the altered immune response, polymorphonuclear neutrophils are hyperactive and degrade the periodontal tissues by releasing tissue-degrading substances and enzymes as reactive oxygen compounds, lysozyme, elastase and collagenases (Loos& Van Dyke, 2020). Consequently, neutrophils cause protective proteolytic responses that disrupt the epithelium; as a result, pathogens can enter the lamina propria and deeper tissues so tissue breakdown and especially bone resorption is initiated (Sedghi et al, 2021). As well, a leakage of the pro-inflammatory mediators into the systemic circulation happens which induces the systemic inflammation of periodontitis (Loos& Van Dyke, 2020).

More precisely, in the immune system response release of proinflammatory cytokines: IL-1a, IL 1b, TNF-alpha, IL-6, IL-10 IL-15, especially TNF-alpha, IL-1 and IL-6 occurs which induces infection and activates monocyte differentiation into macrophages and lymphocyte migration to the infection site (Cardoso et al, 2017).

Another exacerbating factor in periodontitis is that the periodontal pathogens are harbored in the central, anoxic biofilm which is either attached to the root surface or the tooth supragingival so that the periodontal pathogens can resist host defence mechanisms by evasion and antibiotic treatment (Bui et al, 2019; Zhang et al, 2021). As well, the oral pathogenic microbes have some antibiotic resistance genes, especially against doxycycline, amoxicillin, metronidazole or clindamycin (Sedghi et al, 2021).

The systemic spread of periodontal pathogens which may be associated with various complications is caused by periodontal pathogens destroying the epithelium in the periodontal pockets which leads to the invasion of endotoxins and exotoxins in the systemic circulation (Liccardo et al, 2019). Similar findings showed that *P. gingivalis* was detected in the blood plasma and synovial fluid which is a strong indicator for the systemic involvement and causing or influencing systemic diseases (Kriauciunas et al, 2019). Additionally, the breakdown of the inflamed tissues "increases the flow of gingival crevicular fluid" (Zhang et al, 2021) which induces tissue components as heme-compounds and collagen into the gingival sulcus; these are metabolites for the other periodontal pathogens (Zhang et al, 2021; Bui et al, 2019). Another feature of the altered immune response which increases the periodontal tissue breakdown is the enhanced MMP- activity (Malone et al, 2021). The periodontal pathogens can promote inflammation but simultaneously manipulating host genes and immunoregulatory responses (Sedghi et al, 2021). Subsequently, the immune response is either hyperresponsive or hyporesponsive and does not resolve the inflammation in both ways (Loos& Van Dyke, 2020).

3.5. Clinical presentation

Clinical manifestations of periodontitis are clinical attachment loss, alveolar bone loss, periodontal pockets deeper than 4mm with bleeding on probing and/ or pockets deeper than 6mm, gingival bleeding and ultimately eventually tooth loss (Papapanou et al, 2018; Sanz et al, 2020; Cicalau et al, 2021). Usually, periodontitis is only diagnosed in more advanced stages because the disease is relatively asymptomatic in the early stages and thus the patient does not have significant symptoms which are clinically

noticeable (Dannewitz et al, 2021). The periodontitis progression is not linear, but rather occurs in recurrent acute episodes followed by remission periods (Kwon et al, 2021). The diagnosis is based on a periodontal probing depth (PPD) of more than 4 mm, Bleeding on probing (BoP) and clinical attachment loss (CAL) >4 mm on two or more teeth (Moreira et al, 2021; Kwon et al, 2021). Periodontal probing is performed with a special periodontal probe which is also called "WHO probe" and measures the axial distance from the deepest pocket depth to the gingival margin (Dannewitz et al, 2021). Further, the manifestations need to be present on two or more teeth to exclude local factors causing increased PPD and BoP (Moreira et al, 2021). The periodontal evaluation includes the plaque index, mucogingival deformities as gingival recession, tooth mobility, furcation involvement and occlusal trauma (Papapanou et al, 2018; Sanz et al, 2020; Kwon et al, 2021). One of the main symptoms noticed by the patient himself are "black triangles" between the teeth, especially in the anterior region which occur due to tissue recession which is a consequence of tissue breakdown (Dannewitz et al, 2021). As well, the exposed tooth roots are covered by a bacterial biofilm that is frequently calcified (Loos& Van Dyke, 2020; Dannewitz et al, 2021).

3.6. Influencing and modifying factors

The basal conformity of all influencing factors is immune fitness (Loos& Van Dyke, 2020) which can be impaired by the influencing factors. Saliva deficiency increases the occurrence of oral diseases because saliva contains lysozymes, secretory IgA, lactoferrines, defensins and histatins which all act antimicrobial; on the other hand, proteins in the saliva either block or enhance bacterial adherence and act as nutrients for the symbiotic bacteria which stabilizes the oral microbiome (Rosier et al, 2018). Smoking promotes oral inflammation and the release of pro-inflammatory mediators, decreases the microvascular supply of the gingival tissues by local vasoconstriction and exposes the human tissues to the at least 4,5000 toxic components of cigarette smoke (Cardoso et al, 2017; Rosier et al, 2018; Moreira et al, 2021). Smoking also induces many oxidative stress reactions which induce apoptosis and cell damage, but also causes a constant low-level systemic inflammation with associated autoantibodies, reduced PMN functions and hence an altered immune response (Loos& Van Dyke, 2020). As well, smoking promotes the dysbiotic shift because the resistance against pathogenic

bacteria is decreased (Rosier et al, 2018). Nevertheless, the influence of smoking on the periodontium is dose-dependent (Gupta et al, 2018).
Furthermore, there are four genetic and epigenetic factors occurring in periodontitis and other atherosclerotic diseases which both may have an altered inflammatory pathway; smoking is one example of an epigenetic factor (Loos& Van Dyke, 2020). Low socioeconomic level, alcohol and poor oral hygiene tend to a dysbiotic shift (Moreira et al, 2021). Poor oral hygiene causes plaque accumulation which creates an anaerobic environment, causes an host immune response and increases the release of gingival crevicular fluid; all these factors in combination increase the dysbiotic shift because the proteins and the iron components in the gingival crevicular fluid are used as metabolites of periodontal pathogens (Rosier et al, 2019).

Another, anatomic factor for the progression of periodontitis is the thin gingival phenotype which is associated with generally less gingival thickness thinner tissues and thus potentially accelerated tissue breakdown (Jensen et al, 2018).
Comorbidities as diabetes are an influencing factor of periodontitis which is indicated by adding diabetes as a descriptive factor when establishing a periodontal diagnosis (Loos& Van Dyke, 2020).

3.7. Management

The most recent guidelines for the management of periodontitis are the S3 Level Clinical Practical Guideline for treatment of Stage I-III periodontitis (Papapanou et al, 2018; Sanz et al, 2020). These guidelines suggest multiple steps for periodontal treatment. Periodontitis management or treatment consists of surgical and non-surgical treatment. Non-surgical treatment is scaling and root planing as well as home care (improved oral hygiene) which aims to improve most periodontal pockets (Kwon et al 2021). The treatment of inflammation aims on the resolution of inflammation that can shift the dysbiotic imbalance to a close-to-normal state to arrest disease progression (Loos& Van Dyke, 2020).
Step 1 consists mainly of behavioural changes including patient motivation and education (Sanz et al, 2020; Kwon et al, 2021; Rosier et al, 2018). What can be changed by patient education is the frequent carbohydrate intake and the supragingival plaque accumulation which create a beneficial environment for periopathogenic bacteria (Rosier et al, 2018) by acidification via carbohydrate metabolism or inflammation

caused by the plaque. Step 1 also includes the patient education to teach him how to remove dental plaque by himself which means practically how to brush teeth in the most efficient way (Dannewitz et al, 2021).

Step 2 is the supragingival biofilm management and plaque control, including the management of the gingival inflammation and modifying risk factors; The main things in this step are mechanical plaque control with toothbrushes, interdental brushes, dental floss and additional antiseptic mouthrinses (Sanz et al, 2020). Again, these oral hygiene measures promote the interaction of the oral microbiota with the host as a symbiosis which also prevent the dysbiotic shift and the pathogen colonization (Rosier et al, 2018). Practically, Professional Oral Hygiene appointments with education are performed here; an example of education is to show the patient that interdental brushes are more effective than dental floss (Sanz et al, 2020).

Step 3 is the supra-and subgingival cleaning which can be augmented by adjunctive therapies as surgical treatment to treat the pockets which are not responding to conservative periodontal treatment (Dannewitz et al, 2021). Usually, the recall intervals for the patients are in six to eight weeks and then three to six months after the first subgingival plaque removal (Papapanou et al, 2018; Dannewitz et al, 2021). Surgical treatment is indicated especially in stage III and stage IV periodontitis if after the conservative plaque removal some residual pockets deeper than 6 mm or with active periodontitis remain at re-evaluation (Papapanou et al, 2018; Sanz et al, 2020; Kwon et al, 2021; Dannewitz et al, 2021). Surgical treatment aims at periodontal probing depth reduction, clinical attachment level regains, recession and bone gain; the gold performance is the use of enamel matrix derivative (EMD) combined with resorbable guided tissue regeneration (GTR) (Nibali et al, 2019). As well, in the surgical management furcation defects can be closed or converted to class I furcation involvement with EMD and nonresorbable GTR; the best outcome had class II furcation involvements (Jepsen et al, 2020).

Step 4 is supportive periodontal care. This stage includes regular and long-term followups in regular intervals of between three to six months according the risk profile (number of smoked cigarettes per day and the diabetes stage) (Sanz et al, 2020; Kwon et al, 2021).

The successful periodontal treatment is usually difficult and less predictable as periodontitis is mostly only diagnosed in more progressed states when already a significant amount of periodontal tissues is lost (Dannewitz et al, 2021). Further,

smoking cessation is a supportive measure for periodontal management as smoking counts besides Diabetes mellitus as the main modifying factor of periodontitis (Rosier et al, 2018).

3.8. Complications

Loss of teeth due to loss of periodontal tissues is one of the more severe, ultimate oral complications (Sanz et al, 2020; Loos& Van Dyke, 2020). Due to the teeth loss, loss of masticatory function, impaired esthetics and generally tooth mobility due to bone loss occur (Loos& Van Dyke, 2020). Besides that, periodontitis is a risk factor for diabetes mellitus due to a similar inflammatory process (Stoehr et al, 2021) and to rheumatoid arthritis, Alzheimer's disease and non-alcoholic fatty liver disease (Zhang et al, 2021). What happens in microvascular damage during tissue breakdown is a bacterial dissemination and systemic infection, especially by *P. gingivalis* (Liccardo et al, 2019; Zhang et al, 2021). The dissemination of pathogens results in evidence of the periodontal pathogens in the cardiac tissue, pericardial fluids, heart valves and atherosclerotic lesions (Liccardo et al, 2019; Salhi et al, 2019) leading to an increased prevalence of chronic inflammations (Loos& Van Dyke, 2020) and cardiovascular diseases (Liccardo et al, 2019). Also, multiple systemic diseases as rheumatoid arthritis (Sanz et al, 2020) occur due to bacterial dissemination into the bloodstream and concomitant systemic infection (Liccardo et al, 2019; Loos& Van Dyke, 2020; Dannewitz et al, 2021).

In rheumatoid arthritis the joint tissues get destroyed by a chronic-synovitis inflammatory based auto-immune reaction which is associated with periodontitis (Zhang et al, 2021; Lin et al, 2020). In the simultaneous pathogenesis *P. gingivalis* plays a role because it is also found in the synovial fluid, and it induces the stepwise formation of autoantibodies as its byproducts are a cofactor in this process (Zhang et al, 2021). One factor that is increased by P. gingivalis is the production of enzyme "peptidylarganine deiminase and its action" which aids in the production of autoantibodies (Kriauciunas et al, 2019).

Periodontitis is also a risk factor for stroke, coronary heart disease, development and onset of myocardial infarction, atherosclerosis (Liccardo et al, 2019; Dannewitz et al,2021). In artherosclerotic plaque formation the vascular smooth muscle cells get calcified via the ERK1/ 2-RUNX2 gene which is promoted by P. gingivalis (Zhang et al,

2021). This is due to the systemic spread of periodontal pathogens causing a smooth muscle cell proliferation in the coronary heart vessels leading to an aneurysma formation (Salhi et al, 2019; Zhang et al, 2021).

3.9. Prognosis

Periodontitis exacerbates if it is left untreated; this manifests by increasing probing depth, attachment loss, bone defects and ultimatively tooth loss which can be classified in higher stages (Loos& Van Dyke, 2020; Dannewitz et al, 2021). As well, periodontitis is one of the main reasons for tooth loss in adults worldwide (Dannewitz et al, 2021). This is especially important as periodontitis shows only mild or no noticeable problems for the patient, only the far progressed periodontitis shows symptoms as “black triangles” between the teeth which occur due to tissue loss, teeth mobility or gingival recession (Papapanou et al, 2018; Sanz et al, 2020; Dannewitz et al, 2021). The outcome of a successful periodontal treatment is “gingival health on reduced periodontium, defined by BOP <10%, PPD <4mm and no PPD >4mm with BOP” (Papapanou et al, 2018; Sanz et al, 2020). If these conditions are established but the patient shows >10% BOP, the diagnosis of the patient is “stable periodontitis patient with gingivitis” (Sanz et al, 2020). What makes the prognosis of periodontitis indeed more complicated is that most patients are unaware of their disease which is only diagnosed by the dentist during routine check-ups (Dannewitz et al, 2021). Supporting evidence for this the dataset established in 2020 by the German “Kassenzahnärztliche Bundesvereinigung” which is representative for the dental health in Germany; this dataset shows that statistically ten million people have periodontitis, but only one million periodontal treatments are performed per year. As well, when periodontitis is only diagnosed in later, more progressed stages, the treatment outcome is more difficult and less predictable as a significant amount of periodontal tissues is already lost (Dannewitz et al, 2021). As well, smoking cessation is a significant part of periodontal therapy as smoking exacerbates the periodontitis prognosis drastically (Gupta et al, 2018).

4.Associations and interactions between diabetes mellitus and Periodontitis

4.1. Prevalence

Diabetes mellitus and periodontitis are considered as two of the most common diseases worldwide (Portes et al, 2021). The concomitant occurrence of diabetes mellitus and

severe periodontitis is reported to be about 15% with variable data (Nguyen et al, 2020). On the other hand, (Zheng et al, 2021) report that DM increases the risk of having periodontitis by 86% due to the similar risk factors. A difficulty to collect abundant data regarding the prevalence of concomitant diabetes mellitus and periodontitis is the periodicity of the dental visits of around 75% of only once per year or less (Shimpi et al, 2020). Supportive findings regarding the difficulty to establish a prevalence are that most diabetes mellitus patients are asymptomatic except they exhibit severe symptoms, thus similar to periodontitis diabetes mellitus (especially type 2) can be considered as a "silent, non-communicable" disease (Panakhup et al, 2021). Gingivitis is around 14 % more prevalent in patients with type 2 DM compared to patients without diabetes (Graves et al, 2019). Risk groups are male or elderly individuals, minorities, low socioeconomic status, impaired immune response, smoking, obesity, low physical activity, unhealthy diet and poor oral hygiene (Kocher et al, 2018). Regarding the prevalence patients with bad glycemic control (represented by HbA1c levels >7%) are more prone having periodontitis because the oxidative stress promoted by hyperglycemia increases cellular damage leading to periodontitis (Zheng et al, 2021). Vice versa, periodontitis patients are statistically more prone having type 2 diabetes mellitus (Sanz et al, 2018).

As well, type 1 and type 2 Diabetes mellitus have different prevalences of periodontitis (Jensen et al, 2018): type 2 diabetic patients are reported to have periodontitis in around 60% of all patients, whereas patients with type 1 DM have it less often with around 10% (Khouja et al, 2019; Sanz et al, 2018) and patients without diabetes are reported to have periodontitis only in 36% of all patients (Graves et al, 2019). On the other hand, the available data about diabetes mellitus and periodontitis prevalence have to be evaluated carefully as the patient awareness is relatively low, meaning that only half of the affected patients knows that blood sugar control is influenced by periodontal diseases and the compliance of medical screening suggested by dentists after diagnosis of periodontitis is even lower (Oguntimein et al, 2020). Especially the awareness of the bidirectional association of both diabetes mellitus and periodontitis is low (Shimpi et al, 2020; Panakhup et al, 2021). Education provided by health care providers and dentists significantly increased the awareness and aims at the diabetic patients visiting the dentist more often and periodontitis patients undergo frequent check-ups for potential diabetes (Oguntimein et al, 2020).

4.2. Pathogenesis

In general, Diabetes mellitus is rated as one of the two main modifying factors of periodontitis which needs to be mentioned in the description, the other one is tobacco smoking (Jensen et al, 2018; Sanz et al, 2020). Diabetes mellitus is classified as a systemic disease influencing the course of periodontitis (Kalhan et al, 2022). Its influence depends on the course and magnitude (hence stage) of diabetes mellitus (Jensen et al, 2018). As well, diabetes patients are considered as patients with higher risk of having periodontitis (Panakhup et al, 2021).

The clinical presentation of periodontitis is similar in Diabetes mellitus type 1 and type 2 which are the main types of diabetes causing or associated with periodontitis (Cicalau et al, 2021). Type 1 and type 2 DM both cause gingivitis and periodontitis which is more abundant in diabetic patients; poor metabolic control impairs the periodontal health and increases the susceptibility for periodontal diseases (Graves et al, 2019). Both periodontitis and diabetes are chronic diseases based on inflammatory-regulated processes (Kocher et al, 2018; Stoehr et al, 2021; Kalhan et al, 2022). Periodontitis has a similar chronic inflammatory mechanism as cardiovascular diseases and diabetes and a bidirectional interaction is reported (Liccardo et al, 2019). The anaerobic periodontal pathogens cause a non-specific, chronic inflammation with the degradation of the local tissues (Cicalau et al, 2021).

Oral dysbiosis occurs in insulin resistance development (Bui et al, 2019), periodontitis initiation and diabetes mellitus progression (Matsha et al, 2020). Both diseases influence the subgingival microbiome which breaks down the periodontal tissues and affects the inflammation and insulin resistance (Kocher et al, 2018; Kalhan et al, 2022). The dysbiotic shift in the periodontal tissues is additionally associated with insulin resistance development due to the chronic inflammatory events (Bui et al, 2019). *Porphyromonas gingivalis* plays an important role in the simultaneous pathogenesis of both periodontitis and diabetes (as well as Alzheimer's disease and cardiovascular disease) because it interacts with the host genes by causing gene enrichment which also can induce inflammatory reactions at the central nervous system (Zhang et al, 2021). Potential evidence for the systemic inflammatory reactions caused by *P. gingivalis* is the detection of *P. gingivalis* not only in the gingival sulcus, but also in the plasma and synovial fluids (Kriauciunas et al, 2019).

Porphyromonas gingivalis is highlighted by multiple researchers as one of the main pathogens in periodontitis (Bui et al, 2019; Kocher et al, 2018; Zhang et al, 2021; Zheng et al, 2021). This can be explained by focusing on the virulence factors of *P. gingivalis*; Its outer membrane vesicles can penetrate tissues deeply and easily, the outer membrane vesicles are not destroyed by proteases in the immune response, and they also have a higher cell adherence (Zhang et al, 2021). The membrane vesicles of *P. gingivalis* contain 151 proteins which all play a role in the virulence by penetrating host cells, by increased cell adherence and by forming proteases which destroy oral tissues and bone, thus accelerating periodontitis and its spread (Gabarrini et al, 2020). The outer membrane vesicles also increase the adherence and aggregation of *P. gingivalis* with *Candida albicans*, *Streptococci*, *Actinomyces*, and *T. denticola* (Zhang et al, 2021).

An interesting observation is that patients with type 1 DM had diabetes way longer than patients with type 2 DM due to the earlier onset which results in longer exposure to inflammatory mechanisms to exacerbate periodontitis (Zheng et al, 2021). Periodontal pathogens cause extra-oral disease either on direct (breakdown of periodontal tissues) or indirect way (enhances systemic chronic inflammation processes) (Bui et al, 2019). More precisely, the subgingival bacteria and their metabolic end-products and degradation products like the lipopolysaccharides or endotoxins may penetrate the systemic circulation and activate an altered systemic inflammation response which exaggerates the release of proinflammatory mediators (IL-1b, IL-6, CRP, TNF) which also increase the insulin resistance (Kocher et al, 2018; Sanz et al, 2018; Zheng et al, 2021). Shared inflammatory cytokines in DM and periodontitis are IL-6, IL-10 and TNF-alpha; besides that, a genetic predisposition or link is debatable (Sanz et al, 2018; Zheng et al, 2021). The outer membrane vesicles of P. gingivalis stimulate macrophages to release an increased amount of IL 1b, IL-6, IL-10, TNF-alpha and nitric oxide which lead to apoptosis thus also promoting the oral epithelium breakdown (Zhang et al, 2021). In the periodontal inflammation there is an increased amount of IL-1b and IL-6 and transforming growth factor 1b (TGF-1b); these Interleukins and growth factors are also significantly increased in Diabetes mellitus (Cicalau et al, 2021; Kocher et al, 2018).

The key pathogens for diabetes and insulin resistance are *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans* (Bui et al, 2019). In Individuals with Diabetes mellitus, *Actinobacteria* and *Fusobacteria* are very

abundant; on the other hand it was observed that their abundance is constant despite the presence or non-presence of Diabetes mellitus (Matsha et al, 2020). The dysbiotic shift in periodontitis that increases the local inflammatory response in the periodontal tissues also expresses tissue-degrading enzymes in the inflamed gingiva (Kocher et al, 2018). An infection with *Aggregaticbacter actinomycetemcomitans* showed to have a higher rate of bone loss and increased levels of TNF-alpha release (Graves et al, 2019).

Also, the periodontal pathogens influence the inflammatory pathways, which in consequence promotes oxidative stress that disrupts the insulin action mechanism and hence decreases insulin efficiency by insulin production deregulation and alteration of glucose metabolism (Thouvenot et al, 2022). Another feature of the insulin resistance is that consequently the pancreas tries to compensate the insulin resistance by producing more insulin which is not sustainable and leads to pancreas failure (Thouvenot et al, 2022).

A more differential view on the oral microbiome in diabetes patients shows that in case of gingival bleeding, *Bacteroidetes* were more abundant, whereas in diabetic patients with absence of gingival bleeding *Actinobacteria* where more present (Matsha et al, 2020). In both diabetic patients with hyperglycemia and with and without gingival bleeding Proteobacteria were more likely to be abundant than in patients with Normoglycemia; thus it may represent prediabetic or diabetic stages (Matsha et al, 2020; Saeb et al, 2019). This microbial pattern is especially abundant in diabetic patients with a probing depth of up to 4mm (Shi et al, 2018), while with increased periodontal probing depth *Bacteroidetes* are more abundant (Matsha et al, 2020; Shi et al, 2018). But after nonsurgical periodontal treatment the subgingival bacterial load is not different in individuals with and without diabetes (Reddy et al 2022).

What also happens in Diabetes mellitus is that there is an increased activation of periodontal ligament fibroblasts and increased expression of the inflammatory mediators which induce osteoclast formation and osteoblast apoptosis which cause a destruction of alveolar bone by increasing bone resorption and decreasing reparative bone formation (Zhang et al, 2021). IL-6 has in this context a pro-inflammatory action because its anti-inflammatory action is inhibited by TNF-alpha and IL-1; subsequently, C-reactive proteins are released and monocytes differentiate into osteoclasts (Cicalau et al, 2021). Additionally, the formation of new bone and soft tissue repair is decreased due to lower anabolic activities due to decreased or inhibited growth factor expression

as well as a reduced number and an increased apoptosis of osteoblasts, periodontal ligament fibroblasts and mesenchymal stem cells (Graves et al, 2019).

The dysbiotic shift in periodontitis that increases the local inflammatory response in the periodontal tissues also expresses tissue-degrading enzymes in the inflamed gingiva thus accelerating possible tissue break-down (Kocher et al, 2018). Increased systemic inflammatory markers are associated with a local proinflammatory response in the gingiva so both the local and the chronic systemic inflammation exacerbate themselves bidirectionally (Kocher et al, 2018). Graves et al (2019) additionally reported that the inflammatory response changes the oral microbiome to be more pathogenic which leads to a self-exacerbating progression with increased inflammation and bone loss. As well, Periodontitis triggers pancreatic beta-cell failure due to the systemic spread of the periodontal pathogens (Liccardo et al, 2019; Thouvenot et al, 2022) which promotes insulin resistance and induces hyperglycemia (Thouvenot et al, 2022). On the other hand, the interaction mechanisms are still not fully understood yet (Liccardo et al, 2019; Bui et al, 2019) which means it is debatable if certain periodontal pathogens initiate or exacerbate systemic diseases or if systemic diseases cause periodontal pathogens to change (Bui et al, 2019).

Clinically, the attachment loss in type 1 DM patients with a good glycemic control was reported to be around 3.3 mm, whereas type 1 DM patients with a poor glycemic control had an average loss of 6.2 mm; in comparison to nondiabetic patients with normoglycemia, the attachment was higher with 4.3 mm compared to 2.3 mm (Graves et al, 2019). Also, the bone loss with sites of a bone loss of more than 15% was higher (Graves et al, 2019). As well, symptoms of progressing periodontitis which make the patient to seek dental care are reddish or swollen gums, calculus on teeth, associated foul taste and longer looking or loose, movable teeth with bigger than normal spaces between themselves (Sanz et al, 2018).

4.2.1. Glycated hemoglobin

The severity and susceptibility of periodontitis in diabetes patients is higher and can be correlated with glycemic control (Graves et al, 2019). Besides the dysbiotic shift we must think about the reasons causing both the hyperglycemia in diabetes mellitus and the dysbiotic shift in periodontitis. The key element here is the diet: MOREIRA et al (2021) concluded that a higher sugar intake is associated with a higher risk and bigger

extent of periodontitis due to an exaggerated dysbiotic shift (Bui et al, 2019), especially in adolescents and young adults.

The unhealthy diet, which includes a high level of free and added sugars, is also the main cause of visceral fat, obesity and the metabolic syndrome (Moreira et al, 2021; Zheng et al, 2021) and the associated complications of diabetes mellitus (Harreiter et al, 2019; HARREITER et al, 2023). More concretely referenced to periodontitis, the unhealthy diet extending periodontitis is classified as "added sugar intake above 10% of daily total energy intake" (Moreira et al, 2021). Kocher et al (2018) also found out that HbA1c levels higher than 6.5% are already with mild periodontitis (stage I to II). An explanation for the association of the high sugar intake and periodontitis may be the hyperglycemia and glycolysation end products which also cause dyslipidemia and insulin resistance; all together these factors lead to a constant hyperinflammatory state (Moreira et al, 2021). Impaired glycemic control (Liccardo et al, 2019) or fasting plasma glucose level declines polymorphonuclear leukocyte activity and causes damage with subsequent breakdown of the endothelium which is a factor leading to the clinical manifestation of periodontitis (Teshome& Yitayeh, 2016). Also, chronic hyperglycemia decreases neutrophil and macrophage activity and increases inflammatory processes (Cardoso et al, 2017). Coincidentally, insulin resistance and hyperglycemia measured in glycated hemoglobin predict and influence the incidence of periodontitis; among that, hyperglycemia is rather associated with periodontitis (Kocher et al, 2018). Also, "Insulin resistance caused by *P. gingivalis* caused an increase in fasting plasma glucose levels" (Ohtsu et al, 2019).

A high sugar intake modifies the oral biofilm and induces oxidative stress by causing the dysbiotic shift and the altered (dysregulated) immune response (Moreira et al, 2021). Insulin resistance and hyperglycemia measured in glycated hemoglobin also predict and influence the incidence of periodontitis; among that, hyperglycemia is rather associated with periodontitis (Kocher et al ,2018). Also, the high sugar levels elevate the serum alkaline phosphatase and C-reactive protein levels which are associated with alveolar bone loss and thus progressing periodontitis (Moreira et al, 2021). Vice versa, Periodontitis treatment reduces glycated hemoglobin in diabetes patients (Liccardo et al, 2019; Teshomeh& Yitayeh, 2016).

Also, chronic hyperglycemia and hyperlipidemia induce oxidative stress which consequently increases the risk of diabetes complications like delayed wound healing or

microvascular complications as endothelial leakage and decreased vascular diameter (Kocher et al, 2018; Moreira et al, 2021; Cicalau et al, 2021).

Advanced glycation end products which occur due to chronic hyperglycemia accumulate in several tissues as gingiva, bone, kidney and many others, induce the production of reactive oxygen species and subsequently cause the higher levels of inflammatory cytokines; a consequence of that in the periodontal tissues is decreased formation of new bone (Graves et al, 2019).

Another association between periodontitis and diabetes mellitus is the altered microbiome in the gingival sulcus with associated high blood sugar levels in the gingival crevicular fluid; these finding is supported by the finding that periodontitis is more abundant in patients with diabetes mellitus than in patients without diabetes mellitus (Cicalau et al, 2021). Thus, severe periodontitis is classified as a risk factor for poor glycemic control in diabetic patients (Graves et al, 2019). On the other hand, the effects of periodontitis and diabetes mellitus on the polymorphonuclear cells, macrophages and the immune response is rather additive than synergistic, which is represented by PMN-delayed apoptosis and low levels of mature dendritic cells in periodontitis and diabetes mellitus patients (Portes et al, 2021; Rabelo et al, 2019).

4.2.2. Oxidative stress

One way of interaction is oxidative stress in both DM and periodontitis which activates pro-inflammatory pathways as mentioned in the pathogenesis (Sanz et al, 2018; Liccardo et al, 2019) with an increased release of IL-1, IL-6 and TNF-alpha. The proinflammatory pathways caused by oxidative stress lead to an increased cellular breakdown which is one of the reasons of occurring or progressing periodontitis (manifested in clinical attachment loss CAL and increased probing depth) (Zheng et al, 2021). The oxidative stress may also be caused by chronic hyperglycemia and hyperlipidemia which are induced by Diabetes mellitus; this happens by the interaction of the Interleukins and prostaglandins with the free fatty acids, advanced glycation end products and lipids which are typical for hyperglycemia (Cicalau et al, 2021). Smoking also releases reactive oxidative radicals and increases the oxidative stress (Graves et al, 2019). Another reason for increased oxidative stress is the oral dysbiotic shift that increases the occurrence of oxidative reactions (Moreira et al, 2021).

Oxidative stress induces damage to cell DNA, cell matrix and its structural components and apoptosis which induces higher cell and tissue damage which leads to micro- and macrovascular complications and poorer wound healing (Graves et al, 2019). Also, cytotoxic oxidative stress can be a consequence of chronic stress and causes cell necrosis or disorganisation and release of free radicals which increase the imbalance between oxidative and antioxidative properties as well (Cicalau et al, 2021). Another cause of oxidative stress is the high amount of glucose in almost all tissues which induces cytokine expression which produces reactive oxygen species, thus higher glucose levels have a similar effect as inflammation (Graves et al, 2019).

4.2.3. Pro-inflammatory mediators

Chronic inflammation due to periodontitis dysregulates and exacerbates the chronic inflammatory mechanism, subsequently impairs the blood sugar control and increases the insulin needs (Bui et al, 2019; Portes et al, 2021). The key pathogens according to (Bui et al, 2019) for diabetes and insulin resistance are *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans* which also play a major role in periodontitis (Zhang et al, 2021). The immune reaction to these causes the release of systemic inflammatory mediators which occurs in response to high levels of reactive oxygen species, glucose, and advanced glycation end-products in the periodontal tissues in diabetes patients (Graves et al, 2019). The systemic inflammatory mediators released in both Diabetes mellitus and periodontitis are C-reactive protein (CRP), TNF-alpha, IL-6 (Liccardo et al, 2019), INF-alpha, IL-1 and IL-6 shared in chronic inflammation and in periodontitis (Cardoso et al, 2017; Sanz et al, 2018), also IL-10 (Zheng et al, 2021); all of this molecules also interact with the free fatty acids, advanced glycation end products and lipids which are typical in hyperlipidemia (Cicalau et al, 2021). The systemic CRP levels are raised by the periodontal pathogens which induces the release of the proinflammatory cytokines causing insulin resistance (Stoehr et al, 2021); as well, hyperglycemia is associated with an increased amount of advanced glycation end products which bind to macrophages and monocytes which subsequently release more IL-1b, TNF-alpha and Prostaglandin PGE-2 which cause tissue damage (Cicalau et al, 2021).

The changes in the release of cytokine types and levels associated with diabetes mellitus can be differentiated according to the type of diabetes: in type 1 DM and type 2 DM, the

the macrophage number and chemotaxis function of neutrophils is increased in both, whereas in type 1 DM the phagocytic activity of neutrophils is decreased in contrast to a delayed apoptosis in type 2 DM; the prostaglandin PGE 2 release is higher in both, in type 1 DM the cytokines IL-1-beta and TNF-alpha are increased, but in type 2 DM IL1-beta, IL-6, INF-gamma and IL-8 are more abundant (Graves et al, 2019). These findings indicate that the chronic inflammatory mechanism in cardiovascular diseases, diabetes and periodontitis are quite similar (Liccardo et al, 2019; Nguyen et al, 2020). Additionally (Nguyen et al, 2020) observed an impaired immunological response; these are the main and most important factors affecting the deterioration of both diseases (Kocher et al, 2018). Hyperglycemia is also associated with neutrophil hyperfunction which impairs and alters the immune reaction and subsequently provokes a state of chronic inflammation (Cicalau et al, 2021). Among that, the levels of systemic inflammatory factors are raised in the crevicular fluid in teeth with periodontal pockets especially in patients with poorly controlled hyperglycemia (Stoehr et al, 2021). Concomitantely it is reported that constant hyperglycaemia and the increased secretion of TNF-alpha and other prostaglandins are caused by the accumulation of glycation end products (Cicalau et al, 2021). Other studies showed that in the simultaneous occurrence of both periodontitis and diabetes mellitus, macrophages, neutrophils and polymorphonuclear cells are more active than normal, whereas the function of dendritic cells is downregulated (Portes et al, 2021). As well, “pro-inflammatory cytokines as IL-1beta, IL-17, IL-6, TNF-alpha and INF-gamma” were more abundant, whereas IL-10 was reduced (Portes et al, 2021; Elazazy et al, 2021, Masi et al, 2018).

4.2.4. Micro- and macrovascular damage

There can be a direct way of dissemination of the periodontal pathogens into the systemic circulation by tissue trauma, dental procedures, flossing and chewing by rupture of small blood vessels closely to the dental plaque (Bui et al, 2019). Another migration route of pathogens into the bloodstream is due to surgical procedures (Bui et al, 2019) or periodontal bacteremia (Reddy et al, 2022). Also *P. gingivalis* penetrates host cells via its membrane vesicles, it induces oral epithelial cell detachment with subsequent tissue breakdown and thus accelerates its spread by itself (Zhang et al, 2021; Gabbarini et al, 2020). The outer membrane vesicles of *P. gingivalis* also impair periodontal wound healing by inhibiting the angiogenesis, the proliferation of

endothelial cells and the fibroblasts; what happens here on the cellular basis is that the cytokine secretion and cellular signaling molecules are degraded (Zhang et al, 2021). Microvascular damage is caused by hyperglycemia and is manifested by a “thickened basement membrane of the capillaries”, decreased vascular diameter, altered tissue perfusion and hence oxygen distribution and “elimination of toxic products” (Cicalau et al, 2021). Immune cells causing microvascular complications are higher than normal levels of Th-1 and Th-2 lymphocytes which release more TNF-alpha and IL-6 in small blood vessels; in the larger blood vessels TNF-alpha, IL-1, IL-5 and IL18 are more abundant and are strongly associated with macrovascular damage (Zhang et al, 2021, Cicalau et al, 2021).

Pathologies considered as macrovascular damage are diabetic nephropathy, diabetic retinopathy and other vascular complications, especially the risk of cardiovascular mortality is highlighted (Sanz et al, 2018). The pathogenic mechanism behind this is the inflammation-induced death of pericytes and endothelial cells which is more abundant, causing hypoxia (Graves et al, 2019). Besides that, Diabetes mellitus affects many other cell types in the periodontal tissue, for example osteoblasts, osteoclasts, fibroblasts, leukocytes and mesenchymal stem cells (Graves et al, 2019).

4.3. Influencing factors

“Constantly higher levels of HbA1c in diabetes patients who have concomitantly periodontitis increase the risk of diabetes complications” (Zheng et al, 2021). Insulin resistance and hyperglycemia predict the incidence of periodontitis (Kocher et al, 2018). Also, Diabetes mellitus may be the only systemic disorder which is associated with clinical attachment loss in the periodontal tissues (Cicalau et al, 2021).

Severe periodontitis associated with diabetes is way more prone to poor glycemic control (Teshomeh& Yitayeh, 2016). Thus, a “regular standardized assessment of the oral cavity should form a routine part in the clinical evaluation of patients with DM” (Zheng et al, 2021) to control the periodontitis and prevent its progression. Periodontal treatment improves glycemic control in type 2 diabetes for 4 months (Bui et al, 2019).

Healing of the periodontium in diabetes patients is correlated with glycemic control; every percent of reduction of glycated hemoglobin reduces risk of diabetes complications (Teshomeh& Yitayeh, 2016). Diet and lifestyle are also influencing factors of both diseases (Sedghi et al, 2021). Among that, (Moreira et al, 2021)

concluded that a higher sugar intake is associated with a higher risk and bigger extent of periodontitis, especially in adolescents and young adults.

In contrast, poor compliance with prescribed medications against hyperglycemia or recommended lifestyle changes, inefficient medication or glucose level monitoring or limited metabolic control are risk factors, but they are easily modifiable (Kocher et al, 2018). Visceral fat, obesity and metabolic syndrome also exaggerate systemic inflammation because the glycated hemoglobin levels which have a positive correlation to higher chronic inflammation markers as Interleukins (Kocher et al. 2018). The main cause of visceral fat, obesity and the metabolic syndrome is an unhealthy diet which includes a high level of free and added sugars; this feature of the diet also may induce periodontitis by a subsequent dysbiotic shift (Moreira et al, 2021; Bui et al, 2019).

4.4. Management

The management of the simultaneously occurring diabetes mellitus and periodontitis is generally multimodal and aims additionally on both the treatment of Diabetes mellitus on the one hand and periodontitis on the other hand; it is also based on the collaboration of dentists and physicians (Sanz et al, 2018; Panakhup et al, 2021). Treating both at the same time improves both diabetes mellitus and periodontitis as they exacerbate themselves bidirectionally. Association of higher HbA1c levels with periodontitis requires regular screening and diabetes therapy to reduce the risk of diabetic complications (Nguyen et al, 2020). On the other side, initial examination of new patients with diabetes mellitus should involve a screening for periodontitis, more difficult glycemic control and vice versa (Stoehr et al, 2021).

The main way of management is preventing periodontitis exacerbation by oral hygiene and oral health education to prevent marginal periodontium pathologies (Sanz et al, 2018; Cicalau et al, 2021) and prediabetes progression to manifested diabetes mellitus by lifestyle modification as diet and exercise (Kocher et al, 2018). Prevention is usually performed by education of the patients, but also by interprofessional and collaborative care between the general doctors and the dentists; the problem is the lack of understanding of many medical specialists (around 50%) for oral health issues, whereas only 30% of medical professionals referred their patients to the dentist for oral health assessment (Siddiqi et al, 2020). The advantage of prevention is the low cost and to avoid the risk of developing most of the complications of both periodontitis and diabetes mellitus (Panakhup et al, 2021). Prevention also includes screening for diabetes

in periodontal patients by looking for the BMI, to measure the HbA1c levels, to look for first degree relatives with diabetes, a history of hypertension, cardiovascular disease or hyperlipidemia and physical inactivity because all these factors increase the risk of developing diabetes mellitus (Sanz et al, 2018).

Another management option is glycemic control, regular periodontal treatment and follow-up combined with oral hypoglycemic drugs (Teshome& Yitayeh, 2016). Antidiabetic drugs improve gingivitis, but not periodontitis (Kocher et al, 2018), thus Scaling and root planning with the addition of amoxicillin and metronidazole reduces probing depth after 6-12 months and supports clinical attachment gain; problem is increasing resistance against antibiotics (Sedghi et al, 2021). But metabolic control does not decrease the HbA1c levels in short-term perspective despite clinical improvement which suggests that the disease remains low-level active (Reddy et al, 2022). Nonsurgical or conservative periodontitis treatment is the treatment of choice for improving periodontal health, manifested in periodontal probing depth and clinical attachment level; along that, modification of systemic factors is important (Kocher et al, 2018). Nonsurgical periodontitis treatment improves the periodontal health or disease parameters but does not affect glycemic control significantly (Reddy et al, 2022), thus it remains debatable if the periodontal pathogens can be positively correlated with the exacerbation of systemic diseases. On the other hand, Sanz et al (2018) reported that

"periodontal therapy improves serum HbA1c levels (…) although there is limited evidence for adjunctive therapies". Systemic antibiotics combined with nonsurgical periodontal treatment significantly improves periodontal health but does not affect glycemic control (Reddy et al, 2022). The systemic factors can be modified by metabolic treatment to reduce the glycated hemoglobin levels which subsequently decreases the CRP-levels and of other pro-inflammatory mediators (Kocher et al, 2018). Another reported approach is the adjunctive use of plant-based Carvacrol and Magnolol which are both antioxidant, anti-inflammatory, antimicrobial anti-diabetic and antiosteoclastic and subsequently protects the periodontal tissues by an inhibitory effect on the proinflammatory pathways (Maquera-Huacho et al, 2018). Magnolol reduces hyperglycemia and prevents the diabetes complications by antioxidant properties which also reduce the inflammation by blocking or at least decreasing the cytokine release by monocytes and macrophages (Cicalau et al, 2021). The antibacterial and cytotoxic level on the periodontal biofilm of carvacrol is reported to be like chlorhexidine

(MaqueraHuacho et al, 2018). The medication Arestin reduces probing depth and increase in clinical attachment level regain if it is placed locally in periodontal pockets deeper than 5mm in patients with poorly controlled diabetes mellitus (>9%HbA1c) (Reddy et al, 2022). Another medication regimen treatment approach of both diabetes mellitus and periodontitis is the supplementation of omega-3 polyunsaturated fatty acids and lowdose aspirin after nonsurgical periodontal treatment which modulates the host immune response to control chronic inflammatory diseases better [Castro dos Santos et al, 2020]. A life style modification approach in managing simultaneously occurring diabetes mellitus and periodontitis is smoking cessation because smoking exacerbates periodontitis and increases the prevalence of diabetic complications in periodontal patients (Zhang et al, 2021).

4.5. Complications

Bilateral exacerbation of both periodontitis and diabetes mellitus occurs if one or both remain untreated (Teshome& Yitayeh, 2016; Kalhan et al, 2022). Poor glycemic control in diabetes mellitus causes poorer periodontal health and prognosis (Sanz et al, 2018). Migration of pathogens into the bloodstream may occur due to surgical procedures and cause chronic inflammation reactions at distant sites (BUI et al, 2019). Diabetes complications are poor wound healing, periodontitis (3x higher risk), nephropathy, neuropathy, retinopathy (Bui et al, 2019; Kalhan et al, 2022). The risk for diabetic retinopathy, nephropathy and microangiopathy in patients with periodontitis is 2-8x higher than in patients without periodontitis (Sanz et al, 2018; Nguyen et al, 2020; Zhang et al, 2021). The incidence of coronary artery disease, atherosclerosis and myocardial infarcts was reported to be especially higher in patients with periodontitis and type 2 Diabetes mellitus (Khouja et al, 2019; Zhang et al, 2021; Kalhan et al, 2022), but it remains unclear if periodontitis or type 2 Diabetes mellitus has a bigger impact (Kalhan et al, 2022). Generally, cardiovascular complications are occuring 1-2-fold more in periodontitis patients than in patients without periodontitis (Nguyen et al, 2020; Zhang et al, 2021; Kalhan et al, 2022). Khouja et al (2019) reported that Diabetes mellitus type 1 associated with periodontitis is an important risk factor for cardiovascular complications as cardiovascular death or myocardial infarction; similar observations were reported by Kalhan et al (2022). An explanation for the increased occurrence of cardiovascular complications may be that periodontal pathogens penetrate

the blood stream and into the coronary vessels causing vascular lesions (Zhang et al, 2021). In major vascular or cardiovascular complications, the smooth muscle cells proliferate in the aorta and develop to an aneurysmal disease (Salhi et al, 2019). As well, the neuropathic foot ulceration appears to occur statistically more frequent in patients with severe periodontitis (Sanz et al, 2018). On the other hand, most complications of the comorbid patients with both periodontitis and diabetes mellitus (especially type 1) are associated with smoking, which makes the association of diabetes with periodontitis complications and vice versa questionable (Khouja et al, 2019).

4.6. Prognosis

Untreated Periodontitis leads to irreversible damage of periodontal ligament, cement and alveolar bone and consequently possible tooth loss and to impaired glycemic control in diabetic patients (Teshome& Yitayeh, 2016; Papapanou et al, 2018; Liccardo et al, 2019; Bui et al, 2019). Poor glycemic control shows to increase the breakdown of periodontal tissues and associated complications as tooth loss in periodontitis patients (Panakhup et al, 2021). Similar observations were noted by a study which showed that poor response to periodontal treatment increases the risk of occurring diabetes significantly and the association of manifested diabetes mellitus with an increased number of sites with bleeding on probing in the patient's dentition (Holmlund& Lind 2021).

Therefore, Diagnosis by regular screening appointments and treatment of both diabetes mellitus and periodontitis in early stages is essential to prevent major periodontal loss (Kwon et al, 2020; Reddy et al, 2022).

Periodontitis control mostly does not impact and improve glycemic control thus improve diabetes mellitus, but this is questionable as long-term data are not available (Reddy et al, 2022). Other studies showed an association between severe periodontitis and poor glycemic control (Holmlund& Lind, 2021; Panakhup et al, 2021). In contrast, periodontal treatment is reported to be able to reduce HbA1c levels in a short-term perspective (Graves et al, 2019). This is especially observed in Diabetes mellitus type 2, but for DM type 1 there is a lack of data (Reddy et al, 2022).

As well, glycemic control in Diabetes mellitus patients by lifestyle modifications decreases the chronic inflammation reactions and hence also improves the periodontitis

outcome (Graves et al, 2019). Effective maintenance therapy is the long-term treatment of choice for both DM and Periodontitis (Reddy et al, 2022).

5.Conclusions

Diabetes mellitus and Periodontitis are two of the most frequently occurring diseases worldwide with a rising prevalence. Diabetes mellitus is characterised by lack of insulin in type 1 DM with subsequent hyperglycemia and acquired chronic hyperglycemia in type 2 DM. Clinically, Diabetes mellitus is represented by normal (type 1 DM) or increased (type 2 DM) body weight, sweet-smelling urine and polyuria, polydipsia and tiredness. The threshold value of manifested Diabetes mellitus is more than 6.5% (47.5mmol/mol) glycated hemoglobin. Also, chronic hyperglycemia increases the severity of chronic inflammatory processes and alters the immune response. The main way of managing Diabetes mellitus is the insulin therapy to maintain blood glucose levels and glycemic control. Another approach is prevention by education, lifestyle changes and a healthy diet which can prevent the prediabetes progression to manifested diabetes. Complications of diabetes mellitus can affect almost every tissue in the human body and range from minor vascular damage to major vascular damages even to limb loss.

Periodontitis is a chronic plaque-induced disease of the tooth attachment apparatus which is induced by a dysbiotic shift in the dental plaque. The dysbiotic shift is characterized by abundant pathogens as *Porphyromonas gingivalis*, *Treponema denticola*, *Filifactor alocis*, *Streptococcus gordoni*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans* which induce a local chronic inflammatory reaction that spreads into the whole body. Periodontitis manifests by a progressive breakdown of the periodontal tissues. If untreated it can cause tooth loss and induction or exacerbation of systemic diseases because the periodontal pathogens can enter the systemic circulation. The other major part of the periodontal pathogenesis is the altered chronic inflammatory reaction mechanism and response to the periodontal pathogens which has a systemic involvement. In the altered chronic inflammatory reaction increased levels of cytokines as TNF-alpha, IL-1b, IL-6 and IL-10 are released. The treatment of periodontitis includes usually frequent nonsurgical plaque removal and improved patients oral hygiene as well as regular reevaluation appointments.

Both Diabetes Mellitus and Periodontitis are frequently occurring simultaneously and exacerbate each other because of the shared pathogenesis represented by an altered chronic inflammatory reaction. Common factors in both Diabetes mellitus and Periodontitis are the increased levels of TNF-alpha, IL-6 and IL-10. The chronic inflammatory reaction is systemic and it sets the cells under increased oxidative stress and induces cell death, endothelial breakdown and microvascular malfunctions. By that, the amount of periodontal tissue loss is increased and the periodontal dysbiosis is enhanced. Similarly, the amount of glycated end products and glycated hemoglobin is increased and the insulin action is decreased. Difficulties to estimate the prevalence are the low patient's awareness which also makes treatment more difficult because the diagnosis is more difficult. Another factor in this context is that both diabetes mellitus and periodontitis are asymptomatic in the initial stages and only diagnosed in a progressed stage. As well, Diabetes mellitus is considered as the main modifying factor of periodontitis besides smoking.

Common factors exacerbating Periodontitis and Diabetes mellitus are smoking, a low socioeconomic status, an impaired immune response, , obesity, low physical activity, unhealthy diet and poor oral hygiene.

Smoking cessation is an integral part of treating both periodontitis and diabetes mellitus because it has an exacerbating effect on both diseases and increases the risk of possibly occurring complications.

The best way of treating simultaneously occurring periodontitis and diabetes mellitus is on the first line prevention. An optimal regimen to prevent simultaneously diabetes and periodontitis are lifestyle changes, an improvement of the diet which may decrease the plaque accumulation and prevents hyperglycemia; lifestyle changes also include an improvement of the individual oral hygiene which is prevents the progression of periodontitis and is as well a potential contributing factor for glycemic control. Nonsurgical periodontal treatment improves periodontal health and may influence glycemic control. Nonsurgical periodontal treatment decreases the severity of the chronic inflammatory response of the patient and decreases the susceptibility for diabetes and other systemic diseases.

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