Current Oral Health Reports (2023) 10:43–51
https://doi.org/10.1007/s40496-023-00334-3

Metabolic Syndrome and Periodontal Disease

Elif Mutafcılar Velioğlu[1] · **Sefa Aydındoğan**[1] · **Sema S. Hakkı**[1]

Accepted: 24 March 2023 / Published online: 13 April 2023

Abstract

Purpose of Review Metabolic syndrome is a systemic condition that has components such as obesity, dyslipidemia, hyperglycemia, and hypertension and is associated with an increased risk of cardiovascular disease and type 2 diabetes. Periodontitis is a chronic inflammatory disease characterized by progressive attachment loss that develops as a result of the host response to the dysbiotic plaque microbiome. Periodontal diseases can jeopardize systemic health through various mechanisms as well as be detrimental to oral health. The interlinks of these mechanisms and the pathogenesis of metabolic syndrome cause a bidirectional interaction between the two diseases. This review aimed to evaluate studies focusing on potential interaction mechanisms between periodontal disease and metabolic syndrome and present the clinical implications of these interactions.

Recent Findings Studies dealing with the relationship between metabolic syndrome and components of metabolic syndrome and periodontal disease are available in the literature, and it is reported that the two conditions are generally related. According to literature findings, inflammation is a common pathway in metabolic syndrome and periodontal disease. While both diseases can exacerbate the inflammation and affect the other, it is also seen that the severity of the disease increases by being affected by the increasing chronic inflammation itself. The fact that they have common risk factors other than the intersecting pathways in the two diseases in the host inflammatory response strengthens their relationship but prevents the understanding of causality and the visibility of the initiating factor. Although these common risk factors affect the prevalence studies, the immune mechanisms identified to date and the results of longitudinal studies show that this relationship is bidirectional. Fewer data describing the relationship between metabolic syndrome and periodontal disease, which is significant for systemic disease risk. This is explained by the factors that make the standardization of studies difficult. The use of different disease definitions, the existence of different forms of periodontal disease, the multi-component of metabolic syndrome, and different study plans prevent standardization and reduce the number of studies to be included in compilations and meta-analyses that will reveal essential information on the subject.

Summary It is thought that the data of longitudinal studies, which have a standardized study design and use common diagnostic criteria, can more clearly reveal the relationship between periodontal disease and metabolic syndrome. Thus, the direction of the relationship between the two diseases (bidirectional or unidirectional), cause-effect relationship, dose-response relationship, and treatment approaches can be obtained.

Keywords Periodontitis · Metabolic syndrome · Obesity · Hyperglycemia

Introduction

Periodontitis is a chronic inflammatory disease associated with a dysbiotic oral microbiome and altered host response, resulting in progressive destruction of periodontal tissues and tooth loss [1]. Chronic inflammatory periodontal diseases, which affect a large population in the society, have been stated by the World Health Organization as the major cause of tooth loss in adults [2]. Periodontal diseases affect tooth-supporting tissues; however, they are likely to affect systemic health in many ways. It shares risk determinants and risk factors with systemic diseases such as diabetes, cardiovascular diseases, cancer, respiratory system diseases, and rheumatological diseases, which are the cause of the majority of deaths in the population [3]. Studies dealing with the effect of periodontal health and disease status on systemic health report that there is a relationship between

✉ Elif Mutafcılar Velioğlu
mutafcielif@gmail.com

[1] Department of Periodontology, Faculty of Dentistry, Selcuk University, 42250 Selçuklu, Konya, Turkey

periodontal disease and many different systemic conditions, including metabolic syndrome. The relationship between the clinical, histological, and biochemical findings of metabolic syndrome, which includes more than one systemic finding, and periodontal disease, has been discussed separately, and remarkable relationships have been reported [3, 4].

Metabolic syndrome is a cluster of conditions that occur simultaneously and increase the risk of cardiovascular disease and double the risk of type 2 diabetes. The prevalence of metabolic syndrome increases with age and varies by ethnicity and gender [5]. Various metabolic syndrome definitions differ slightly depending on the issuing institution. The most commonly used definition was announced by National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [6]. Metabolic syndrome is a metabolic disease characterized by the combination of factors such as high blood pressure, dyslipidemia (high triglyceride levels and low low-density lipoprotein levels), high plasma glucose levels, and central obesity, which pose an increased risk of cardiovascular disease and type 2 diabetes mellitus (DM). Three of these five components must be present together to define the diagnosis of the syndrome [7]. Prediabetes is also considered part of the metabolic syndrome, as it is associated with insulin resistance and is a high precursor to new-onset type 2 diabetes [8].

Since the 1999 AAP classification for periodontal diseases and conditions, a great deal of literature has been reported in terms of existing and possible relationships between periodontitis and systemic diseases. In addition to the need for revision in many aspects of the 1999 classification, the emphasis on the interaction of systemic disease-periodontal status is a remarkable aspect of the *2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions* [9]. In periodontal pathogenesis, different pathways have been demonstrated that associate periodontitis with systemic diseases. The main interaction mechanisms are the spread of pathogenic bacteria through the vascular system and the negative effect of inflammatory mediators arising from periodontal inflammation on systemic chronic inflammation. Studies show that periodontitis increases the overall inflammatory burden, which is strongly associated with coronary artery disease and diabetes. Diabetes was included as a risk factor in the 2017 classification. It is also a remarkable change that C-reactive protein (CRP), which expresses systemic inflammation, and biochemical biomarkers are included in the classification to draw attention to the "dimension of the biology of periodontitis," although it is not currently a grade-modifying criterion due to the need for supporting evidence [10].

In the consensus report of workgroup 3 of the *2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions: Periodontal manifestations of systemic diseases and developmental and acquired conditions*, it was pointed out that there is a moderate relationship between obesity-metabolic status and periodontal disease by referring to current meta-analyses on the topic [11], and it is stated that additional longitudinal studies are required to clarify this relationship more clearly [12]. In this review, the relationship between periodontal disease with metabolic syndrome and various systemic conditions defining this syndrome as diabetes, hyperlipidemia, and obesity was further explored.

Metabolic Syndrome and Periodontal Disease

When the results of studies dealing with the relationship between metabolic syndrome and its components with periodontal disease are evaluated, it is seen that there is a consensus on the existence of a possible relationship. However, it is known that the results show significant variations due to different study designs and participant criteria [13•]. Different definitions of periodontal disease, individual differences in periodontitis clinics, and host response may explain these variations in terms of periodontology. The necessity of a large number of criteria for the diagnosis of metabolic syndrome and sometimes the lack of a common scientific language on these criteria cause unclear result for its relationship with periodontal disease in the literature. According to some studies, the more significant the current metabolic syndrome indicators are, the higher their effectiveness in periodontal disease [14–16]. Conversely, some studies indicate that even at least one of the metabolic syndrome components states its presence, such as obesity or hyperglycemia, may have an impact on periodontal status without a diagnosis of metabolic syndrome [14].

In a systematic review and meta-analysis including 19 cross-sectional and 1 longitudinal studies, 7 of these studies were included in the meta-analysis, which determined that there is a definite relationship between the presence of periodontitis and increased risk of metabolic syndrome. While the results of this study confirm a significant relationship between periodontitis and metabolic syndrome, it is reported that the mechanisms and magnitude of this relationship remain unclear [17]. In another meta-analysis, which included 26 studies evaluating the relationship between periodontal disease and metabolic syndrome, it was determined that individuals with metabolic syndrome have a 38% higher probability of having periodontitis [18]. However, from another point of view, some studies have reported that the presence of periodontitis increases the risk of metabolic syndrome. The relationship between periodontal disease and metabolic syndrome has been proven by the data of cross-sectional studies. However, it is not possible to know the initiating cause of the relationship and the results related

to this cause. It constitutes an important field of study that seeks answers whether periodontitis or metabolic syndrome that causes this relationship and affects the other first. To elucidate these mechanisms and pathogenesis, it is essential to follow both conditions in their developmental processes. Hence, longitudinal studies on the subject have key importance in illuminating the periodontal disease-metabolic syndrome interaction. However, it is very difficult to implement study plans in which these multifactorial and multisymptomatic diseases can be evaluated longitudinally, in which effective criteria can be standardized and evaluated by excluding other related factors [12].

In a longitudinal study, it was determined that the risk of at least one metabolic syndrome marker occurring at the end of 4 years was 60% in the presence of periodontitis [19]. In another longitudinal study with a 5-year follow-up, it was reported that individuals with a body mass index less than 22, between 25 and 30, or greater than 30 differed in the development of periodontal disease, and this difference was reported to be in the form of a higher risk of periodontal disease development as the body mass index increased [20]. In another longitudinal study with a 5-year follow-up, it was determined that 511 individuals with 2 or fewer metabolic syndrome components developed metabolic syndrome at the end of 5 years. Among the individuals included in the study, it is noteworthy that 44% less metabolic syndrome develops in individuals who brush their teeth at least 3 times a day [21].

Interaction Pathways of Periodontal Disease and Metabolic Syndrome/Obesity

Effect of Obesity/Metabolic Syndrome on Periodontal Disease

Obesity is generally defined by the body mass index formed as a result of epidemiological studies. Accordingly, the body mass index defines 25–29.9 kg/m^2 as overweight, and ≥30 kg/m^2 defines obesity [22]. It is known that body fat distribution based on waist circumference measurements as well as body mass index is important in evaluating obesity-related mortality and morbidity associated with cardiometabolic risk. There are also some methods that show body adipose tissue distribution more clearly than waist circumference measurements [23, 24]. Dual-energy X-ray absorptiometry scan, air or water displacement bioimpedance, and skin caliper are among these methods [25]. It is recommended that the evaluation of obesity should be more accurate when evaluating body fat distribution and body mass index together. In addition to diagnosing obesity with numerical data, another definition that emphasizes its effects on the organism is quite remarkable: "Chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences" [26].

The first study to associate periodontal disease with obesity reported increased bone resorption and periodontal inflammation in genetically obese rats [27]. Long after this study, periodontal disease and obesity were associated for the first time in a cross-sectional human study [28]. The Third National Health and Nutrition Examination Survey (NHANES), which evaluated the larger populations from multiple perspectives, confirmed the association of body composition with periodontal disease [29]. Studies dealing with the relationship between periodontal disease and obesity have been enriched in the literature, with the recent prevalence of obesity worldwide and in all age groups, and with a better understanding of its effects on the organism. Despite the heterogeneity between these studies, it seems to be a common opinion that there is a dose-dependent relationship between obesity and periodontal disease.

The relationship between obesity and periodontitis is mainly based on increased inflammation and the negative effect of this increase on the organism [30•]. Adipose tissue, not only as energy storage but as an endocrine organ, is responsible for increased pro-inflammatory and decreased anti-inflammatory cytokine release, causing chronic systemic inflammation. Adipose tissue synthesizes proinflammatory cytokines such as visfatin, leptin, resistin, and anti-inflammatory mediators such as adiponectin. It is observed that while proinflammatory adipokine synthesis from adipose tissue increases with obesity, the synthesis of anti-inflammatory adipokines such as adiponectin decreases [31]. In addition to the immune response balance shifting towards hyperinflammation, the deterioration of the balance between reactive oxygen species and antioxidants in both obesity and periodontal disease causes increased oxidative stress. In an experimental animal study, decreased gingival antioxidant levels were found in obese rats compared to individuals with normal weight [32, 33]. Adipokines such as leptin, resistin, and ghrelin can be detected in GCF and differ from normal-weight individuals, reflecting their serum levels in obese individuals [34–36]. In a study that detected increased serum tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) levels in obese individuals, it was reported that gingival crevicular fluid TNF-α levels were increased in obese individuals compared to normal-weight individuals. The identification of these proinflammatory mediators, inflammatory markers, and specific adipokines in crevicular fluid and their reflection in serum concentration provide some support to explain the possible bidirectional link between obesity and periodontal disease.

At the same time, it is thought that immune response deficiencies and impaired host response in obesity may create

a pathway in the periodontal disease-obesity relationship. It is known that free fatty acids can bind to Toll-like receptors just like periodontal bacteria [37]. Since this connection occurs continuously due to increased free fatty acids in obesity, it is seen that the sensitivity of host defense cells' response to Toll-like receptors in the fight against bacterial infiltration hinders [38]. As another example that shows the importance of the balance in the immune response, it has been reported that lipoxins (Lipoxin A4), which are responsible for the resolution of inflammation, are lower in individuals with metabolic syndrome and that lipoxin levels are negatively correlated with both periodontal parameters and metabolic syndrome [39].

Dysbiotic microflora causes increased intestinal permeability and thus systemic inflammation. An altered gut microbiome profile is also observed in obesity, and systemic inflammation appears to be higher than in normal weight. In this way, it is thought that it can exacerbate periodontal inflammation. It is known that oral microflora itself changes in obesity compared to normal-weight individuals. Although it is thought that long-term further studies are needed to determine the reason for this difference in terms of causality, studies are reporting increased periodontal pathogen levels in obese individuals [40, 41].

Although the literature support on the subject is insufficient, it is reported that gingival vascular circulation may be impaired in obesity. Altered microvascular circulation is detected in obesity, increased vessel diameter in terminal arterioles, and consequently decreased blood supply [42].

Effect of Periodontal Disease on Obesity/Metabolic Syndrome

There is relatively little literature on the effect of periodontal disease and health status on obesity. The effect of periodontal disease on uncontrolled weight gain and adipose tissue increase can be associated with some simple but important mechanisms and other elaborate and complex mechanisms. Decreased masticatory function in the presence of periodontal disease and deterioration of dentition integrity with missing and mobile teeth affect nutrition quite negatively. Individuals tend to eat easily swallowable, processed high-carbohydrate, fiber-poor foods. The effect of this situation on obesity is reported as an inevitably simple but effective mechanism.

Periodontal disease causing chronic low-grade inflammation constitutes the main pathogenesis. Increased gingival crevicular fluid (GCF) and salivary proinflammatory cytokine levels are encountered in periodontal disease [43]. It has been observed that these mediators, such as TNF-α, IL-1β, and reactive oxygen species, which increase with the severity of the disease, also increase in the serum levels of systemically healthy individuals with periodontitis [44]. In addition, it is known that adipokines such as visfatin, leptin, resistin, and ghrelin are released from periodontal tissues similar to adipose tissues, and changes in their levels are observed in the presence of periodontal disease. Just like in obesity, increased proinflammatory visfatin and decreased anti-inflammatory adiponectin levels were observed in the presence of periodontitis [45•]. Ghrelin, which stimulates appetite, is released from adipose tissue as well as from periodontal tissues. In addition to the shift of inflammatory balance to hyperinflammation, it is thought that periodontal disease may also directly induce obesity since it has been determined that increased levels of ghrelin released from periodontal tissues increase appetite in the presence of periodontitis [36]. It is thought that gout dysbiosis, which we mentioned before, may be affected by the periodontal disease as well as obesity. Although there is insufficient evidence yet, changes in the gut microbiome have been reported due to the presence of periodontal disease [46].

The Relationship of Periodontal Disease with Dyslipidemia, Hyperglycemia, and Hypertension

Periodontal Disease and Hyperlipidemia

In systematic reviews of studies dealing with periodontal disease and dyslipidemia, it is reported that periodontitis affects serum lipid levels. In the two systematic reviews conducted on the subject, it is seen that 4 studies, 1 of which is a longitudinal study, are common. The results of these studies summarize that increased serum lipid levels are observed in periodontitis. Increased cholesterol, triglyceride, low-density lipoprotein, and reduced high-density lipoprotein levels have been reported in individuals with periodontitis [47, 48]. In the indicated longitudinal study, it was determined that periodontitis was associated with the development of hyperlipidemia at a higher rate compared to periodontal health. In another longitudinal study, it was observed that individuals with high periodontal scores developed hyperlipidemia 1.9 times higher in a 4-year period [19]. In another study examining dyslipidemia and periodontal disease, it was determined that serum and gingival crevicular fluid TNF-α and IL-1β levels were correlated with total cholesterol and high-density lipoprotein (HDL) ratio. It was reported that serum proinflammatory cytokines may have an important role in the relationship between periodontal disease and hyperlipidemia [39].

Just as with other components of metabolic syndrome, there is a bidirectional relationship between hyperlipidemia and periodontal disease. It has been observed that increased inflammation in periodontal disease affects lipid metabolism and causes inflammation-related lipid and lipoprotein

metabolism alterations. Increased low-density lipoprotein (LDL) synthesis, adipose tissue lysis, increased de novo hepatic fatty acid synthesis, suppression of fatty acid oxidation, and disruption of LDL clearance cause inflammatory dyslipidemia [49, 50]. From the other side of this two-way relationship, it is seen that dyslipidemia increases the severity of the periodontal disease. We can explain this with proinflammatory cytokine synthesis induced by free fatty acids, altering the host response and contributing to low-dose inflammation [51]. Along with these, it has been determined that oxidized LDL, which can bind to Toll-like receptor-2 (TLR-2), can directly destroy bone tissue by stimulating osteoclastogenesis [52].

Periodontal Disease and Hyperglycemia

The relationship between periodontal disease and diabetes has been proven and clearly demonstrated in the literature for a long time. Diabetes is vitally connected with periodontal disease. Uncontrolled diabetes exacerbates periodontal disease and adversely affects the diagnosis of treatment. The presence of periodontitis also makes it difficult to control diabetes. Because of the two-way relationship in the treatment of the individual, a holistic approach is necessary to combat both periodontal and hyperglycemia together. Reviews and meta-analyses that deal with the subject show that periodontitis patients have poor glycemic control compared to periodontally healthy individuals, whether they have diabetes, prediabetes, or not. However, it has been determined that diabetes-related complications are observed more frequently in individuals with both diabetes and periodontitis than in individuals without periodontal disease. Again, individuals who are systemically healthy but have periodontitis have a higher risk of developing diabetes [53]. While diabetes has a higher prevalence in individuals with periodontitis than in periodontally healthy individuals, it is reported that the risk ratio of patients with periodontitis is 2.27 compared to periodontally healthy individuals [54]. In summary, diabetes and periodontal disease affect the general health of the individual in a strong interaction.

There is a two-way interaction between periodontal disease and diabetes. Diabetes shows its effect on periodontal disease in several different ways [55]. In uncontrolled diabetes, increased advanced glycation end products affect periodontal tissues by stimulating proinflammatory cytokine synthesis and disrupting collagen metabolism and turnover [56]. At the same time, advanced glycation end products cause alveolar bone loss directly through apoptosis of osteoblasts [57]. Periodontal disease is exacerbated as hyperglycemia causes changes in host response such as neutrophil phagocytosis and chemotaxis [58, 59]. From another point of view, periodontal disease causes insulin resistance with chronic inflammation, and the pathways responsible for keeping the blood glucose level in balance are interrupted. In addition, hyperglycemia is exacerbated due to the synthesis of cytokines such as IL-6, resistin, and TNF-α, which increase in periodontal disease and adversely affect insulin resistance [60, 61].

Periodontal Disease and Hypertension

The reviews evaluating the literature data on the subject report that there is an increased risk of developing hypertension in the presence of periodontal disease [62]. A meta-analysis of studies dealing with blood pressure and periodontal status confirms the relationship between hypertension and periodontal disease.

The results of another study argue that periodontitis may be a precursor to the development of hypertension, although it is not statistically significant [45•]. When possible mechanisms are examined, it is known that periodontal disease stimulates atherogenesis. Bacteria, bacterial products, and increased proinflammatory cytokine synthesis disrupt the endothelial structure and increase the development of atherogenic plaque and thrombus [63]. These mechanisms form the basis of all cardiovascular diseases such as stroke, MI, and hypertension. All metabolic syndrome components together increase the risk of morbidity and mortality due to the increased risk of cardiovascular disease.

Effect of Periodontal Treatment on Metabolic Syndrome—Effects of Treatment Approaches on Metabolic Syndrome on Periodontal Tissues

The relationship between periodontal disease and metabolic syndrome seems to exist, although all pathogenic pathways have not been elucidated and the causality relationship has not been fully resolved. Perhaps the main data on the clinical implications of this relationship will be seen in treatment responses. The effect of periodontal treatment or/and improvement of metabolic syndrome components on each other of these conditions is of key importance. When the effect of non-surgical periodontal treatment on serum adipokine levels (1 year after treatment) was examined, a difference was found between obese and non-obese individuals [64]. In another study, a decrease in saliva resistin levels was observed with periodontal treatment, but this change was not correlated with clinical periodontal parameters [65]. In another study, periodontal improvement was observed in both obese and non-obese individuals after treatment, and it was stated that obesity was a secondary factor in the effectiveness of periodontal treatment, and the severity of the periodontal disease has primary importance [66]. When serum and gingival

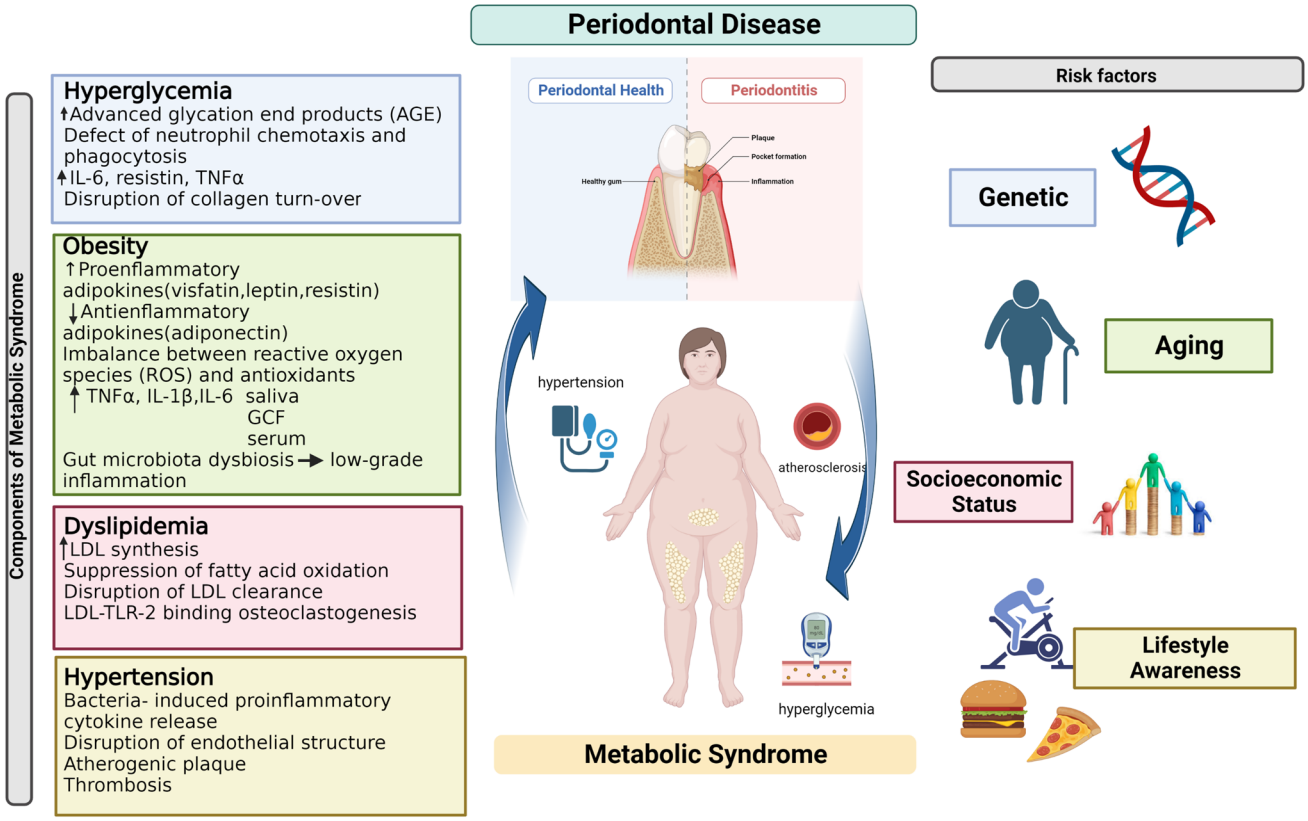

Fig. 1 Bidirectional interaction between metabolic syndrome and periodontal disease and common risk factors. *AGE* Advanced glycation end products, *IL-6* Interleukin-6, *TNFα* Tumor necrosis factor-alpha, *IL-1β* Interleukin 1-Beta, *GCF* Gingival crevicular fluid, *LDL* Low-density lipoprotein, *TLR-2* Toll-like receptors-2

crevicular fluid reactive oxygen species and resistin levels were examined after periodontal treatment, it was found that the periodontal parameters of non-obese individuals showed a better improvement. In addition, it was determined that plasma reactive oxygen species decreased more in individuals with normal weight [67].

In a study dealing with the results of non-surgical periodontal treatment in individuals with metabolic syndrome, decreased high-sensitivity C-reactive protein of total leukocyte counts and triglycerides with a significant increase of HDL levels was detected in the 2nd month after treatment. There are also other studies showing the decrease of CRP after periodontal therapy with adjunctive antimicrobial therapy [68, 69]. Bizarre et al. reported that non-surgical periodontal therapy in individuals with metabolic syndrome resulted in improvement in all metabolic syndrome components including waist circumference, blood pressure, high-density lipoprotein, triglycerides, and glucose levels [70]. Diet and weight loss are known to be effective in controlling periodontal inflammation. The reduction of proinflammatory cytokines with weight loss is effective in periodontal inflammation as a result of systemic low-grade inflammation resolution and it is also found to provide healing of periodontal pockets with moderate depth [71].

Conclusion

Periodontal disease and metabolic syndrome are related because they have common risk factors and common immunomodulatory mechanisms (Fig. 1). Metabolic syndrome results in cardiovascular diseases, which are among the leading causes of death in the world. With a better understanding of the effect of periodontal disease on this syndrome, the importance of periodontal health and periodontal treatment in systemic health will increase. Thus, both oral and systemic health can be achieved by new treatment approaches in accordance with the holistic approach in that the entire systemic condition of the individual is evaluated together. Up-to-date data should be supported by more systematic reviews and meta-analyses evaluating the results of studies including longitudinal studies and that are standard in terms of disease definitions and criteria.

Declarations

Human and Animal Rights and Informed Consent No animal or human subjects by the authors were used in this study.

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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