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Periodontal, metabolic, and cardiovascular disease: Exploring the role of inflammation and mental health

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The objective of this paper is to review the role of inflammation and psychiatric disorders in the well-recognized links between periodontal disease, cardiovascular disease and metabolic diseases, such as obesity, diabetes mellitus and metabolic syndrome, and to document reasons supporting a mediating or moderating role of inflammation or mental illness.

Abstract

Previous evidence connects periodontal disease, a modifiable condition affecting a majority of Americans, with metabolic and cardiovascular morbidity and mortality. This review focuses on the likely mediation of these associations by immune activation and their potential interactions with mental illness. Future longitudinal, and ideally interventional studies, should focus on reciprocal interactions and cascading effects, as well as points for effective preventative and therapeutic interventions across diagnostic domains to reduce morbidity, mortality and improve quality of life.

Keywords

Periodontitis; metabolic syndrome; cardiovascular disease; mental illness; inflammation

Scope of the problem

Periodontal disease

The term periodontal disease refers to pathologic inflammatory conditions affecting the gingiva and supporting bone and connective tissue (periodontal tissues) surrounding the teeth. Periodontal disease is characteristically chronic in nature, commonly occurring in response to oral bacterial plaque and biofilm formation. The two primary periodontal diseases are gingivitis and periodontitis. Gingivitis is characterized by inflammation of the gingiva that is reversible (with proper oral hygiene) and without evidence of periodontal breakdown [1–3]. Over time, untreated gingivitis can progress to destructive periodontitis [4]. Periodontitis, in contrast, is characterized by gingival inflammation that spreads beyond the gingiva, resulting in the irreversible breakdown of the connective tissue attachment to the root, and alveolar bone resorption in a susceptible person [3]. Progressive destruction of connective tissue attachment and alveolar bone resorption results in apical migration of the gingival epithelium and pocket formation. Over time, untreated periodontitis can result in progressive destruction of the periodontium, resulting in tooth mobility, decreased masticatory function, and eventual tooth loss [5].

Over 700 different strains of bacteria have been identified in the human oral cavity, with distinct subsets often predominating in different habitats, which among others, include teeth and periodontal sulcus. *Streptococcus sanguis* (*S. sanguis*), *Streptococcus oralis*, *Actinomyces odontolyticus* and *Actinomyces naeslundii* typically colonize the supragingival areas of the tooth [6–8]. In contrast, *Streptococcus sanguis*, *Streptococcus oralis*, *Actinomyces naeslundii*, *Actinomyces odontolyticus*, *Veillonella parvula*, and *Fusobacterium nucleatum* frequently colonize subgingival sulcus [8, 9]. In the presence of chronic inflammation, an increase in periodontal pocket formation is associated with a concomitant development of an anaerobic subgingival microbiota composed of anaerobes and microaerophilic gram-negative bacilli [10, 11]. The subgingival microflora in periodontitis changes from being gram-positive predominately, to spirochetes, obligated anaerobes and gram-negative organisms, such as *Tannerella forsythia*, *Porphyromonas gingivalis* (*P. gingivalis*), *Campylobacter rectus*, *Treponema denticola*, *Seimonas noxia*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans* [9–11]. Although periodontal

diseases generally represent polymicrobial infections, certain oral bacteria, such as *P. gingivalis*, are strongly linked to periodontitis.

One of the important challenges in epidemiologic studies has been to characterize the incidence and prevalence of periodontitis, given the application of different diagnostic criteria and assessment methods [12, 13]. In order to standardize the assessment of patients with suspected periodontitis and to get more reproducible and reliable data, World Health Organization (WHO) in 1982, developed the “Community periodontal index of treatment needs” [14]. Case definitions have also been proposed by Centers for Disease Control and Prevention (CDC) and the American Academy of Periodontology (AAP) for performing population-based periodontitis surveillance, which are as follows: “No periodontitis” is defined as “No evidence of mild, moderate, or severe periodontitis.” “Mild periodontitis” is defined as “ 2 interproximal sites with clinical attachment loss (CAL) 3 mm, and 2 interproximal sites with periodontal probing depth (PPD) 4 mm (not on same tooth) or one site with PPD 5 mm.” “Moderate periodontitis” is defined as “ 2 interproximal sites with CAL 4 mm (not on same tooth), or 2 interproximal sites with PPD 5 mm (not on same tooth).” “Severe periodontitis” is defined as “ 2 interproximal sites with CAL 6 mm (not on same tooth) and 1 interproximal site with PPD 5 mm” [15].

The prevalence of periodontitis is high among United States (US) adults, paralleling the rates of other major chronic illnesses, and constitutes a major public health concern [16]. In the most recent National Health and Nutrition Examination Survey (NHANES), 46% of the US adult population 30 years or older, comprising nearly 65 million adults, had periodontitis, with 8.9% exhibiting severe periodontitis [17]. In the US, from 2011 to 2012, periodontitis was reported in 44.7% (SE: $\pm 2.4\%$) of the adults aged 30 years [17]. The estimation for 2011 to 2012 was consistent with the 47.2% (SE: $\pm 2.1\%$), which was reported by NHANES from 2009 to 2010. The prevalence of periodontitis was 45.9%, for the total combined period of 2009 to 2012 (represented by approximately 141 million adults aged 30 years) [17]. As part of the Healthy People 2020 national health objective [18] and a major strategic objective of the Centers for Disease Control and Prevention (CDC) [16, 19] for the adult population in the US, efforts to reduce and monitor severe and moderate periodontitis are being done through health promotion activities and national disease surveillance.

There are two categories of the risk factors for periodontitis—namely, non-modifiable and modifiable [20]. Non-modifiable risk factors include age, ethnicity, genetic factors, and male gender [16, 21–24]. Large studies have consistently reported finding an increase in the prevalence and severity of periodontitis with age [17, 25, 26]. In addition, the prevalence of periodontitis has been reported to be higher in males [17, 27]. In the most recent NHANES, a 50% higher risk of periodontitis was found in males as compared to females [16]. With regard to the ethnicity, the prevalence of periodontitis has been reported to be lowest in non-Hispanic whites (40.8%), followed by non-Hispanic Asian Americans (50.0%), and highest in Hispanics (63.5%) and non-Hispanic blacks (59.1%) [17]. Moreover, the prevalence of severe periodontitis has also been reported to be more in Hispanics and non-Hispanic blacks, adults aged 50 years, and in males [17]. On the other hand, modifiable risk factors, such as diabetes mellitus (DM), smoking, alcohol consumption, sedentary lifestyle [28], stress,

osteoporosis, and viral infection, that contribute to other major chronic conditions also appear to play an important role in the pathophysiology of periodontitis [16, 23, 24, 29, 30]. The prevalence of periodontitis has been reported to be higher in adults, who had less than high school education level, were current smokers, and were under 100% of the federal poverty level (FPL) [17]. Moreover, the prevalence of severe periodontitis has been reported to be more in people living below 200% of FPL [17]. In fact, odds of having periodontitis in smokers are four to five times higher as compared to non-smokers [31]. Also, smoking intensity and periodontitis severity are positively related to each other [23].

Increases in the extent and severity of periodontitis can adversely impact quality of life [32]. Advanced periodontitis can result in pathologic tooth movement and loss [33]. In adults, periodontitis is the most important cause of tooth loss [34]. Abnet et al. (2005) [35] conducted a prospective cohort study in approximately 30,000 healthy participants from rural part of China over a period of 15 years, to assess the association between tooth loss and cause-specific and total mortality. They found a 13% greater incidence of mortality from any cause in the participants, who had more than the age-specific median number of teeth lost [35]. Also, in this cohort, the risks for the most common causes of death, i.e., stroke, heart disease, and upper gastrointestinal cancer, were increased by 12%, 28%, and 35%, respectively [35]. In another study from Japan, a higher risk of fatality due to cardiovascular disease (CVD) and respiratory disease was present in participants with 19 or fewer teeth, who also had difficulty eating, when compared with the participants having 20 or more teeth [36]. Multiple studies have reported that periodontal disease is associated with increased risk of death in older and younger adults from Northern Ireland and US [37, 38], in people with renal disease from Taiwan [39], in non-smokers from US [40], and in Pima Indians from US with type 2 DM [41]. Other prospective studies have also reported an association between tooth loss and increased total mortality [42–44], as well as death due to CVD [44–46], respiratory disease [47], and cancer [45, 47, 48], in geographically varied populations [41, 42, 45, 47]. Periodontal disease may impair appropriate nutritional intake, perhaps due to difficulty or pain of chewing, possibly leading to increased morbidity and mortality in these subjects [49].

Cardiovascular diseases

Atherosclerotic cardiovascular disease (ASCVD) constitutes a major burden of mortality worldwide. According to the WHO, approximately 17.5 million deaths in 2012 were attributed to ASCVD, constituting around 31% of the total deaths worldwide [50]. The most common forms of ASCVD are myocardial infarction (MI), cerebrovascular disease (CBVD) and peripheral arterial disease (PAD). In 2015, 366,801 deaths occurred due to coronary heart disease (CHD) [51]. Approximately 795,000 persons suffer a new or recurrent cerebrovascular event (CVE), with 185,000 being recurrent events and 610,000 being first events [51]. Moreover, in 2015, 1 in every 19 deaths in the United States were due to a stroke [51]. PAD leads to a considerable decrease in the arterial lumen of the arteries, which have their origin distal to the aortic bifurcation and usually occurs along with atherosclerosis, with intermittent claudication being its most common symptom [52, 53]. Nearly 8.5 million people aged 40 years and older are affected by PAD, and its prevalence increases with rising age from 1.6% in those aged 40 to 49 years to 22.7% in people aged 80

years or more [51]. Some studies have illustrated that PAD has been associated with increased morbidity and mortality with CVD [54–57]. The mortality due to CVD increases six times due to the presence of PAD [58].

Metabolic diseases

Metabolic syndrome (MetS) is defined as the presence of three out of the five interrelated risk factors for diabetes and cardiovascular disease, i.e., raised blood pressure, dysglycemia, obesity (particularly central adiposity), low high-density lipoprotein cholesterol levels, or elevated triglyceride levels [59]. There is a rising interest in MetS, as it is recognized as a risk factor for CVD and DM independently [59]. MetS has progressively turned up to be a predominant factor in the development of ASCVD over the last couple of decades [60]. The entire group of risk factors for CVD in MetS, including hypertension, dyslipidemia, type 2 DM, along with ASCVD, which is its main clinical outcome, contributes greatly to the morbidity and mortality worldwide [61, 62]. The MetS prevalence has increased in adolescents and has a hidden impact on the adults as well, with the rise in prevalence of obesity [63–65]. A number of studies have shown an increased prevalence of MetS in adolescents who are overweight, and also development of MetS in childhood [66–68]. The deficiency of insulin secretion or action results in a metabolic condition called DM, which has long-term complications like atherosclerosis, nerve damage, and microvascular damage [69]. Also, the occurrence of diabetes is rising worldwide in all population sections, which also includes children [70]. Data from NHANES 2011–2014 estimated that diagnosed DM was present in 23.4 million adults and undiagnosed DM was present in 7.6 million adults in the US [51]. On the other hand, DM was present in about 186,000 people that were under the age of 20 years [51]. In US adults > 20 years of age, about 1.7 million new cases of DM (type 1 or type 2) were diagnosed in 2012 [51]. DM is also associated with significant mortality. In fact in 2015, 79,535 individuals in the US, including 36,412 females and 43,123 males, had DM listed as the underlying cause of their death [51]. The estimated overall underlying-cause age-adjusted death rate attributable to DM in 2015 was 21.3 per 100,000 deaths [51].

Psychiatric disorders

Major depression, bipolar disorder, schizophrenia, anxiety disorders, and dementia constitute a major part of the burden of psychiatric illness. Nearly 17.6% of the population worldwide suffers from mental illnesses [71]. Estimates predict that psychiatric disorders will probably rank second highest on the list of causes of morbidity by 2020 [72]. It has to be taken into account that many people have very poor compliance to treatment and many go undiagnosed, due to which complete remission is not possible and it could also result in worsening of the symptoms [73, 74]. Moreover, death by suicide, an important cause of mortality associated with major psychiatric disorders, was the tenth leading cause of mortality in the US in 2014 and claimed about 45,000 deaths in the year 2016 [75, 76]. Remarkably, 54% of the individuals who died by suicide in 2015 did not have a mental health condition, and the rates of death by suicide have shown more than 30% increase from 1999–2016 across 25 states in US [76].

Inflammation as a common denominator

Inflammation in periodontal disease

Inflammation has a significant role in the pathogenesis of periodontal disease. Moreover, elevated pro-inflammatory mediator levels in gingival crevicular fluid (GCF) can act as the markers for the disease activity and severity of acute periodontitis (AP) [77, 78]. The literature shows that inflammatory mediators like IL-1 β may act simultaneously to provoke important feedback and regulatory mechanisms which govern the harmfulness and severity of inflammatory lesions [79]. Continued tissue destruction and pathologic wounding may be a result of these cytokines, because of the persistent presence of bacterial plaque as an etiologic agent [80], and overproduction of cytokines like IL-1 β might contribute towards this tissue destruction.

Being a marker for activated cell-mediated immunity [81], neopterin has various applications in medicine. Interaction between phagocytic cells (including macrophages, monocytes, dendritic cells and granulocytes) and T-helper (Th)1 lymphocytes results in the formation of neopterin [81–83]. The major stimulus for production of neopterin is interferon-gamma (IFN- γ) [82]. However, other pro-inflammatory signals, such as TNF and lipopolysaccharide (LPS) can also elevate levels of neopterin [84]. In fact, immune-associated oxidative stress is indicated by the concentration of neopterin in the bodily fluids [85], and its concentrations correlate with reactive oxygen species (ROS) production induced by IFN- γ [86]. As periodontitis involves inflammation, it is plausible that neopterin levels would be associated with severity of periodontitis as well. In a case-control study by Ozmeriç et al. (2002) [87], as compared to the systemically and periodontally healthy individuals, systemically healthy individuals with aggressive periodontitis (AgP) had significantly higher salivary neopterin levels, and there was a non-significant difference in the urinary neopterin levels within these groups of individuals. The authors of this study also reported a significantly higher total amount of neopterin in GCF of individuals with AgP, as compared to the healthy controls [87]. Similarly, in a pilot study on 29 patients having periodontitis with involvement of varying number of teeth, salivary neopterin levels increased significantly with the number of affected teeth [88]. In particular, individuals having more than 20 teeth affected with periodontitis had significantly higher salivary neopterin concentrations as compared to the individuals with lesser than 20 diseased teeth [88]. Also, there was no significant difference in the urinary neopterin levels between these two groups of individuals [88]. In yet another study, a positive correlation between GCF neopterin concentrations and CAL was reported, with the highest GCF neopterin concentrations observed in the group of individuals with moderate to severe periodontitis (mean = 51 nmol/l), and the lowest concentrations in the healthy group of individuals (mean = 1.36 nmol/l) [89].

Inflammation in cardiovascular diseases

Inflammation has been implicated in the pathogenesis of MI [90, 91], stroke [92, 93] and PAD [94, 95] as well. Atherosclerosis is the major contributing factor in most of the cases of CBVD/stroke and CVD. Deposition of cholesterol, cholesterol esters, and calcium within the vessel walls in atherosclerosis eventually leads to narrowing of the arterial lumen [96]. A

variety of cell types, such as immune cells and fibroblasts, are also present in these cholesterol-rich plaques [97, 98]. Thrombi may result from the rupture of atherosclerotic plaques, which may result in stroke or MI, after they travel distally to occlude artery/arteries. Pathogenesis of atherosclerosis involves local and/or systemic inflammatory processes, infections, and possibly autoimmune phenomenon as well [99]. A number of factors may contribute towards increased local arterial inflammation, such as immune reactions directed against the vascular wall, lipid imbalances and hemodynamic stress. These factors could together lead to initiation or progression of atherosclerotic plaques, and even complicated atherosclerotic lesions [100]. Moreover, individuals with atherosclerosis have been reported to have higher levels of serum inflammatory biomarkers, such as C-reactive protein (CRP) [101], cell adhesion molecules, various inflammatory cytokines and fibrinogen [102]. Neopterin has also emerged as a predictive and an independent marker of risk assessment for CVD [103]. In fact, importance of neopterin is not only limited to its association with systemic inflammatory response in atherogenesis, but it may also have a role in destabilization of the atherosclerotic plaque by contributing to the inflammation within the plaque [103, 104].

Inflammation in metabolic diseases

A number of studies have pointed towards links between inflammation and obesity. Obese subjects have been reported to have elevated levels of tumor necrosis factor-alpha (TNF), CRP, interleukin (IL)-6, fibrinogen and other acute-phase reactants [105–112]. Pro-inflammatory cytokines, including TNF, resistin, IL-6, plasminogen activator inhibitor (PAI)-1 and monocyte chemoattractant protein (MCP)-1 may be secreted by hypertrophic adipocytes [113]. TNF has been reported to have direct effects on adipocyte insulin resistance [114, 115]. Additionally, intracellular insulin signaling has been shown to be impaired by both TNF and IL-6 [116, 117]. A close relationship exists between the plasma levels of CRP, TNF and IL-6, and insulin resistance and obesity [108, 118].

Several studies have also suggested associations of inflammatory mediators, such as CRP and IL-6, with type 2 DM, hyperglycemia and insulin resistance [119–124]. Also, localized islet inflammation has also been reported in type 2 DM [125], and it has been hypothesized that type 2 DM might involve an innate immune system pathology [126]. The coexistence of a procoagulant and a proinflammatory state has also been reported to occur in metabolic syndrome that is characterized by high fibrinogen and C-reactive protein levels [127, 128]. The data also suggests that metabolic syndrome may contribute to the greater risk for CVD and type 2 DM via endothelial dysfunction, which might be precipitated by this chronic inflammatory state [129, 130]. Levels of C-reactive protein rises because of the low-grade inflammation, which is associated with raised hypertension risk (one of the components of MetS) [131]. In fact, oxidative stress has also been implicated as the shared pathologic cause of various components of MetS [132].

Inflammation in psychiatric disorders

A pro-inflammatory state has also been reported to exist in major psychiatric disorders, such as schizophrenia [133–136], bipolar disorder [137–140] and depression [141–144]. Moreover, neuroinflammation has been implicated in suicidal behavior [145] and in the

pathophysiology of Alzheimer's disease [146] as well. Meta-analyses also point towards an evidence of immune activation in the postmortem brain samples of individuals who died by suicide, and in the blood and cerebrospinal fluid (CSF) of suicide attempters [147–149]. Moreover, mRNA transcripts of inflammatory cytokines have also been identified in suicide victims' orbitofrontal cortex [150]. It was also reported that the brains of patients who died by suicide had pronounced microgliosis [151]. Additionally, aggression, an endophenotype associated with suicidal behavior [152], can be exacerbated by the effects of individual cytokines, at least partially [153–155]. The anterior prefrontal cortex of teenagers who died by suicide has been reported to have increased levels of IL-1 β , IL-6 and TNF at both the mRNA and protein levels [156]. Another finding that supports the role of inflammation of the central nervous system in contributing to suicidal behavior is the significantly elevated levels of IL-6 in the CSF of suicide attempters [157].

Moreover, neopterin has implications for psychiatric disorders as well, such as major depression [158], bipolar disorder [159] and schizophrenia [160, 161]. Significantly higher plasma neopterin levels have been reported in patients with depression, as compared to healthy controls [144, 162]. Urinary neopterin levels in depressed patients have also been reported to be significantly higher as compared to healthy controls [163, 164]. Similar finding was reported by a more recent study [165], which also indicated that 6-months after an acute ischemic stroke, neopterin could be an independent predictor for the development of major depression. Interestingly, serum neopterin levels were reported to be significantly higher before treatment in anti-psychotic naive schizophrenia-patients, as compared to healthy controls, which reportedly declined significantly after 3 months of treatment with anti-psychotic medications [166].

Evidence connecting periodontal disease to metabolic, cardiovascular and psychiatric disorders

Cardiovascular diseases and periodontal disease

In this section, we will discuss the studies that have looked at the possible associations between periodontal disease and various CVDs like atherosclerosis, MI, CBVD/ stroke and PAD. Strong evidence has emerged establishing an association between periodontitis and CVDs, such as ASCVD [167], PAD [168, 169], CBVD [170], and IHD [171]. However, it has been difficult to conclude a causal association between periodontitis and CVDs because both these conditions share common risk factors and exhibit multifactorial etiologies. Nevertheless, the consistency in the association between periodontitis and CVDs has been shown in systematic reviews [172, 173]. Although multiple cross-sectional, cohort, and case-control studies have also shown a significant association between periodontitis and MI [174–185], these findings have not been consistent [40, 186–191].

An observational study by Mattila et al. (1993) [167] was the foremost evidence that proposed a relationship between ASCVD and periodontitis, which reported that when compared to the healthy controls, the patients who were admitted to the hospital emergency units for acute coronary syndromes had poorer dental hygiene [192]. Subsequently, additional study depicted that bad oral hygiene resulting in periodontitis, can have a part to

play as a CVD risk factor [26]. It has been shown by a population-based study that periodontitis was related to an elevated risk of major adverse cardiac events including the occurrence of MI [193]. Some studies have reported this association between periodontitis and MI in Iranian and Turkish populations [194, 195]. On the other hand, the prevalence of advanced periodontitis and edentulousness was higher in the hospitalized patients with MI as compared to the group who did not have MI [196].

A case-control study showed that there was a significant increase in risk of MI in patients with periodontitis even after adjusting for possible confounding factors [183]. According to the report by Bahekar and colleagues, in patients with periodontitis, the incidence of CHD is higher with a relative risk (RR) of 1.14 [95% confidence intervals (CI): 1.074–1.213], as well as the prevalence of CHD in the periodontitis patients was higher with an odds ratio (OR) of 1.59 (95% CI: 1.329–1.907) [197]. The association between periodontitis and recurrent MI was also reported by Renvert and group [178]. In a prospective cohort study by DeStefano et al. (1993) [198], which was based on the data from the National Health and Nutrition Epidemiologic Follow-Up Study including 9760 participants, who were followed-up for 14 years, stated that the RR for MI among individuals aged 25 to 75 years with no teeth was 1.23 (95% CI: 1.05 to 1.44), when compared to the individuals with periodontitis or gingivitis. Furthermore, several systematic review studies and meta-analyses showing an association between CVD and periodontitis have been published [171, 173, 197, 199–204]. Humphrey and group showed an increase of around 24% to 35% in CHD risk with the varying severity of periodontitis [173]. This study demonstrated a higher CHD risk with tooth loss and periodontitis, having a RR of 1.34 (95% CI: 1.10–1.63) and 1.24 (95% CI: 1.01–1.51) respectively, and also a rise in the risk of CHD in patients with gingivitis was reported, which was not statistically significant [173].

Additionally, a report by Mustapha and colleagues suggested that there was an increased risk of developing CHD in those with raised systemic bacterial exposure markers such as CRP, periodontal bacterial burden and periodontitis, as compared to those without periodontal disease [203]. A study has shown an association between the presence of cardiac or valvular calcifications, which indicate subclinical atherosclerosis, and severity of periodontitis [205]. In patients with type 1 DM, a significant relationship between periodontitis duration and progression and development of coronary artery calcium has been reported [206]. However, there is a possible association between periodontal disease and coronary artery disease [198, 207], which is not dependent on diabetes.

Moreover, dental indices have been shown to be associated with new coronary events in individuals with diagnosed coronary artery disease [208] and with cerebral infarctions [209]. Also, increased arterial stiffness was reported in patients with periodontitis as compared to controls [210, 211]. Carotid-artery intima and media thickness (CIMT) has been reported to be associated with increased risk of having CVDs and acute MI [212]. One of the studies that showed an association between periodontal disease and increase in the CIMT was the Atherosclerosis Risk in Communities study [213], in which severity of periodontal disease was taken as a criterion to group the patients. As compared to individuals with no periodontal disease, the odds of having CIMT ≥ 1 mm was higher in patients having severe and moderate periodontal disease, with an OR of 2.09 (95% CI: 1.73–2.53) and 1.40 (95%

CI: 1.17–1.67), respectively [213]. Another study demonstrated unilateral carotid calcifications visible on panoramic radiographs in 31.3% and bilateral calcifications in 7.2% of patients with periodontitis [214]. An association among systemic inflammation, atherogenesis in carotid arteries and periodontitis has been suggested as well. A study by Tapashetti and colleagues [215] depicted that elevated levels of circulating CRP were found in patients with periodontitis compared to controls, (19.58 ± 17.03 vs. 5.54 ± 1.63 , $p < 0.004$), and greater CIMT was reported in patients with periodontitis (1.09 ± 0.45 vs. 0.57 ± 0.06 , $p < 0.001$). Additionally, the raised CRP had a correlation with increase in CIMT [215].

Several systematic reviews and meta-analyses assessing the relationship between CBVD and periodontitis have been published [170, 201, 216]. A meta-analysis of cohort studies reported an elevated CVE risk in patients with periodontitis and tooth loss, with RR of 1.63 (95% CI: 1.25–2.00) and 1.39 (95% CI: 1.13–1.65), respectively [216]. Another meta-analysis that included retrospective and prospective studies, depicted that risk of stroke was elevated by periodontitis with RR being 2.63 (95% CI: 1.59–4.33) for the retrospective studies, and 1.47 (95% CI: 1.13–1.92) for prospective studies [170].

PAD has also been associated with periodontitis. A cross-sectional study [217] including 1343 Korean adults aged over 40 years, who were enrolled from a community-based cohort of Yangpyeong County, reported periodontitis as a risk factor for having PAD and that the risk of having PAD in periodontitis patients is 2.03 times (95% CI: 1.05–3.93) more, when compared to the ones without periodontitis. Calapkorur and colleagues [218] have illustrated in a cross-sectional study on 60 patients, that the odds ratio for developing PAD are increased by periodontitis to 5.84 (95% CI: 1.56–21.91). Sorto-Barreras et al. (2013) [168] conducted a case-control study in Mexican population in which periodontitis was found to be associated robustly with the risk of having PAD (OR: 8.18, 95% CI: 1.21–35.23). After adjusting for gender, age, smoking and DM, a five-fold increase in the risk of having PAD (OR: 5.45; 95% CI: 1.57–18.89) in patients with periodontitis was shown in a case-control study by Chen et al. (2008) [169]. They assessed 25 patients with femoro-popliteal and/or aorto-iliac disease, who underwent bypass surgery [169]. The atherosclerotic specimens from the anastomotic location of the distal bypasses were assessed with the help of polymerase chain reaction in order to detect periodontopathic bacteria, and these bacteria were detected in 52% of these specimens [169]. Furthermore, the detection frequency of *P. gingivalis* was higher in patients having Fontaine grade III and grade IV level of severity of PAD, in comparison to those having grade II (57.1% vs. 22%, $p = 0.09$) [169]. These findings were consistent with those of the studies that have been done more recently [217, 219]. Mendez et al. (1998) [220] used the data from both the Dental Longitudinal Study of the US Department of Veterans Affairs and Normative Aging Study, to study the association between periodontal disease and peripheral vascular disease by using multivariate logistic regression analysis, in which 1030 subjects were followed-up for over 25 to 30 years for the development of PVD. Development of PVD was seen in 80 of those initially healthy subjects. They found a 2.27 times increased risk of developing PVD (95% CI: 1.32–3.9, $p = 0.003$) in the participants who had clinically significant periodontal disease in the beginning, as compared to controls [220]. In another prospective study by Hung et al. (2003) [221], 45136 eligible men from the Health Professional Follow-up Study, who did not have

cardiovascular diseases in the beginning, were followed-up. The authors found that 342 of these men had developed PAD over 12-years of follow-up. They calculated a relative risk of 1.41 (95% CI: 1.12–1.77) for developing PAD in those with a history of periodontitis, when controlled for cardiovascular risk factors, and there was no association between PAD and tooth loss in those who did not have periodontal disease (RR: 0.92; 95% CI: 0.61–1.38) [221]. Thus, a significant association was seen between incident tooth loss and PAD, particularly in men who had periodontal disease [221]. A recent meta-analysis by Yang et al. (2018) [222] found that the risk of periodontitis has been significantly increased in patients with PAD when compared to the participants without PAD (RR: 1.70, 95% CI: 1.25–2.29, $p = 0.01$), implying that a significant association is there between periodontitis and PAD.

Although it has been postulated that periodontal disease can alter the CVD risk [223], a causative connection has not been found. It is possible that CVD and periodontal disease are associated with each other, however, one does not result in causing the other [224]. For many decades, this has remained unclear as only a small number of studies have evaluated the consequence of periodontal treatment on CVD [225]. Uncertainty exists regarding the involvement of tooth decay, preceding periodontal disease, changes in diet following tooth loss, tooth removal procedure, or some other factors, as mediators in the association between tooth loss and CVD [226].

Metabolic disease and periodontal disease

An association between severity and frequency of periodontitis and obesity has been shown by a number of studies [227–229]. Periodontal disease has also been associated with obesity in adolescence [230]. An association between lifestyle factors and periodontitis has been investigated in a cross-sectional study involving physical activity, however, the study was unsuccessful to detect any association between them [231]. On the other hand, a cross-sectional study by Wakai et al. (1999) described a negative correlation between periodontitis and physical fitness, following adjustment for plaque, smoking, fasting plasma glucose, and age [232]. A largescale prospective study [28] looked for the association of walking, physical activity and periodontitis in 39,461 US-based health professional males, whose baseline age was 40–75 years, and reported an inverse, linear association between periodontitis and sustained physical activity and somewhat increased risk of periodontitis in men watching more television (depicts a sedentary lifestyle), which was statistically significant with a linear trend. It has been depicted that spending more time watching television has a positive correlation with obesity [233, 234], and an association between obesity and augmented risk of periodontitis has also been reported [229]. Moreover, the risk of getting obese [235] as well as diabetic [236] is lowered by exercise. Better insulin sensitivity as well as metabolism of glucose is linked to increased physical exercise, independent of obesity and diabetes [237, 238]. Additionally, diabetes is a well-known risk factor for periodontitis [239, 240], and obesity has been demonstrated to be individually related to periodontitis [228, 229].

In 1997, periodontal disease was described as the sixth complication of diabetes by the American Society of Diabetes [241]. Diabetes increases the possibilities of developing periodontal disease and alters its severity [239, 242–245]. Diabetic patients are more likely

to have inflammation of gingiva, dental calculus, deeper periodontal pockets and higher values for indices of plaque [246]. The individuals with diabetes tend to have more widespread dental caries [247–249], xerostomia [250] and tooth loss [251], in comparison to healthy individuals. They require periodontal treatment and prophylactic procedures more often [252]. There is sudden periodontal destruction and higher severity of periodontitis observed in diabetics with uncontrolled blood glucose level compared to the diabetics with a blood glucose level that is well-controlled [253, 254]. The severity, risk and degree of periodontitis have also been ascribed to the hyperglycemic status [255]. Moreover, the risk of periodontitis decreases with improved glycemic control in diabetics [256]. Type 2 diabetics, who have poor metabolic control, also have a greater risk of having infectious diseases like periodontitis [244, 257, 258].

It is possible that the relationship between DM and periodontitis might be a bidirectional one. A study performed in Pima Indians, depicted that the severity and prevalence of periodontitis is more in people with diabetes [244]. In diabetic patients, periodontal pockets have been illustrated to be more extensive and they develop earlier in life [259]. According to the NHANES III, the prevalence of severe periodontitis was considerably greater in patients with hemoglobin A1c (HbA1c) level of >9% as compared to the non-diabetics [254]. Moreover, several studies report that the severity of periodontitis is related to elevations in HbA1c [260, 261]. On the other hand, the studies that looked for an association between the time duration of diabetes and periodontitis have had inconsistent results. For example, a study described that the time duration of diabetes was not related to periodontitis [262], and other studies reported that the prevalence of periodontitis increased with increase in duration of diabetes [263–265].

An increased intake of whole-grain and fiber-rich foods has been related to better insulin sensitivity [266, 267], and thus resulting in a better glycemic control. A prospective study [267], involving 34160 male health professionals with baseline age of 40–75 years, conducted by Merchant et al. (2006), found that there was a 23% less likelihood of getting periodontitis in men who were in the highest quintile of whole-grain intake, when compared to those who were in the lowest quintile (multivariate RR: 0.77; 95% CI: 0.66–0.89; *p* for trend <0.001), upon adjustment for smoking, alcohol intake age, body mass index, total energy intake, and physical activity. Thus, increasing dietary intake of whole-grains without raising total caloric intake may lessen the risk of having periodontitis, as well as diabetes. Some studies have reported a relationship between periodontitis and glucose intolerance [268]. As compared to the former assumptions, periodontal disease condition is found to be more common in children suffering from diabetes [269], and also its severity increases with rising glucose levels in the blood [270].

According to a study, more plaque deposits and poor oral hygiene were found in diabetic patients as compared to non-diabetics [240]. Interestingly, diabetic individuals with well-controlled diabetes are likely to go more often to see the dentist [271], and have healthier oral hygiene habits as compared to the diabetics with poorly controlled diabetes [271, 272]. The individual attributes, which are responsible for maintaining good oral hygiene [273–275] as well as in controlling diabetes, or the influence of good dental care on HbA1c, may play an important part in this. Merchant et al. (2012) [276] reported that the majority of the

children who had diabetes did not floss and brush their teeth as frequently as recommended. However, a study which was conducted in people with type 2 diabetes, was unable to find any influence of good oral hygiene on HbA1c levels [277]. Also, there are inconsistencies in results regarding the relationship between diabetes and good oral hygiene practices in children and adolescents [278, 279].

Some reports have stated that bad periodontal health was present in people who had MetS as compared to those who did not have it [280, 281]. A dose-response relationship was present between various components of MetS and clinical markers of periodontitis, like PPD and loss of CAL [282]. Furthermore, some reports have stated the association of periodontitis with hypertension, obesity, dyslipidemia and hyperglycemia (components of MetS) [283–288]. A study by Lee et al. (2015) [289] evaluated the links between gingivitis and MetS parameters in a Korean adolescent population generated by representative nationwide sampling. A significant association was found between gingivitis and low HDL-cholesterol, as well as between gingivitis and the number of positive MetS parameters in adolescents [289]. Another study [282] reported that periodontal disease and levels of HDL cholesterol were associated with each other among female adults. As reported by Morita et al. (2009) [290], there was a significant increase in OR of the presence of periodontal pockets with the increased number of MetS components. Additionally, some studies have reported associations between MetS components and periodontal disease in adolescents as well [230, 291]. Hence, it has been proposed that periodontal disease should be identified as a component of MetS, as it is frequently altered in DM and a number of other systemic diseases [292].

Psychiatric disorders and periodontal disease

There has been increasing focus of attention towards the adverse physical health suffered by the people with severe psychiatric illness, specifically regarding CVD, diabetes, cancer, and chronic lung disease [293]. Oral health has not been given much attention, although it is a crucial part of our overall health [294], and is associated with a number of chronic diseases [173, 295–302]. There is an elevated risk of having dental problems in patients with psychiatric disorders. One study, from Italy, studied psychiatric inpatients, and gum disease was found in 99% of the patients [303]. According to one Australian study, including psychiatric outpatients, 59% of the patients were found to have moderately deep pockets [304]. Additional three studies reported that deep pockets were found in 15% to 28% of psychiatric inpatients as well [303, 305, 306]. A meta-analysis reported that the likelihood of having periodontal disease was 50 times more in patients having severe mental illness (95% CI: 3.43–7.02) [307].

The reason behind this may be the lack of self-care, medication side-effects, poor compliance with dental treatments, negative outlook towards the physician and trouble accessing health care services [308]. Poor oral hygiene also accompanies depression and anxiety [309]. Moreover, bad oral health, particularly associated with tooth loss, could also lead to difficulty with communication, affecting other psychological and social aspects of human life [294]. Ugly, ill-fitting and painful dentition or dentures can cause issues with eating and speaking, and can contribute to social isolation, social withdrawal and low self-

esteem. On the other hand, it is possible that patients with periodontitis would have social stigma from their altered appearance due to tooth loss, as well as halitosis [310], which could precipitate or worsen the negative thought patterns about themselves, thereby contributing to depression and/or anxiety [311].

Furthermore, depressed patients can have dental caries that could be attributed to dry mouth as a side effect of anti-depressants, and to bad oral hygiene as a result of self-neglect leading to poor oral hygiene and poor nutrition [312, 313]. Bipolar affective disorder patients deal with additional issues. During the manic phase, overenthusiastic flossing and tooth brushing may cause mucosal or gingival lacerations or dental abrasions [313]. Lithium as a medication for bipolar disorder, has been linked to stomatitis and xerostomia [313, 314]. Moreover, almost 50% of the dental patients have some anxiety regarding their visits to dentists, which in few cases results in a specific phobia called dental phobia [315, 316]. Dental pain perception may also be increased by anxiety or depression, irrespective of the severity of the oral condition. For instance, a somatic symptom disorder, called burning mouth disorder, occurs in people who have clinically healthy oral mucosa and is frequently related to anxiety or depression [317].

Other reasons for having a greater risk of oral health problems in individuals with psychiatric illnesses might be co-morbid substance use disorders (alcohol, tobacco, and psychostimulants), excessive consumption of sugary drinks, and financial and other difficulties in getting dental care [318–320]. Dry mouth or xerostomia is frequently associated with opportunistic gingivitis because of nutritional deficiencies caused by anorexia nervosa and psychosis [321]. In patients with bulimia, there are alterations in the secretion of saliva due to pathological changes in parotid gland [322]. Individuals suffering from severe mental illnesses like schizophrenia and dementia have more tooth decay and gum problems resulting from bacterial infection, instead of attrition, abrasion, or erosion. The explanations are similar as in other psychiatric illnesses, which include side effects of psychotropic medications like mood stabilizers, antidepressants, and antipsychotics [323]. Psychotropic medications having anticholinergic effects, can also lead to xerostomia as a side effect [314, 322, 324].

Immune mediation explaining the association of periodontal disease with cardiovascular, metabolic and psychiatric disorders

Cardiovascular and periodontal disease

How may periodontal disease lead to CVDs, including atherosclerosis, stroke/CBVD, MI and PAD? In periodontitis, which is predominantly a chronic condition, innate immune mechanisms also operate through certain acute-phase reactants, thereby indicating the presence of systemic inflammation in periodontitis [325, 326]. Some of the pro-inflammatory properties of the acute-phase reactants are stimulation of the regeneration and repair of a variety of tissues, activation of complement factors, and neutralizing invasive pathogens. Among these, fibrinogen, CRP and PAI-1 are the acute-phase reactants that have received most attention. Interestingly, meta-analytical studies have concluded that inflammation plays a key mediating role in the positive association between cardiovascular

disease and periodontal disease [202, 203, 216, 327–329]. Modest rise in serum CRP is associated with augmented risk of cardiovascular disease in otherwise healthy persons [330, 331]. TNF has a major function in initiating the inflammatory response [332]. The association of blood TNF levels with CIMT and with risk factors for CVD is known [333]. Therefore, if these markers are also associated with periodontal disease, they might be the possible mediators in the association between CVD and periodontal disease. There is evidence that periodontal disease is related not only to CVD, but also with its risk factors. The conclusion of the results of a study [334] suggests that periodontal disease is connected to biomarkers of dyslipidemia and endothelial dysfunction, for instance, t-PA, CRP and low-density lipoprotein cholesterol (LDL-C), which are recognized risk factors for CVD.

A number of possible mechanisms linking periodontitis and CVD have been proposed in various studies, with the most important being the systemic inflammation, direct vascular injury and molecular mimicry [26]. Links between inflammatory responses that impact CVD and the inflammation due to periodontal microbial pathogens, appear in various forms.

Inflammatory markers and mediators: Periodontitis is associated with local elevations in inflammatory cytokines, as well as systemic elevations in inflammatory cytokines and acute phase proteins [335]. As compared to the periodontally healthy individuals, the patients with periodontitis have higher concentrations of a number of inflammatory markers and mediators in their systemic circulation, including CRP [336–340], fibrinogen [338, 341, 342], haptoglobin [336, 338], platelet-activating factor (PAF) [343, 344], IL-6 [345], and IL-18 (IL-18) [338]. Interestingly, the systemic levels of IL-4 and IL-10, both of which are anti-inflammatory cytokines, have been reported to be reduced in patients with chronic periodontitis [338, 346]. Hypothetically, these observations could be explained via two pathways:

- a. As suggested by the existing literature, periodontitis not only affects the oral cavity but possibly has systemic effects as well. An association between periodontitis and modest systemic inflammatory response has been demonstrated. Even though the mechanism leading to this association is not clear, periodontitis might act as a remote source of low-grade inflammation systemically. This association might be a possible explanation for the observed metabolic control impairment in diabetic patients and elevated risk of CVDs in the future, as seen in individuals with periodontitis.

The indication regarding production of inflammatory cytokines and other mediators within the periodontal lesions has been supported by ample data [347]. Hypothetically, it is possible that these mediators from the periodontal lesions “spill over” into the systemic circulation and may attain concentrations that are sufficient enough to have their effects on the organs and tissues located distally from the oral cavity, provided their bioactivity is remains preserved. Eventually, other organs including the liver may be affected by these inflammatory mediators, thereby leading to induction of an acute-phase response, which could influence more organs in the body. Ultimately, development of atheromas may be initiated or accelerated due to inflammatory changes induced in the endothelium,

including promotion of cytokine production and up-regulation of adhesion molecules. However, the evidence that supports such a mechanism for inflammatory mediators having access to the systemic circulation is not strong [348].

- b. Microorganisms from the oral cavity have been shown to cause a number of oral infectious diseases, including periodontal disease. A large number of microbes reside in the oral cavity with different species found at different sites, including cheek, gum, teeth, palate or gingival sulcus, and they interact with their human host in the state of disease and health [349]. The oral cavity of an adult person can have approximately one billion bacteria in total. It has been well established that the oral cavity is a source of systemic infections, and in inflammatory conditions like periodontitis, the bacteria pass into the bloodstream due to disruptions in the integrity of the tissue [350, 351]. The relationship between dental procedures and bacterial endocarditis has been very well established and since then the guidelines for antimicrobial prophylaxis are valid in patients undergoing dental procedures, who have preexisting risk factors [352, 353]. In fact, patients with periodontitis have episodes of bacteremia even after minor trauma, including tooth-brushing [350, 354, 355]. Additionally, the prevalence of bacteremia following brushing, chewing, scaling or flossing has been associated with the periodontal status, with patients with periodontitis having higher biodiversity and higher prevalence/incidence of bacteria in the bloodstream, as well as in the periodontal tissues, as compared to the healthy individuals and patients with gingivitis [356]. Specifically, periodontal destruction and inflammation has been attributed to the presence of greater levels of a bacteria in the sub-gingival plaque, named *P. gingivalis* [357, 358]. Moreover, oral infection with periodontal disease pathogens like *P. gingivalis* in animal models of infection has been indicated to induce promotion of inflammatory reactions in sites that are located far away from the mouth, including the atheromatous lesions [359–361]. Similarly, pathogens such as *P. gingivalis*, *S. sanguis* and *Chlamydia pneumoniae* (*C. pneumoniae*) have been also been reported to be found in human atherosclerotic plaques [355, 362, 363]. Within the atheromas, local as well as systemic inflammatory reactions may be stimulated by the periodontal bacteria themselves, or the proinflammatory components released from them [348]. It is possible that bacterial components/bacteriainduced alteration of serum lipids, inflammatory and endothelial cell receptor engagement, endothelial cell invasion and bacterial component/bacterial seeding of atheromas, together may further promote these inflammatory responses and play a role in the growth of atheromas [356, 364]. Initiation of an inflammatory cascade after proliferation of *P. gingivalis* in the intima of coronary arteries leads to apoptosis [365] and subsequent endothelial dysfunction [366]. *P. gingivalis* also mediates atherosclerosis by stimulating foam cell production in the intimal layer of the blood vessels [223]. Also, matrix metalloproteinases (MMPs) have been implicated in both rupture of atherosclerotic plaques [367], as well as periodontal destruction [368]. Additionally, oral bacteria, such as *P. gingivalis*, have been reported to induce MMPs that might also lead to rupture of

atherosclerotic plaque [369]. However, limited evidence from human studies exists that implicates MMPs mediating the association between CVD and periodontitis [370, 371]. Similarly, PAF and PAF-acetyl hydrolase, have been implicated in explaining the links between CVD and periodontitis; however, the data related to this is limited [343, 344, 372, 373].

As seen in other inflammatory processes or chronic infections, the host reacts in a similar fashion to short-lived bacteremia and systemic cytokine dumping from smoldering periodontitis lesions. For instance, in patients with periodontitis, increased levels of IL-6 have also been reported, which are known to induce hepatocytes and produce CRP, pro-coagulant mediators and other acute-phase reactant proteins [326]. CRP, which is a marker of systemic inflammation and an acute-phase reactant, is produced in response to various inflammatory cytokines within the liver [374]. Elevated levels of CRP (>2.1 mg/l) have been described as a risk-predictor for CVD and have been the focus of attention as an important marker for atherosclerosis [102, 375–380]. A higher incidence of acute thrombotic events including MI and stroke has been associated with increased levels of CRP (>2.1 mg/l) [377, 381]. Even in healthy individuals, CRP levels >2.1 mg/l may serve as a marker for an increased long-term risk of CVD as it has been associated with a chronic pro-coagulant state [102, 378]. However, it needs to be underscored that CRP is only a non-specific marker of the acute-phase response, which implies that mild increases in CRP can be accounted for by many other known and unknown potential stimuli, including but not limited to smoking, trauma, chronic inflammatory conditions and/or infections, as well as obesity [376, 380, 382]. However, the evidence is lacking that can implicate CRP having a definitive role in the pathogenesis of atherosclerosis [383].

As described above, evidence from many studies indicates that both stroke and MI, together with underlying atherosclerosis, are all positively associated with periodontitis [200, 384–387]. In consequence of the hypothesized association of CVD with certain inflammatory and infectious diseases, the ongoing inflammatory processes in atherosclerotic lesions may also be exacerbated by the chronically elevated CRP levels in periodontitis patients, which in turn may contribute to a greater risk for CVE and CVD [96, 388–390]. Meta-analytical evidence also points towards an induction of a systemic inflammatory state in chronic periodontitis, which is marked by increased levels of CRP in patients with periodontitis as compared to controls [391]. However, as there are certain common risk factors for both periodontitis and CVD, including smoking, certain studies performed statistical correction for these variables and found that the associations between periodontitis and serum levels of CRP or/and IL-6 still remained statistically significant [328, 337, 339, 340, 345, 392–394]. Moreover, it has been reported that as compared to individuals with either periodontitis or CVD, the patients who have both these conditions have the highest levels of inflammatory mediators, such as CRP, α_1 -antichymotrypsin and serum amyloid A, thereby suggesting an additive effect of each of these conditions on systemic inflammation [395–398]. Hence, it is possible that the association between CVD and periodontitis can, at least in part, be explained by elevated levels of several inflammatory mediators that are common to both disorders. On the other hand, it is also possible that the levels of these inflammatory mediators, only reflect the

intensity of systemic inflammation in CVD, which in turn may be affected moderately by inflammation in periodontitis [399].

Thrombotic and hemostatic markers: A number of thrombotic or hemostatic markers, such as fibrinogen, PAI-1, von Willebrand factor (vWF), as well as markers of platelet activation have been hypothesized to be implicated in the links between CVD and periodontitis. Greater plasma levels of fibrinogen result in higher blood viscosity and shear stress, which in turn can promote platelet aggregation and endothelial cell activation [400]. Fibrinogen has also been reported to be a risk marker for atherosclerosis and CVDs, as well as an indicator of systemic inflammation [400–403]. In fact, structural components of atheromatous lesions comprise fibrinogen and its degradation products, and within these lesions, degradation products of fibrinogen can bring about the promotion of platelet aggregation and induction of inflammatory cytokine production [404]. It is well known that tissue plasminogen activator (t-PA) plays a very important part in dissolving the blood clots [405] and plasma t-PA, which when raised might possibly be an indicator for endothelial dysfunction, has been reported to be associated with higher risk of CHD [401]. Platelets release vWF which facilitates initial hemostasis [406]. As compared to individuals having either chronic periodontitis or CVD, serum fibrinogen levels have been reported to be higher in individuals having both these disorders [407]. Platelet activation has also been reported to play a role in enhancing the development of atheromas [408]. Studies examining markers of platelet activation, have also reported increased levels and expression of these markers in periodontitis patients [409, 410]. However, data related to the levels of PAI-1, a pro-atherogenic protease inhibitor [411], in periodontitis patients appears to be conflicting [412–414] and its role in linking CVD with periodontitis is still skeptical.

Autoreactive antibodies: Under stress, such as during inflammation, heat-shock proteins (HSPs) have a protective effect on human cells, including endothelial cells, and can further interact with both the adaptive and innate immune responses to produce HSP-specific antibodies and T-cells [415]. Similarly, under stress, bacteria also express antigens that could mimic human HSPs, and thus could stimulate the production of autoreactive T-cells and antibodies to human cells [416]. Multiple studies have reported the expression of HSPs, which have been implicated in atherosclerosis, by periodontal pathogens such as *P. gingivalis* [417–419]. Also, in periodontitis patients, evidence exists regarding the presence of elevated levels of these HSPs [420], together with their ability to induce inflammatory processes that could promote atherosclerosis [421]. Moreover, a number of studies have reported the existence of cross-reactivity between human endothelial cell-HSPs and periodontal bacterial-HSPs [422–425], thereby suggesting that inflammation in atherosclerosis may be promoted by HSP-induced immune responses.

Anti-cardiolipin (anti-CL) and anti-oxidized low-density lipoprotein (anti-oxLDL) antibodies have also been implicated in increased risk for CVD [426–428], and also promote systemic inflammation [364]. Anti-oxLDL antibodies have also been reported to be produced in the GCF of patients with periodontitis [429]. Also, there is evidence that points towards an existence of cross-reactivity of these antibodies towards components of periodontal pathogens [430, 431]. Moreover, as compared to healthy subjects, elevated levels

of both these antibodies have been reported in patients with periodontitis [432–434], with a reported decrease in levels of anti-CL antibodies after periodontal therapy [435, 436], pointing towards a periodontal source of these auto-reactive antibodies.

Thus, pathogenic inflammatory responses in atherosclerosis may be impacted by a number of antibodies. Moreover, elevated systemic antibody responses to several periodontal microorganisms are known to exist in patients with periodontitis. “Molecular mimicry” could operate, resulting in periodontal pathogen-induced formation of cross-reactive antibodies that may eventually lead to recognition of antigens in the host. Under certain circumstances, the risk for atherosclerosis may be augmented or atherosclerosis may be accelerated by these antibodies via promoting lipid entry into the macrophages, blocking anti-atherogenic effects of protective molecules, or by increasing inflammation of the endothelial lining [364].

Lipids: Elevated serum LDL-C is a well-known risk factor for CVD [331, 437]. A number of studies have implicated serum lipids in patients with periodontitis, as potentially playing a role in its association with CVD via inflammatory pathways. As compared to healthy controls, patients with chronic periodontitis have been reported to have higher serum levels of total cholesterol [438–440], LDL [438–440], oxidized low-density lipoprotein (ox-LDL) [434], small dense LDL [420, 435, 441] and triglycerides [434], all of which are known to be pro-atherogenic [442]. Also, lower levels of high-density lipoprotein (HDL), an anti-atherogenic lipid sub-type, have been reported in patients with chronic periodontitis, as compared to healthy controls [434, 435, 438]. Moreover, following periodontal therapy in patients with chronic periodontitis, improvement in serum lipid profiles has been reported [412, 435, 443, 444]. Most of the complications of DM have been linked to hyperglycemia, but there also occurs a disruption in the metabolism of fatty acids leading to hyperlipidemia [445]. A study showed an elevated serum triglyceride levels in patients with adult periodontitis [283]. This study also speculated the hypothesis that triglycerides may be a common link between coronary artery disease, adult periodontitis, and DM, owing to an increased reaction to cell agonists including bacterial [283].

It has also been demonstrated that *P. gingivalis* raises the levels of LDL and total cholesterol in blood by upregulating the protein, which affects the blood levels of LDL cholesterol in mice [447]. The inflammatory response in the atheromas may be enhanced by the adaptive immune responses and thereby exacerbate the baseline inflammation. In response to the bacteria within the intimal plaques in atherosclerosis, antibodies produced may either cross-react with modified LDL leading to inflammatory cells incorporating more lipids within the walls of the vessels, or may cross-react with endothelial cells, or could be pro-inflammatory. Th1 responses in the atheromas may be triggered by some of these antibodies, or by inflammatory cytokines, thereby furthering macrophage activation and promoting inflammation [356]. Moreover, it has been postulated that periodontal microbes affect glycogenesis in liver [448], insulin action [449], and can result in change of gut flora resulting in metabolic alterations and systemic inflammation [450]. Hence, in periodontitis patients, serum levels of lipids are elevated, which tend to be potentially inflammatory, including triglycerides, very low-density lipoproteins (vLDLs) and LDLs. Sub-forms of these lipids are more likely to be encompassed in the atheromas, as they may have greater

susceptibility to being altered and may enter the blood vessel wall with greater ease. These processes could quicken the growth of localized atheromatous lesions, and may thus, advance their maturation.

Genetic markers: Individual variations in the inflammatory response in both atherosclerosis and periodontal infection may be explained by certain genetic markers. For example, evidence from genomewide association studies have consistently implicated the *ANRIL* locus and its variants, as being associated with CVDs [451–458] and type 2 DM [459–461]. Interestingly, variants at this locus have been consistently found to be associated with AgP as well [462–464]. Even though, it has not yet been determined that a causal role exists for *ANRIL* variants in both CVD and periodontitis, however, it is possible that it has a role in the common inflammatory pathways for both these disorders. Also, additive effects of some or all of the above mechanisms may together operate in individual patients, thereby affecting inflammation in their cardiovascular system.

Metabolic diseases and periodontal disease

A number of conditions, such as hyperlipidemia [465], periodontitis [466, 467] and insulin-dependent diabetes mellitus (IDDM) [468], have been linked to the excessive production of cytokines like IL-1. Production of IL-1 in gingival tissues in periodontitis may result in pathologic injury and continuous tissue destruction, when local bacterial infections like *P. gingivalis* infection are persistently present [469]. Moreover, macrophage function abnormalities triggered by a rise in serum lipid levels, might possibly change the secretion of cytokines required for the process of natural healing [470]. A trend was observed for raised IL-1 levels in GCF [471] in patients with type 2 diabetes having hyperlipidemia as well. Thus, a vicious cycle could emerge, with periodontitis leading to inflammation and metabolic disease that could further augment inflammation, which in turn might further worsen periodontitis and metabolic disease. Also, there is a vicious circle between inflammation furthering hyperglycemia and insulin resistance, both of which also worsen inflammation [223, 326, 391, 449], thereby adversely affecting metabolic control and potentially leading to the development of complications related to DM [472]. Furthermore, in terms of TNF, a cytokine that has been well-known to induce insulin resistance [115, 473–477], its levels in the plasma of adult patients with type 2 DM have been reported to be related to the severity of periodontitis in a dose-response fashion [478].

Diabetes mellitus may itself contribute to the development of periodontitis. In order to explain the pathogenesis for an accelerated periodontal destruction in diabetic patients, a ‘two-hit’ model has been proposed [472]. Several animal [479–482] and human [483–485] studies have reported the presence of a hyperinflammatory phenotype in DM, which has been associated with neutrophil priming mediated by increased protein kinase C activity and levels [486]. Some studies have illustrated raised production of IL-1 β in GCF of IDDM patients who had periodontitis [446], and elevated IL-1 β , TNF, and prostaglandin E2 production by monocytes of IDDM patients [487]. Hence, the hyperinflammatory state could potentially magnify the local, as well as the systemic inflammatory response to pathogens. This alteration of host response to bacterial challenge has been hypothesized to be mediated by cytokine dysregulation due to prolonged TNF expression [481, 488]. Also,

evidence from human and animal studies has indicated that collagen degradation is increased and its synthesis is reduced in DM [489–491], which could further contribute to progression and development of periodontitis [492, 493]. Similarly, evidence from multiple animal and human studies indicates that in DM, enhanced alveolar bone destruction may occur secondary to hyperglycemia-mediated modulation of receptor activator of nuclear factor-kappa B ligand (RANKL) to osteoprotegerin ratio in periodontal tissues [494–496], and the process of osseous repair following resorption of bone could be impaired due to increased apoptosis of bone-lining cells and fibroblasts [497–499]. Hence, all these factors could together contribute to uncoupling of bone destruction and repair in diabetics with periodontitis.

Moreover, interaction between receptor for advanced glycation end products (RAGE) that is a member of the immunoglobulin superfamily of cell-surface molecules and is a multiligand signaling receptor, and its ligands called advanced glycation end products (AGEs), has also been hypothesized to mediate periodontal disease in DM. Several findings from a number of studies support this hypothesis, including increased expression of markers for oxidative stress and of AGEs in gingival tissues of patients with diabetes and periodontitis [500], increased gingival tissue RAGE expression in diabetics who also had periodontitis [501], increasing serum levels of AGEs being associated with increasing severity of periodontitis associated with diabetes [502], and suppression of collagen production by fibroblasts in the periodontal and gingival ligament that was mediated by AGEs [503, 504]. Similarly, findings from in vitro and animal studies have also supported this hypothesis [505–510].

Thus, according to the ‘two-hit’ model, in an environment of enhanced RAGE expression, bacterial challenge could precipitate impaired repair and exaggerated inflammation of the periodontal tissue in diabetics, thereby resulting in severe and accelerated periodontal tissue damage [472]. Also, increased blood glucose levels result in the formation of AGEs, which also bind to RAGE present in the periodontium resulting in an inflammatory reaction [511]. A study by Lalla et al. (2000) demonstrated that blockade of RAGE receptor in mice with diabetes lessened the inflammatory reaction and resulting destruction of alveolar bone [508].

Also, metabolic syndrome and periodontitis may be linked through common pathophysiological pathways as both of these disorders have been associated with systemic inflammation. Insulin resistance that has been reported in individuals with periodontitis, may be precipitated by a complex interplay of the host inflammatory response to alterations of lipid levels, adiposity and periodontal infections [512]. Decreased levels of leptin, an anti-obesity adipocytokine [513], in the gingival tissue and the GCF have been related to worsened periodontal status [514–516]. Interestingly, on the other hand, serum leptin levels tend to increase with greater periodontal destruction [516]. This could be explained by either possibly higher rate of leptin removal from gingiva after gingival inflammation-mediated vasodilation, or probable rise in the serum leptin levels as a means to offset inflammation in periodontitis [515, 516]. Adiponectin is an adipocytokine whose lower levels have been associated with diabetes, obesity and insulin resistance [517]. Even though an in-vitro study has reported that adiponectin may have an anti-osteoclastic effect in periodontitis [518], limited and conflicting data exists regarding its potential role in the inflammatory links between periodontitis and MetS [519–521]. Resistin is also an adipocytokine, which has a

pro-inflammatory action [522], and has been implicated in insulin resistance [523]. Moreover, a positive association between bleeding on probing and serum resistin levels, as well as the presence of higher serum levels of resistin have been reported in periodontitis patients, as compared to healthy controls [520, 521].

Additionally, in mice, it has been reported that *P. gingivalis* induced up-regulation of a protein known to play a critical role in regulating circulating LDL cholesterol levels resulted in increased circulating levels of total and LDL-cholesterol levels after an intraperitoneal infection with this organism [447]. Also, an alteration of the gut microbiota has been reported in mice after oral administration of *P. gingivalis*, which coincided with increased systemic inflammation and insulin resistance [450].

Oxidative stress in mediating links between periodontal disease and metabolic and cardiovascular diseases

Oxidative stress due to raised reactive oxygen species (ROS) levels has been involved in the pathological mechanism of developing a number of diseases, such as DM and CVDs [524–526]. Additionally, MetS has various component disorders that share a common pathologic phenomenon, i.e., oxidative stress [132]. A decline in response of periodontal tissue against bacterial plaque may occur because the antioxidant defense mechanism in periodontal tissue can be altered in MetS [132, 527]. Individuals with periodontitis tend to have a decreased anti-oxidant capacity and an increased pro-oxidative state, which could together promote reduction in insulin sensitivity that could be further worsened by consumption of diet rich in fat by these individuals [528]. However, oxidative stress may itself contribute to periodontal disease pathogenesis [529, 530]. Periodontal disease itself increases the activity of neutrophils by enhancing oxidative stress markers and chronic inflammation [530]. A study by Marchetti et al. (2012) [287] proposed that there might be a raised production of ROS in obese patients and that they also require additional insulin for the maintenance of blood glucose levels, which can lead to the development of type 2 diabetes. AGEs are also produced as a result of oxidative stress [531] and hyperglycemia, which as described above, may also contribute to the destruction of the periodontal tissue.

Psychiatric disorders and periodontal disease

Psychosocial stress, a common risk factor for various psychiatric disorders [532], and also markedly increased during exacerbations of mental illness, induces a number of interactions between cells of the immune systems and sympathetic nervous system, sensoric peptidergic nervous system and the neuro-endocrine system, including hypothalamic, pituitary, adrenal-derived and other hormones, which in turn could influence periodontitis [533, 534]. In particular, overactivation of HPA axis has been implicated in major depression [535], which is associated with heightened release of glucocorticoids from the adrenal cortex and of corticotropin-releasing hormone from the hypothalamus [536]. A number of immunosuppressive actions of glucocorticoids, such as inhibition of antibody secretion [immunoglobulin (Ig) IgA and IgG] [536], inhibition of production of cytokines [537], reduced accumulation of macrophages, eosinophils, and neutrophils at sites of inflammation and decreased number of circulating lymphocytes, monocytes, and eosinophils [538, 539], together may increase the susceptibility to acquire periodontal infection and also exacerbate

the periodontal disease. In fact, as compared to healthy controls, levels of IL-6 and cortisol in the GCF have been found to be elevated in women with depression [540, 541]. Moreover, in a rat-model of ligature-induced periodontal disease, administration of an antidepressant fluoxetine was reported to protect against periodontal bone resorption and destruction of collagen fibers by suppressing the proinflammatory responses [reduction of IL-1 β and cyclooxygenase (COX)-2 mRNA expression], as well as the proteolytic enzyme activity (MMP-9) [542]. Periodontal destruction may also be enhanced by release of prostaglandin and proteases, which in turn is mediated by stress-induced secretion of catecholamines from the autonomic nervous system under stress [543, 544]. Moreover, altered nutrition associated with periodontal disease [545] may affect the gut microbiota [546], which may further have an influence on the psychiatric symptoms [547] through the gut-brain connection, as evidenced by a number of animal [548–554], clinical [555] and imaging studies [556]. Furthermore, gut-microbiota have immuno-modulatory effects on the brain [557–559], and oral pathogens of periodontitis in turn may alter the gut-microbiota [450, 560, 561], thereby affecting psychiatric symptomatology. Since, inflammation and psychiatric disorders are predictively connected, thus increased inflammation in periodontal disease may causally contribute to psychiatric disorders as well.

Effects of periodontal treatment

Effect of periodontal treatment on cardiovascular diseases

Certain studies have reported an association between periodontal treatment and a decrease in the risk of cardiovascular events. Lee et al. (2015) performed a retrospective cohort study on more than 700,000 patients with/without periodontal disease and reported that as compared to the subjects without periodontal disease, the risk of acute myocardial infarction was highest in patients with periodontal disease who received no treatment for it (hazard ratio [HR] = 1.23, [95% CI: 1.13–1.35]), followed by the patients with periodontal disease who received intensive treatment (HR = 1.09 [95% CI: 1.03–1.15]), and was the least in patients with periodontal disease who received only dental prophylaxis (HR = 0.90, [95% CI: 0.86–0.95]) [562]. Thus, even though intensive periodontal treatment slightly raised the risk for acute myocardial infarction, it was still less than that related to no periodontal treatment at all. In another retrospective cohort study on more than 15,000 patients with diabetes, Peng et al. (2016) [563] reported that as compared to the patients that had received non-advanced periodontal treatment, the patients receiving advanced periodontal treatment (including sub-gingival curettage and flap operations) had significantly lower rates of heart failure (HR = 0.60 [95% CI: 0.45–0.80]) and myocardial infarction (HR = 0.92 [95% CI: 0.85–0.99]). However, the difference in the rate of stroke was not significant between these two groups (HR = 0.95 [95% CI: 0.85–1.06]) [563]. Moreover, as compared to the subjects who respond well to periodontal treatment, poor responders have been reported to have a significantly higher incidence rate ratio for CVD (1.28 [95% CI: 1.07–1.53; $p = 0.007$]), which increased further in subjects with the most remaining teeth up to 1.39 (95% CI: 1.13–1.73; $p = 0.002$) [564]. Thus, progression of CVD might be influenced by successful periodontal treatment.

Moreover, measures/markers of CVD risk are also affected by periodontal treatment. Evidence from randomized controlled trials has demonstrated that as early as one to two

months after periodontal treatment, a reduction occurs in the systemic levels of CRP, E-selectin, and IL-6 [565–568], as well as in the number of pathogenic microorganisms in dental plaque [569]. Also, endothelial function tends to improve by 2 months after periodontal treatment [568]. In a meta-analysis, Orlandi et al. (2014) [570] arrived at a conclusion that improvement of endothelial function and reduction in systemic inflammation occurred with periodontal treatment, with one study reporting that these effects significantly lasted for 3–12 months post-treatment [571]. Also, following periodontal treatment in patients with periodontitis and/ or CVD, including full-mouth extraction, a decline in the serum fibrinogen levels has been reported [572–574]. In studies examining measures of cardiovascular outcomes post-treatment for periodontitis, even though a transient increase in brachial artery flow-mediated dilation (FMD), a marker of endothelial dysfunction [575], has been reported within 24 hours of periodontal treatment [568], other studies have reported an improvement in measures of cardiovascular pathology, including the measures for endothelial dysfunction, Framingham Risk Score and systolic blood pressure, as early as 1–2 months post-periodontal treatment [131, 576–578]. Teeuw and colleagues performed a meta-analysis on 25 studies and reported that the interventions to treat periodontitis resulted in the improvement of endothelial function and a reduction in atherosclerotic disease biomarkers profile of atherosclerosis [210]. Vidal and colleagues [579] conducted an interventional prospective cohort pilot study consisting of 26 patients (53.6 ± 8.0 years old), who had generalized chronic periodontitis and refractory hypertension. There was a significant reduction in all the assessed cardiovascular risk markers with periodontal treatment. Left ventricular mass was decreased by 12.9 g, pulse wave velocity was decreased by 0.9 m/s ($p < 0.01$), median values of diastolic blood pressure and systolic blood pressure were decreased by 10.0 mmHg and 12.5 mmHg, respectively, and levels of IL-6, fibrinogen, and CRP were reduced by 1.4 pg/dl, 37.5 mg/dl ($p < 0.01$) and 0.5 mg/dl, respectively, after 6 months of periodontal treatment [579]. Thus, in refractory hypertensive patients, there was a significant reduction in the levels of IL-6, CRP, fibrinogen, arterial stiffness, blood pressure, and left ventricular mass, with periodontal treatment, thereby possibly reducing the risk for CVD [579]. However, the data which illustrates that periodontal treatment affects ASCVD risk is inadequate; although the randomized controlled trial demonstrating the effect of periodontal treatment on endothelial dysfunction [568] indicates that the evidence for these effects is reasonable, as ASCVD could be predicted by endothelial dysfunction [580]. Hence, even if there is a very small positive impact of periodontal treatment on risk of CVD, this could be a major advancement in community health for the prevention of CVD. Additionally, a study by Blum et al. (2007) [581] demonstrated that periodontal treatment improved the vascular endothelial function effectively, and may be helpful in the prevention of PAD by protecting the vascular injury. Moreover, studies on periodontal therapy employing conservative approaches, such as scaling, root planing and antibiotic treatment, have reported a post-treatment reduction in the systemic levels of certain acute-phase reactants, as well as inflammatory mediators, including CRP, IL-6, TNF, fibrinogen, PAI-1, and WBC counts [131, 412, 572–574, 576–578, 582–584]. However, some studies have suggested otherwise, with no changes observed in the serum levels of acute-phase reactants and inflammatory mediators after conservative treatment for periodontitis [585, 586]. Similarly, results from meta-analyses examining the effect of periodontal treatment on the serum levels of CRP have been mixed [391, 587].

On the other hand, periodontal treatment in itself may present as a moderate stimulus for temporarily inducing an increase in inflammation [588], and it has been associated with endothelial dysfunction 24 hours post-treatment [568] and a transient rise in systemic pro-thrombotic/inflammatory mediators lasting for at least one week [588]. The trauma and bacteremia following periodontal treatment may explain these findings [356]. However, this increase in inflammation is temporary and is outweighed by the reduction in inflammation that is lasting and prolonged. In a self-controlled case series study, Minassian et al. (2010) [589] reported a significantly greater incidence rate ratio (1.50 [95% CI: 1.09–2.06]) in the first 4 weeks after invasive dental treatment, even after exclusion of subjects with prescriptions for antiplatelet or salicylate drugs before treatment, and individuals with coronary artery disease, diabetes or hypertension. Moreover, the increased rate of vascular events normalized to baseline values within 6 months of receiving treatment [589].

Effect of periodontal treatment on metabolic diseases

Merchant et al. (2016) performed a prospective cohort study on individuals receiving care at Veterans Health Administration medical facilities, in order to evaluate the effects of long-term periodontal care (with mean follow-up period of 1.7 years) on HbA1c in type 2 diabetics, who also had periodontal disease [590]. In this study, marginal structural models were applied to account for potential selection bias and confounding [590]. HbA1c was reported to decrease by -0.02% and -0.074% , after periodontal treatment at baseline and follow-up, respectively [590]. Moreover, individuals with higher baseline HbA1c values had greater reduction in HbA1c ($\text{HbA1c} = -0.25\%$) after receiving periodontal treatment [590]. It is possible that among individuals with diabetes, periodontal treatment may lead to improved glycemic control and insulin sensitivity, by reducing circulating inflammatory mediators, including TNF [591–594], CRP [591, 592, 594, 595], fibrinogen [593] and IL-6 [592, 596], and by increasing the levels of adiponectin [592, 597]. Even among individuals without DM, systemic inflammation may be reduced by periodontal treatment [223, 391]. With periodontal treatment, a reduction in HbA1c was found in people with diabetes [598]. Also, outcomes from the Post AV Nodal Ablation Evaluation (PAVE) study indicated that in overweight people, the treatment of periodontitis might be less impactful [599]. Additionally, periodontal treatment, be it non-surgical periodontal treatment or supragingival therapy, when performed in diabetic patients who have well-controlled blood glucose level, did improve periodontal problems with no harmful effects on diabetes when the patients were tested after 4 months after receiving periodontal treatment [246]. Few studies have stated that there occurs an improvement in periodontal health in individuals with diabetes with the non-surgical periodontal therapy and/or subgingival scaling [600–603], and a different study emphasized that periodontal treatment with subgingival curettage, root planing, and extractions as a treatment, if required, led to improvement in glycemic control in diabetics [604].

Effect of periodontal treatment on psychiatric disorders

To our knowledge, there are no studies that directly report the effects of periodontal treatment on psychiatric disorders or outcomes. However, one study by Ozcelik et al. (2007) [605] had assessed the effects of one-week long surgical (SG), surgical plus enamel matrix protein derivative (S+EMD), and non-surgical (NS) periodontal treatment modalities on Oral

health-related quality of life (OHQoL). Two questionnaires, Oral Health Impact Profile-14 (OHIP) and General Oral Health Assessment Index (GOHAI) were used in this study to evaluate OHQoL, and these questionnaires also included measures of a number of psychological (self-consciousness, worry, anxiety, etc.) and behavioral impacts (irritability, limiting social contact, dietary changes, etc.) [605]. The authors reported that starting from the first post-treatment day until the 7th post-treatment day, the individuals in the SG group had significantly ($p = 0.001$) worst OHQoL scores (including more psychological and behavioral impacts) than the NS and S+EMD groups [605]. Interestingly, in the SG group, after initial worsening of the psychological and behavioral impact sub-scores of OHQoL for the first 1–2 days post-treatment, these scores returned to the baseline values only after 6–7 days [605]. On the other hand, the sub-scores for psychological and behavioral impact domains of OHQoL in the NS and S+EMD groups, started to improve from baseline values on day 1 post-treatment, and continued to decline till day 7 after treatment [605]. These observations can be possibly explained by the fact that surgical periodontal intervention could lead to a much more severe and prolonged pro-inflammatory response, thereby releasing inflammatory mediators, which as described in earlier sections, may contribute to psychiatric symptoms. Moreover, improved outcomes on OHQoL scores in the S+EMD group as compared to the SG could be attributed to the periodontal tissue regenerative properties of the enamel matrix protein derivative [606], which might attenuate the duration and severity of the pro-inflammatory response following the surgical intervention for periodontitis.

Effect of periodontal treatment on neopterin

After periodontal treatment in individuals with moderate to severe periodontitis, a drastic decrease (from 51 nmol/l to 1.77 nmol/l) in the level of GCF neopterin concentrations was observed [89]. Similar results have also been reported in other studies on patients with periodontitis [607, 608], as well as in patients with a combination of periodontitis and/or DM [609]. On the other hand, a study by Bodur et al. (2003) [610] reported no significant differences in both pre- and post-periodontal treatment-GCF neopterin levels between the group of patients with AgP and periodontally healthy controls. However, mean salivary neopterin concentrations were significantly higher in patients as compared to the controls, but there was no significant difference between the pre- and post-periodontal treatment levels of salivary neopterin concentrations among the AgP group [610]. Moreover, after periodontal treatment, urinary neopterin levels were significantly higher in the AgP group, when compared with pre-treatment urinary neopterin levels and with the urinary neopterin levels of the control subjects [610].

Implications, conclusions and future directions

Periodontal disease, CVD, metabolic diseases and psychiatric disorders pose a major global health-burden. They share multiple risk factors and have a multifactorial bi-directional, as well as, multi-directional etiology. As described above, robust evidence depicts an association between these disorders, which points towards inflammation being one of the major links between them.

Periodontal disease has been associated with significant worsening of quality of life [32, 611–615], and periodontal treatment has been reported to improve the quality of life of patients [615–617]. Additionally, as described in greater detail above, periodontal treatment reduces the morbidity associated with co-morbid systemic diseases, such as CVD and diabetes, in patients with periodontitis [590]. Hence, it becomes essential to prevent and manage periodontal disease to reduce its burden of morbidity and mortality in various populations.

From the viewpoint of public health, the prevention and treatment of periodontitis are possible; therefore, improvement in oral health is possible by effectively implementing the treatment measures and prevention programs. The underlying principle behind the diagnosis, treatment and prevention of periodontitis is evading the detrimental effects of periodontitis, like alveolar bone loss and resulting tooth loss, and preserving the dentition of a person. Periodontitis can be managed with treatment, but there is very little knowledge on how to prevent it [30]. Few studies have demonstrated that tooth-brushing, specifically with fluoride containing toothpaste, decreases dental caries [618]. On the other hand, daily procedures like use of chewing gum or tooth-brushing, can also result in episodes of bacteremia in patients with periodontitis, and it can occur multiple times daily [619–622], which, as described above, could also contribute to CVD. It is likely that the benefits of oral hygiene possibly outweigh the risks associated with it due to bacteremic episodes. However, benefits of maintaining good oral hygiene in periodontitis have not been reported in other studies [623–625]. It is also likely that in addition to oral hygiene, other factors like genetic predisposition, may have a greater part to play in the etiology of periodontitis than was formerly speculated [21, 22]. However, in children, timely detection of oral conditions as well as a good oral hygiene, are very crucial in the treatment and prevention of periodontal disease [626, 627]. As gingival bleeding is more frequent in children with diabetes, oral hygiene is specifically necessary in them [240, 628].

It is essential that dentists and general practitioners (including cardiologists, endocrinologists, and perhaps, psychiatrists) co-operate for the promotion of oral and general health by increasing access to periodontal treatment, coordinating referrals between them, and increasing awareness about the links between these disorders. Dentists should be watchful for the presence of risk factors for periodontitis, CVD and MetS in their patients, which can be modified via lifestyle changes. Once identified, such risk factors should be addressed in a comprehensive periodontal treatment setting by the dentists by advising their patients on lifestyle changes, such as physical exercise, consumption of whole grain or high-fiber diet and smoking cessation. Mental health professionals should include oral health considerations in the comprehensive assessment and treatment of individuals with severe mental illness. There is an availability of standard checklists for assessing oral health [305, 629–631], which can be utilized by all health professionals, and thereby facilitate the screening for co-morbid periodontal disease in their patients. Similarly, interventions including iatrogenic dry mouth management, early dental referral, and help in maintaining good oral hygiene, can be employed by all physicians. American Heart Association (AHA) guidelines should be followed to reduce the risks associated with comorbid periodontitis in patients with a history of CVD. The patients of periodontitis in whom additional risk factors for ASCVD are present, such as overweight/ obesity, smoking, hypertension and who have

not visited a doctor in the past year, should be referred for a routine physical examination. This forward leaning stance is critical, as periodontal disease is often under-treated [25] because it does not present with any pain in early stages of the disease and progresses slowly [632].

In brief, psychiatric illnesses may represent an important link between periodontal disease, metabolic diseases and CVDs. As described above, inflammation is a critical pivot between all these conditions. However, this relationship has an element of complexity. Early on, after periodontal therapy, an increase in the serum levels of the markers of CVD risk during the period of first 24 hours [568] to 4 weeks [589, 633], points towards an increased risk for inflammation-mediated adverse outcomes during this time period. Hence, it becomes essential to individually personalize the timing of monitoring and treating psychiatric, metabolic and cardiovascular co-morbidities for each patient relative to individual time points, (e.g., according to the interval of time elapsed since they had an intervention for periodontal disease). Also, expansion needs to happen in terms of the clinical settings, where recommendations for maintaining a good oral hygiene and referrals to a dentist's office for treating dental health issues are made, including the cardiology, endocrinology, primary care and mental health clinics. Similarly, it becomes important to screen patients' psychiatric, cardiovascular and metabolic health issues in a dentist's office.

As described above in various sections, there are gaps in the scientific data that are short of causal links between periodontal disease and CVD, metabolic diseases, and psychiatric disorders. Even though, it has been established that well-designed randomized controlled trials should be preferred to determine a causal inference from an exposure towards an outcome [634], there could be certain scenarios, e.g., in studies evaluating the effects of periodontal treatment to an outcome [590], where randomization cannot be feasible, thereby making an RCT prone to confounding. Also, standard methods for controlling confounding (e.g., regression analyses) can be rendered inappropriate when a time-varying confounder is affected by prior treatment, as the covariate could play the role of both a mediator as well as a confounder of the effect of treatment on outcome over-time [635, 636]. Interestingly, a new class of causal models called marginal structural models, can utilize observational data to estimate the causal effect of a time-dependent exposure, while taking into account the occurrence of time-dependent covariates that could also function concurrently as intermediate variables and confounders [636, 637]. These models are designed to control for the effects of confounding variables that are affected by previous treatment or that change over time, by utilizing a multi-step estimation procedure [636]. These models create an artificial population by using inverse-probability (of exposure) weights, and in this population, causal effects can be estimated after removing imbalances among co-variables [590, 636, 638]. Thus, using marginal structural models on large epidemiological data can uncover potential causal links between periodontal disease and CVD, metabolic diseases, and psychiatric disorders.

Future studies should focus on: 1) redoing previous work connecting periodontitis and metabolic/cardiovascular health with measurement of indicators of the presence and severity of mental illness, with adjustment and stratification, 2) studying periodontal disease in pregnancy and the effect of treating it on metabolic factors (e.g., diabetes), and mental health

in mothers and development in the offspring, with measurement of mediators of inflammation, 3) investigating the effect of psychiatric treatment, in those with untreated mental illness, on periodontal health, 4) exploring how periodontal disease could also contribute to mental illness, rather than only on how psychiatric disorders could affect periodontal disease, 5) analyzing dental health in individuals with vs. without suicide attempts, 6) performing neuroimaging analyses, functional and structural, and glial imaging in individuals with vs. without periodontitis (before and after), 7) identifying the group of individuals most at risk for psychiatric exacerbation due to periodontitis or its treatment, 8) analyzing in large registries the effect of periodontal treatment on mental health and metabolic disease and use marginal structural modeling to account for bias, 9) investigating inflammatory markers for predicting severity and timing of possible interventions, and monitoring of these patients, 10) identifying interventions that would have the greatest overall impact across domains, and the groups of individuals, who would benefit most from periodontal disease prevention and treatment, 11) comparing medications for similar indications in a randomized fashion to determine the best agent to use in individuals with or at risk for periodontitis, 12) increasing adherence to preventative and treatment strategies for periodontal disease in individuals with mental illness, and 13) exploring genetic, epigenetic and environmental factors in large population studies that put individuals at shared risk for periodontal disease, mental illness, metabolic and cardiovascular disease.

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List of abbreviations

AAP	American Academy of Periodontology
AGEs	Advanced glycation end products
AgP	Aggressive periodontitis
AHA	American Heart Association
anti-CL	Anti-cardiolipin
anti-oxLDL	Anti-oxidized low-density lipoprotein
AP	Acute periodontitis
ASCVD	Atherosclerotic cardiovascular disease
C. pneumoniae	Chlamydia pneumoniae

CAL	Clinical attachment loss
CBVD	Cerebrovascular disease
CDC	Centers for Disease Control and Prevention
CIMT	Carotid-artery intima and media thickness
CHD	Coronary heart disease
CI	Confidence intervals
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CVD	Cardiovascular disease
CVE	Cerebrovascular event
COX	Cyclooxygenase
DM	Diabetes mellitus
FPL	Federal poverty level
GCF	Gingival crevicular fluid
GOHAI	General Oral Health Assessment Index
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HR	Hazard ratio
HSPs	Heat-shock proteins
IDDM	Insulin-dependent diabetes mellitus
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IHD	Ischemic heart disease
IL-	Interleukin
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LPS	Lipopolysaccharide
MCP-1	Monocyte chemoattractant protein-1
MI	Myocardial infarction

MetS	Metabolic syndrome
MMPs	Matrix metalloproteinases
NHANES	National Health and Nutrition Examination Survey
NS	Non-surgical
OHIP	Oral Health Impact Profile-14
OHQoL	Oral health-related quality of life
OR	Odds ratio
ox-LDL	Oxidized low-density lipoprotein
P. gingivalis	Porphyromonas gingivalis
PAD	Peripheral arterial disease
PAI-1	Plasminogen activator inhibitor-1
PAF	Platelet-activating factor
PAVE	Post AV Nodal Ablation Evaluation
PPD	Periodontal probing depth
RAGE	Receptor for advanced glycation end products
RANKL	Receptor activator of nuclear factor-kappa B ligand
ROS	Reactive oxygen species
RR	Relative risk
S. sanguis	Streptococcus sanguis
SG	Surgical
S+EMD	Surgical plus enamel matrix protein derivative
Th	T-helper
TNF	Tumor necrosis factor-alpha
t-PA	Tissue plasminogen activator
US	United States
vLDL	very low-density lipoprotein
vWF	von Willebrand factor
WHO	World Health Organization

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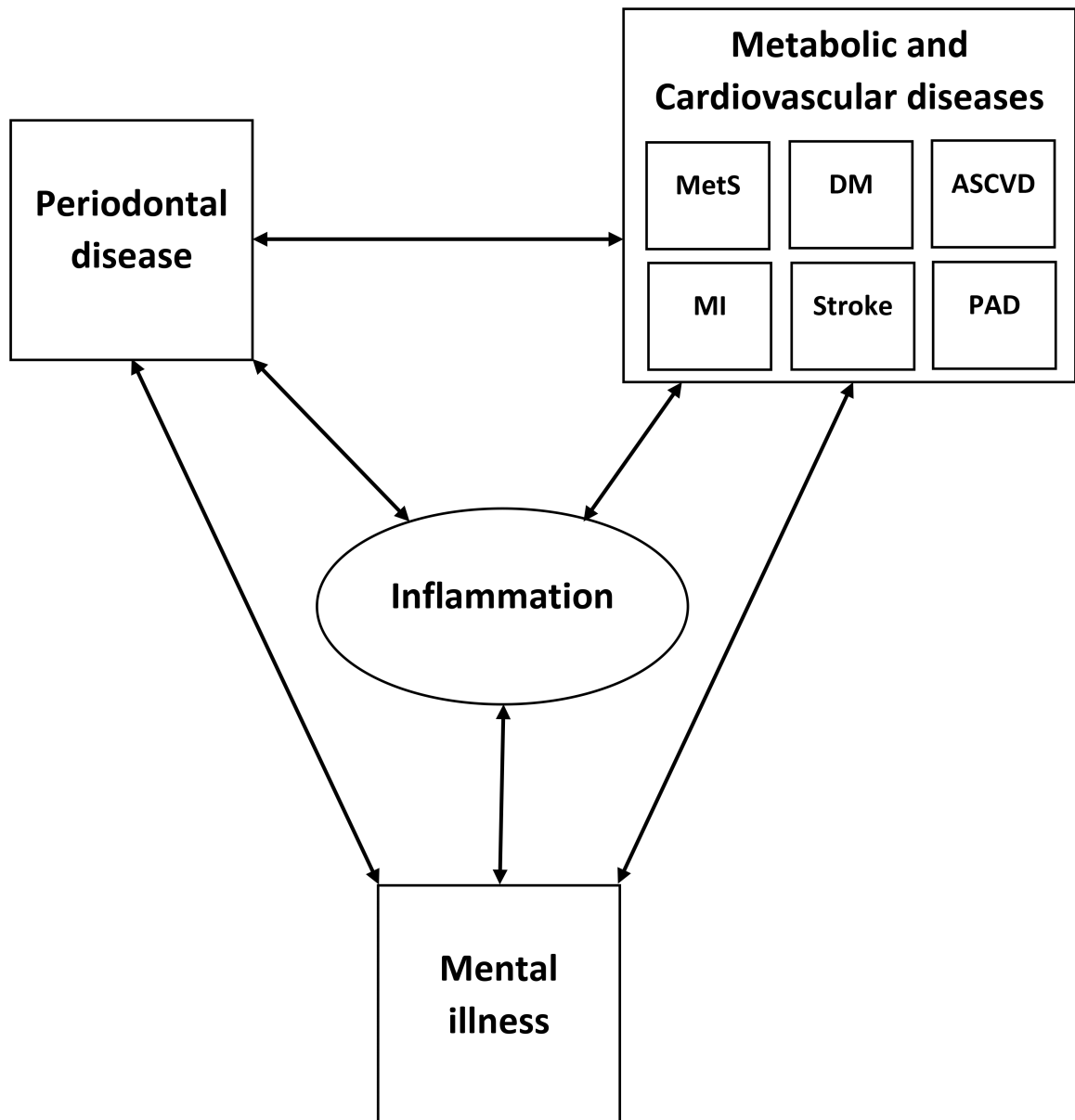


Figure 1: A graphical representation depicting the links between periodontal disease, metabolic diseases, cardiovascular diseases, and mental illness, with inflammation as a common mediator between these disorders. (MetS: Metabolic syndrome; DM: Diabetes mellitus; ASCVD: Atherosclerotic cardiovascular disease; MI: Myocardial infarction; PAD: Peripheral arterial disease).