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Effect of periodontal treatment on biomarker levels: An Update

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Abstract

The risk of unfavorable systemic outcomes is thought to be increased by periodontal infections. The characteristic feature of the periodontal disease is the immune-inflammatory process that increases level of several proinflammatory cytokines such as IL-1, IL-6, TNF- α, PGE-2, and IL-8. The main role of these cytokines are to initiate inflammatory response in alone or in coordination with other metabolic factors. Standard nonsurgical therapy such as scaling and root planing (SRP) are reported to be gold standard for the periodontitis patients. In the past studies have evaluated the association of the biomarkers with the non-surgical periodontal treatment. However, there is no such comprehensive review is available that have discussed this association in details. Hence, this review is undertaken to discuss the past studies conducted in this field. The available evidence suggests that routine nonsurgical periodontal therapy, which primarily consists of scaling and root planning of the dentition, may help patients to reduce their CRP and other serum inflammatory markers between periodontal maintenance visits.

Keywords: Periodontitis, Periodontal treatment, Inflammatory biomarker, CVD, Oxidative stress markers

Introduction

The relationship between oral disease and systemic disease has become a major source of worry since oral infections and disorders may contribute to pathologic processes occurring elsewhere in the body (1). Poor oral health, which is predominantly caused by periodontal disease and accompanying tooth loss, has been linked to an increased risk of diabetes, cardiovascular disease (CVD), unfavorable pregnancy outcomes, lung disorders, and all-cause mortality, among other diseases (2).

The main characteristic feature of a periodontal disease is an immune-inflammatory process that causes accumulation of bacterial biofilm on the surface of the teeth. In individuals with this condition the gingival tissue, cementum, alveolar bone, and periodontal ligament gets affected. The most common clinical sign associated with this condition is bleeding in gingival region, resorption of the alveolar bone, halitosis, and in worst cases spontaneous tooth loss (3).

Apart from causing damage to the underlying periodontal tissues by the bacterial infection, several other indirect pathways also causes damage to the periodontium. The breakdown of the periodontium by bacterial virulence factors exposes cells and underlying periodontal tissues (4). As a result, bacterial components such as lipopolysaccharides (LPS) stimulate cells like lymphocytes, monocytes, and fibroblasts. This process in turn releases proinflammatory cytokines such as IL-1, IL-6, TNF- α, PGE-2, and IL-8. The main role of these cytokines are to initiate inflammatory response in alone or in

coordination with other metabolic factors (5). These pro-inflammatory cytokines also induces production of reactive oxygen species causing moer harm to the cells. In the pase several studies have pointed out association of periodontal diseases with cardiovascular conditions and with myocardial infraction (6).

Periodontitis patients exhibit greater biochemical markers of systemic diseases such atherosclerosis than age- and gender-matched controls, according to studies. However, the present data on periodontal systemic relationships is inconsistent, and there is little indication that periodontal therapy affects systemic health (7). Standard nonsurgical therapy such as scaling and root planing (SRP) are reported to be gold standard for the periodontitis patients. In the past studies have evaluated the association of the biomarkers with the periodontal treatment. However, there is no such comprehensive review is available that have discussed this association in details. Hence, this review is undertaken to discuss the past studies conducted in this field.

Association of biomarker with periodontal treatment

1. **I*nflammatory biomarkers***

The level of inflammatory biomarker has shown to be increased in periodontitis. Hence, periodontal therapy was shown to be associated with the decreased level of pro-inflammatory biomarkers. Hossain Bokhari et al conducted a pilot study where the association of non-surgical periodontal treatment with the different inflammatory markers such as CRP, fibrinogen, and WBC counts were evaluated. This study included angiographically characterized individuals with coronary heart diseases (CHD, N=27) with non-CHD patients (N=18). The clinical measures bleeding on probing (BOP) and probing depth were used to assess periodontal disease (PD). Non-surgical periodontal therapy includes basic dental hygiene training along with scaling and SPR. Inflammatory indicators (CRP, fibrinogen, and WBC counts) were assessed in the bloodstream before and after periodontal therapy. It was shown that after therapy among participnats the biomarkers levels were reduced significantly (P-value<0.05). Thus this study concluded that among patients with CHD or the control periodontal therapy resulted in significant in blood inflammatory markers. This could lower the risk of CHD in the patients who are being treated (8).

Periodontal infection may be linked to the systemic inflammatory consequences through chronic inflammation. Inflammatory biomarkers such as C-reactive protein (CRP) have been linked to a higher risk of clinical outcomes in type 2 DM and cardiovascular diseases (9,10). to selectively eliminate bacteria from dysbiotic subgingival biofilms may result in the development of a persistent low-grade inflammatory phenotype Because of this, periodontal treatments that are anti-infective and that minimize exposure to subgingival pathogenic bacteria are a potential anti-inflammatory strategy (11).

In a systematic review and metanalysis conducted by Demmer et al it was concluded that periodontal treatment can cause modest decrease in the level of CRP. In this meta-analysis randomized controlled trials were included and among all the studies 20 were included with 2561 patients. This study reported that the mean difference between the CRP level among test and control were different pre and post treatment. In 40% of the trials the mean CRP level was more than 3 mg/L. In studies involving a control group that did not receive treatment, the mean difference in CRP final values between experimental treatment and control groups was significantly different (P=0.005). This result indicates that experimental therapy was superior to control treatment. Trials in which the experimental group received antibiotics had stronger effects, and the mean difference in CRP final values between the experimental treatment and the control group was -0.75 mg/L. Studies involving an active treatment comparator found no evidence of a treatment impact in their results. Although the interaction between studies that included

patients with co-morbidities and studies that included "systemically healthy" patients was not statistically significant (P=0.48), treatment effects were larger in trials that included patients with co-morbidities (11).

In a recent study it was reported that periodontal treatment can help in lowering the glucose concentrations and other inflammatory markers among patients with type 2 DM. Moreover, it was also reported that periodontal treatment can improve the kidney and vascular functions. In this study the intensive periodontal treatment were compared with the controlled periodontal treatment. It was reported that compared to the controlled treatment plan, intensive treatment plan were able to decreases the HbA1c level among diabetics (12). In another study it was also reported that even in patients who are not diabetic, periodontic treatment improves the endothelial functionality (13).

In another study it was reported that at an average follow-up of three years, improvements in clinical and microbiological periodontal condition are associated with a lower rate of carotid artery IMT development (14).

In patients with depression an association is reported with the periodontal disease. Through neuroimmune interactions, a dysregulated immune response originating in the peripheral nervous system can cause depressed symptoms. Inflammatory oral disease has been shown to be a significant inducer of chronic neuroimmune response, which has been shown to be associated with depression (15). However, Petit et al reported that no association exist between the periodontal treatment and the biomarkers level in depressive patients (16).

Koudou et al reported that in Gingival crevicular fluid (GCF) the level of biomarkers increases early post-operatively, which is followed by a decrease in their levels three months after the treatment is administered. A significant tool for understanding the processes connected with healing following periodontal therapy is the evaluation of levels of GCF markers linked with inflammation and regeneration. Multiplex bead immunoassay methods, in particular, are particularly well suited for this purpose. In this systematic review total of 366 publications were included. This review reported non-surgical periodontal treatment primarily increases the level of GM-CSF, IL-1α, IFN-γ, IL-6, IL-1β, TNF-α, MCP-1, and MIP-1α. However, in the following weeks the levels were reduced. After 3 months of the treatment values of all the biomarker in the GCF reduced significantly from the initial values (17).

2. Biomarkers for oxidative stress

Although periodontitis is caused by a biofilm of bacteria in the subgingival periodontal pocket, the majority of tissue deterioration appears to be caused by an aberrant host response to certain bacteria and their products (18). Proliferative enzymes and reactive oxygen species are released in an increased manner during the aberrant reaction, which results in exacerbated inflammation (ROS). Innumerable research studies have demonstrated a relationship of chronic periodontal disease and systemic diseases such as obesity and metabolic syndrome as well as type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease (19,20).

In a systematic review by da Silva et al it was reported that periodontal treatment was able to lower the level of oxidative stress markers. However, this value were similar to the values obtained for periodontically healthy subjects. The most common marker reported to be reduced by the treatment was 8-hydroxydeoxiguanosine (8-OHdD) in both saliva and GCF. The total oxidant status were reduced after the treatment in serum, saliva and also in GCF (3).

Among smokers and non-smokers, Hendek et al reported that it is possible that periodontal therapy will be beneficial in decreasing oxidative stress in patients with periodontitis. Both periodontitis groups had considerably greater levels of 8-OHdD in GCF when compared to the two periodontally healthy groups. The levels of

8-OHdG in gingival fluid and saliva were considerably reduced in both periodontitis groups following the initiation of periodontal treatment (21).

In contrast to the studies, in another systematic review Akhtar et al reported that the concentrations of the oxidative stress markers (OSM) are highly variable among studies. The change of OSM varied from 0% to 81% in the studies that were included in the review. It was observed in eight investigations that there was a statistically significant reduction in OSM. The unweighted percent change was calculated using 5 studies, while the weighted percent change was calculated using 5 studies. This study concluded that the OSM concentrations in periodontitis patients are highly variable, indicating a significant degree of variability. OSM decreased as a result of non-surgical treatment (22).

3. CVD markers

The immunological response in periodontitis is thought to influence systemic inflammatory load by raising the release of serum markers of inflammation, which is thought to be the mechanism linking periodontitis and coronary heart disease. According to the findings of several research, periodontitis is connected with elevated levels of serum inflammatory markers that are associated with atherosclerosis (23).

In patients with coronary artery disease studies have shown the level of inflammatory markers and its association with the non-surgical periodontal therapy.in a study conducted among patients with risk of cardiovascular disease it was shown that a significant reduction is reported in ESR and triglycerides levels in test group compared to the control subjects. This value decreased further after 6 months treatment. In addition, level of total cholesterol and CRP also decreased (23).

According to the findings of a cross-sectional study, serum hs-CRP levels in subjects with either angiographically proven coronary artery disease or chronic periodontitis were elevated two-fold compared with those of healthy individuals, whereas the levels were elevated threefold in subjects with both diseases (CAD plus periodontitis) (24).

In another study by Bokhari et al it was reported that non-surgical procedure can reduce the CRP level in systemic circulation (25). According to the findings of another study conducted by Zhou et al., non-surgical periodontal therapy can lower serum TNF-alpha, IL-6, and CRP levels in chronic periodontitis patients with stable coronary heart disease (26). According to a recent study, the level of systemic markers of atherosclerosis in chronic periodontitis patients with concomitant atherosclerosis can be changed significantly in comparison to systemically healthy patients and chronic periodontitis after nonsurgical periodontal treatment, according to Ertugrul et al. It is also known as scale and root planing, and it is a regular dental procedure that involves the removal of dental plaque and calculus from tooth surfaces, as well as oral hygiene guidelines to help patients maintain good oral health (27).

In contrast, Hada et al. found that both the intervention and control groups experienced a modest increase in the level of CRP over the 6-month follow-up period. However, the intervention group experiencing a less significant increase compared to the control group at 6 months. The findings indicate that scaling and root planing may have a favorable effect on the serum inflammatory markers fibrinogen, TNF-, and interleukin-6, despite the lack of data on these secondary outcomes in the research. All of the trials considered showed an improvement in periodontal parameters, as well as a decrease in systemic inflammatory indicators, as compared to baseline (28).

Rastogi et al reported that periodontal treatment have significant effect on the probing depth and bleeding on probing. Moreover, they have also reported that the markers of CAD such as CRP and WBC counts also lowered after the treatment (29).

In another study Safitri et al reported that scale root planing treatment is helpful in lowering the levels of atherosclerotic inflammatory biomarkers in periodontitis patients who also had

atherosclerosis. As a result, nonsurgical periodontal therapy may have greater ability to minimize the risk of atherosclerosis, which plays a significant role in the development of cardiovascular disease. Reviews of experimental and observational research with longer follow-up periods are required in order to produce more credible findings (30).

Conclusion

The available evidence suggests that routine nonsurgical periodontal therapy, which primarily consists of scaling and root planning of the dentition, may help patients with stable coronary artery disease to reduce their CRP and other serum inflammatory markers between periodontal maintenance visits. However, the available evidence is limited. A safe anti-inflammatory intervention, scaling and root planning is performed in the majority of cases without requiring the use of antimicrobial pharmacological agents, reducing the risk of adverse events and providing new treatment options for patients who are contraindicated for anti-inflammatory medications such as statins or ibuprofen. However, there exists a contrasting opinion in reported results and hence larger cohort studies are required with a longer follow-up duration that can add a value in preventing the secondary inflammatory conditions associated with the periodontitis. It is necessary to conduct more prospective randomized clinical trials with longer follow-up durations in order to determine whether routine periodontal treatment combined with the maintenance of good oral hygiene is beneficial in the prevention of secondary vascular events in patients with stable coronary heart disease by reducing systemic inflammatory burden.

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