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Effect of Dental Scaling and Root Planing on Serum Inflammatory Markers in Patients with Coronary Heart Disease: A Systematic Review

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Abstract

Background: Coronary heart disease is a common manifestation of atherosclerosis. Various inflammatory markers including C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and fibrinogen play role in the development of atherosclerosis. Periodontitis is the inflammation of teeth supporting structures initiated by bacteria of the oral biofilm. Several studies have shown that periodontitis is associated with increased levels of serum inflammatory markers involved in atherosclerosis. Recently, there is an increasing number of trials investigating the effect of scaling and root planing on reducing level of systemic inflammation between periodontal maintenance visits in patients with coronary heart disease to decrease the inflammatory burden in this targeted population and the risk of secondary cardiovascular event. **Objective:** The aim of this study is to conduct a systematic review to investigate the effect of dental scaling and root planning on reducing the serum levels of inflammatory markers in patients with stable coronary heart disease. **Method:** Electronic searches were conducted in PubMed, Scopus, Cochrane Library, ClinicalTrials.gov, World Health Organization (WHO) International Trials Registry Platform, and Google Scholar beta to identify randomized controlled trial evaluated the effect of scaling and root planing on the level of serum inflammatory markers in patients with stable coronary heart disease to those who have coronary heart disease but received no treatment or simple oral hygiene measures only. **Results:** A total of 358 studies were initially identified from the search; 4 studies met the inclusion criteria and were selected for this systematic review. All of the included studies have considered C-reactive protein as a main outcome measure. Only one study considered evaluating the effect on fibrinogen, another study on interleukin-6, and two studies on tumor necrosis factor-alpha. In general, the results of the included randomized controlled trials appear to support the effectiveness of scaling and root planing in reducing serum levels of inflammatory markers. However, most of the studies involved small sample sizes except for one study, and there was inconsistency between the studies in the time considered for assessing the change in the level of serum inflammatory markers. **Conclusion:** There is a low evidence from the current literature supporting the effect of scaling and root planing in reducing systemic inflammatory markers including C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and fibrinogen in patients with stable coronary heart disease. Future research should include observational studies to assess the effect of scaling and root planing in reducing the inflammatory burden in this targeted population and the risk of secondary cardiovascular event.

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Abstract

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Effect of Dental Scaling and Root Planing on Serum Inflammatory Markers in Patients with Coronary Heart Disease: A Systematic Review

Background:

Coronary artery disease is the most common type of cardiovascular disease affecting 16.5 million Americans (Benjamin et al, 2017). Coronary heart disease is a common manifestation of atherosclerosis. Inflammation plays a pivotal role in the development of atherosclerosis and the acute activation of the vascular wall with consequent local thrombosis and vasoconstriction (Liuzzo, 2001). Various inflammatory markers express different aspects of the inflammatory processes that contribute to atherosclerosis (Ikonomidis et al, 2012). A decently studied serum inflammatory marker is the C-reactive protein. C-reactive protein is a non-specific highly sensitive systemic marker of inflammation and a predictor of incident coronary heart disease (Koenig et al, 1999). A cut-off level of high sensitivity C-reactive protein (hs-CRP) of 2 mg/L seems to discriminate high from low risk patients with stable or unstable coronary disease or even apparently healthy individuals for short and long-term prognosis of cardiovascular event (Zakynthinos et al, 2009). Plasma fibrinogen have also been associated with atherosclerosis progression in patients with stable coronary heart disease (Danesh et al, 1998; Green et al, 2009; Shojaie et al, 2009). Moreover, Interleukin-6 plasma level could reflect the extent of inflammatory reactions in atherosclerotic vessels and improve the prediction of coronary heart disease risk (Luc et al, 2003). Recent large trial demonstrated that Interleukin-6 was independently associated with the risk of major coronary events in patients with stable coronary heart disease and may be a potential future target for the treatment of stable coronary heart disease (Held et al, 2017). During the past years, many efforts have been made to identify different risk factors for coronary heart disease and their contribution to systemic inflammation in order to offer targets for therapeutic and preventive interventions.

Mattila et al. (1989) conducted the first two case-control studies to examine the role of chronic dental infections including periodontitis as risk factors for coronary heart disease. Periodontitis is a chronic inflammation of teeth supporting structures. It involves a complex immune/inflammatory cascade that is initiated by the bacteria of the oral biofilm that forms naturally on the teeth (Cekici et al, 2000). The association between coronary heart disease and periodontitis has

been investigated by a significant body of evidence. A meta-analysis indicates that both the prevalence and incidence of coronary heart disease are significantly increased in periodontitis (Bahekar et al, 2007). Another systematic review and meta-analysis identifies periodontal disease as a risk factor for coronary heart disease that is independent of traditional coronary heart disease risk factors (Humphrey at al, 2008). Recent systematic review indicates the association between periodontitis and atherosclerosis, with elevated levels of inflammatory markers, mainly C-reactive protein and IL-6 (Almeida et al, 2017).

The proposed mechanism that links periodontitis with coronary heart disease is that the immune response in periodontitis affects systemic inflammatory burden by increasing the release of serum markers of inflammation. Several studies have shown that periodontitis is associated with increased levels of serum inflammatory markers involved in atherosclerosis. Loos at al. (2000) found higher serum concentrations of C-reactive protein, IL-6 and neutrophils in patients with generalized and localized periodontitis than in controls. A Case-control study showed an increased plasma concentration of risk markers for atherosclerosis such as C-reactive protein, fibrinogen and IL-18, particularly in patients with severe periodontitis (Buhlin, et al, 2009). Another study demonstrated that chronic periodontitis results in higher serum concentrations of C-reactive protein, IL-6, total leukocyte count and neutrophil. They found that patients in both chronic generalized and chronic localized periodontitis have higher mean CRP levels than in control group and that CRP level in the chronic generalized periodontitis group was statistically significant when compared to the control group (Gani et al, 2012).

Interventional studies showed that periodontal therapy can reduce systemic inflammation and level of serum inflammatory markers mainly C-reactive protein in otherwise healthy subjects (Caula et al, 2014; Leite et al, 2014). Recently, there is an increasing number of trials investigating the effect of mechanical non-surgical periodontal therapy in reducing levels of serum inflammatory markers in patients with coronary heart disease. The first prospective study to demonstrate the presence of higher circulating levels of the proinflammatory cytokines MCSF, IL-6, and IL-1b levels in patients with chronic stable angina compared with healthy controls, also showed that aspirin can reduce cytokines and CRP levels which may explain parts of its therapeutic action (Ikonomidis et al, 1999). A cross-sectional study found that 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 in subjects with both diseases (coronary artery disease plus chronic periodontitis) the levels were elevated three-fold (Kumar et al, 2014).

Bokhari et al. (2012) showed that in coronary heart disease patients with periodontitis, non-surgical mechanical periodontal therapy significantly reduced systemic levels of C-reactive protein, fibrinogen and white blood cells. Another study conducted by Zhou et al. (2013) concluded that non-surgical periodontal therapy decreased serum TNF-alpha, IL-6 and CRP levels in chronic periodontitis patients with stable coronary heart disease. Recently, Ertugrul et al. (2017) demonstrated that the level of systemic markers of atherosclerosis can be changed significantly in chronic periodontitis patients with concomitant atherosclerosis in comparison with systemically healthy patients and chronic periodontitis after non-surgical periodontal treatment. This periodontal treatment modality, also known as scaling and root planning, is a routine dental procedure that involves removal of dental plaque and calculus from teeth surfaces including oral hygiene instructions to maintain oral health.

In this study, we aim to systematically review the literature to assess the quality of the included studies, and to determine if they provide any evidence on the effect of scaling and root planing, which is the routine periodontal treatment in maintaining lower level of serum inflammatory markers in patients with stable coronary heart disease.

Objectives:

The aim of this study is to conduct a systematic review to investigate the effect of dental scaling and root planning on reducing the serum levels of inflammatory markers in patients with stable coronary heart disease.

Materials and Method:

Criteria for considering studies for this review

Type of studies

Studies assessing the effect of non-surgical scaling and root planing on the level of serum inflammatory markers in patients with stable coronary heart disease will

be included in the review. Randomized trials that compare the effect of non-surgical periodontal therapy on serum inflammatory markers in subjects with coronary heart disease compared to those who have coronary heart disease but received no treatment or simple oral hygiene measures only, will be eligible for the inclusion in the systematic review as they represent the most definite way of determining whether a cause-effect relation exists between treatment and outcome.

Type of participants

Studies were eligible for the inclusion in this review when they fulfilled the following criteria:

1. Patients with stable coronary heart disease confirmed by coronary angiography, and or history of angina or myocardial infarction.
2. Patients with chronic periodontitis with pocket depths of 4 mm or more are measured at more than one site and have no acute dental infection.
3. Included participants should not have received periodontal treatment within the past 6 months.
4. Blood samples collected at baseline just before the scaling root planning and at follow up time ranges from 2 to 6 months.

Type of Intervention

The intervention is non-surgical mechanical periodontal therapy, a procedure involving supragingival and subgingival scaling and root planning of teeth with oral hygiene instructions will be compared to no treatment or only simple oral hygiene instructions.

Type of Outcome measures

- **Primary outcome:**
  The main outcome was chosen to be a sensitive indicator in predicting cardiovascular risk: Reduction in serum concentration of C-reactive protein

- **Secondary outcomes:**
  Reduction in serum concentration of other proinflammatory biomarkers: including IL-6, TNF-α and fibrinogen

Exclusion Criteria:

- Studies considered the use of adjunctive local or systemic antimicrobial therapy
- Studies included smokers, pregnant patients or patients with other severe systemic conditions that could affect level of serum markers.
- Pilot studies
- Non-English literature
- Animal studies.

Electronic Searches

The following databases were searched with no publication year or publication status restrictions:

- PubMed (to May, 2018), using the strategy in Appendix 1
- Scopus (to May, 2018), using the strategy in Appendix 2
- Cochrane Central Register of Controlled Trials (CENTRAL) (to May, 2018), using the search strategy in Appendix 3

Searching other resources

The following trial registers were searched for completed studies:

- U.S. National Institutes of Health Trials Registry (ClinicalTrials.gov)
- World Health Organization (WHO) International Trials Registry Platform (www.who.int/ictrp/en/)

Gray literature was searched using the following resource:
- Google Scholar beta

Search Strategy

To identify studies considered for this review, searches conducted for each electronic database were modelled on a detailed search strategy developed for PubMed and modified for each database to accommodate differences in controlled vocabulary and syntax rules. The search was based on keywords and “Mesh” terms shown in appendices 1, 2 and 3.

Selection Process

The titles and abstracts identified through the electronic searches were screened and then assessed for eligibility criteria by full text as per PRISMA. RefWorks reference management software was used to merge search terms and deduplicate from the different databases. Studies not meeting the inclusion criteria were excluded and the reason for their exclusion is outlined (Table 2). The screening and selection process is demonstrated in a PRISMA flow diagram (Figure 1).

Data collection & management

Data extraction template from Cochrane Consumers and Communication Review Group for included studies (2015) available at http://cccrg.cochrane.org/author-resources, was used to record characteristics of the included studies in a table considering the following data (Table 1):

- General information (author, year, title, journal, dental procedure)
- Trial characteristics (sample size, type of study design, method of randomization, allocation concealment, blinding)
- Type of intervention (number of intervention groups, time between intervention and blood sampling, frequency)
- Characteristics of participants (total number of participants, age, gender, diagnostic criteria for both CVD and periodontitis)
- Type of outcome measures (Outcomes definitions and unit of measurements, time of collection)
- Miscellaneous (conclusion and source of funding/conflict of interest)

Assessment for the Risk of Bias

Two review authors independently assessed the risk of bias of the included randomized controlled trials using the Cochrane Collaboration tool criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins et al, 2011), at http://handbook.cochrane.org.

The following domains were assessed:

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)

- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other potential sources of bias, such as confounding bias.
  The judgements for assessing the risk of bias were categorized as 'low risk', as 'high risk, or as 'unclear risk' and interpreted as follows:

    - Low risk of bias: plausible bias unlikely to seriously alter the results if all domains were at low risk of bias.
    - Unclear risk of bias: plausible bias that raises some doubt about the results if one or more domains were at unclear risk of bias.
    - High risk of bias: plausible bias that seriously weakens confidence in the results if one or more domains were at high risk of bias.

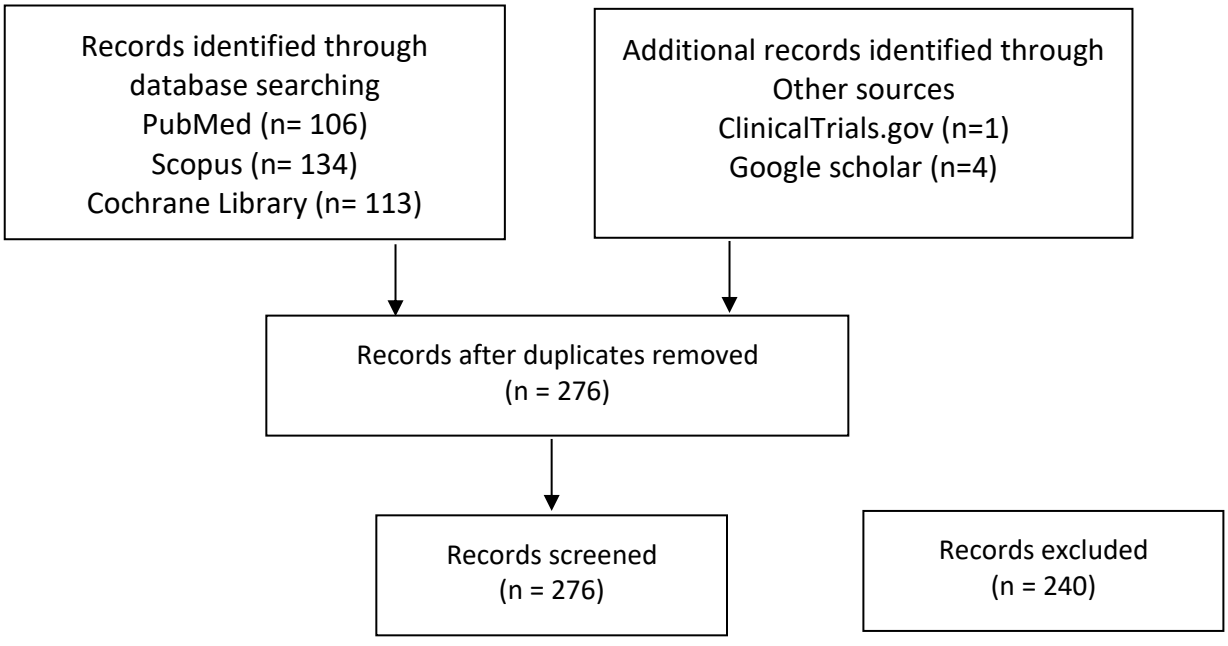
Statistical Analysis

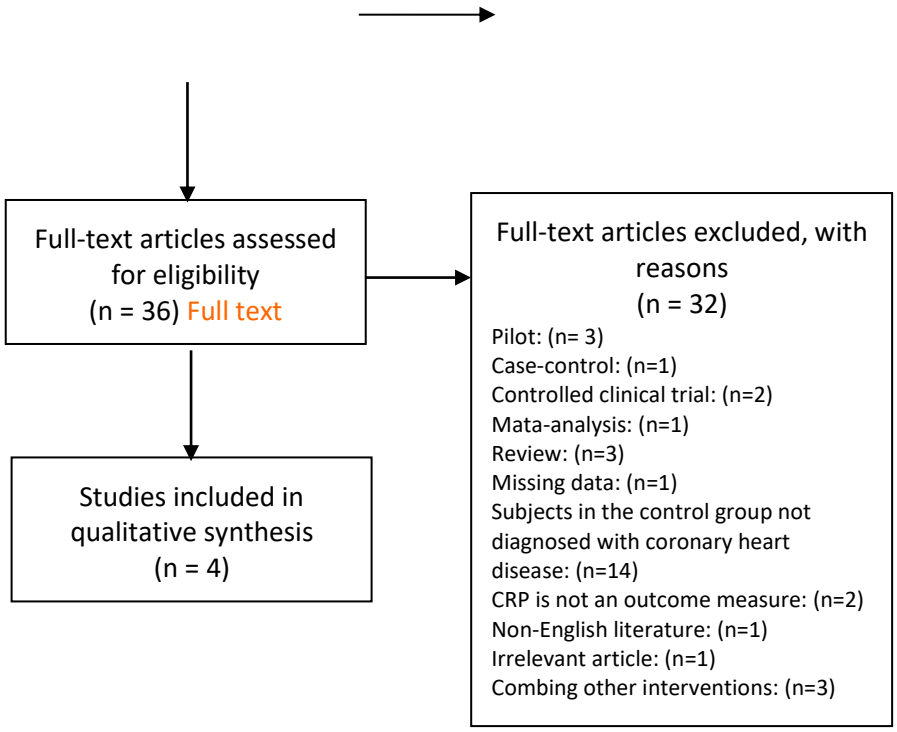
Assessment of heterogeneity

Statistical heterogeneity, which is the percentage of variation across the studies not due to chance was assessed using the I^2 statistics.

- 25-50% small degree of heterogeneity
- 50-75% moderate degree of heterogeneity
- 75-100% large degree of heterogeneity

Figure 1: Study Flow Chart





Results

A total of 358 studies were identified. Searching in PubMed and Scopus resulted in 106 and 134 studies, respectively. Searching in Cochrane Central Register of Controlled Trials resulted in 113 trials. Considering other sources, only 1 eligible study from clinicalTrials.gov and 4 eligible studies from Google Scholar could be retrieved. The search of the World Health Organization (WHO) International Trials Registry Platform resulted did not identify any relevant trial. After deduplications of the results using RefWorks reference management software, we resulted in 276 studies. Screening by title and abstract resulted in the elimination of most of the studies that were clearly ineligible. Full text evaluation of the remaining 36 articles resulted in excluding 32 articles and the identification of 4 eligible studies assessing the effect of non-surgical periodontal therapy on serum inflammatory markers in patients with periodontitis and coronary heart disease (Table 1). Reasons for excluding the 32 articles after full text evaluation are listed in (Table

2). Refer to ‘Study flow chart’ showing the stages of the screening and the number of studies filtered at each stage (Figure 1).

Study Characteristics

The four selected studies were randomized controlled trials published in English. One Study was conducted in Pakistan (Bokhari et al, 2012), One in China (Zhou et al, 2013), and two in India (Hada et al, 2015; Koppolu et al, 2013). The included studies involved a total of 502 participants with 307 patients in the intervention group and 195 in the control group. The mean age ranges from (49.0±0.6 to 62.11±9.30) years in the intervention group and from (50.1±0.9 to 62.48±12.24) years in the control group. In the study conducted by (Bokhari et al, 2012) 64 subjects were dropped out from the trial due to changes in their medical history or due to personal and logistic reasons. Ten patients out the 64 were exited from the study because they received percutaneous cardiac intervention (PCI) or other cardiac intervention. In another study (Hada et al, 2015) twelve patients were excluded because they were hospitalized for cardiac reasons. Only one patient was lost from (Koppolu et al, 2013) study and no patient withdrew from the study by (Zhou et al, 2013). The intervention of the 4 studies was non-surgical scaling and root planing combining curettes and ultrasonic instruments at baseline with no adjunctive antimicrobial or laser therapy.

Although the included studies have met all planned inclusion criteria, they differed in many ways. Number of scaling and root planing sessions varied among the studies between 2 to 4 sessions in 24 hours to 3 weeks interval. In addition, the time for sample collections also differs among the trials. Other than baseline sample collection, one trial (Koppolu et al, 2013) considered re-sampling at 2 months follow up and another trial (Zhou et al, 2013) at 3 months. In the study done by (Bokhari et al, 2012) blood samples were collected at two intervals, 1 month and 2 months and in (Hada et al, 2015) blood sampling was at three intervals, 1 month, 3 months and 6 months follow ups. C- reactive protein was reported in all of the studies, whereas TNF-α in 2 studies and IL-6 and Fibrinogen each in one study. Regarding the diagnostic criteria for stable coronary heart disease, two studies (Bokhari et al, 2012; Zhou et al, 2013) clearly stated that the diagnosis of stable CHD has to be proven angiographically. In the other two studies the criteria were history of cardiovascular event. Moreover, the studies considered different diagnostic criteria for periodontitis for the inclusion of their participants. Further details in ‘Characteristics of the included studies’ (Table 1).

Risk of Bias in Included Studies

Quality assessment of selected studies was performed with the Cochrane Collaboration tool for assessing risk of bias (Higgins et al, 2011).

Randomization was clearly reported in 2 studies, in which allocation of patients into intervention and control groups was concealed using sealed envelopes (Bokhari et al, 2012; Hada et al, 2015). In (Zhou et al, 2013) Patients were given the option to be in the intervention group or the treatment group, which considered a high risk of selection bias. The process of randomization and allocation concealment were not clearly described by (Koppolu et al, 2013).

Due to the nature of the intervention (scaling and root planing) blinding of patients was not possible in all of the trials. Blinding of outcome assessment was mentioned by two trials (Bokhari et al, 2012; Hada et al, 2015), but was not clear for the other two studies (Koppolu et al, 2013; Zhou et al, 2013). All of the studies demonstrated low risk attrition bias and selective reporting bias (Table 3).

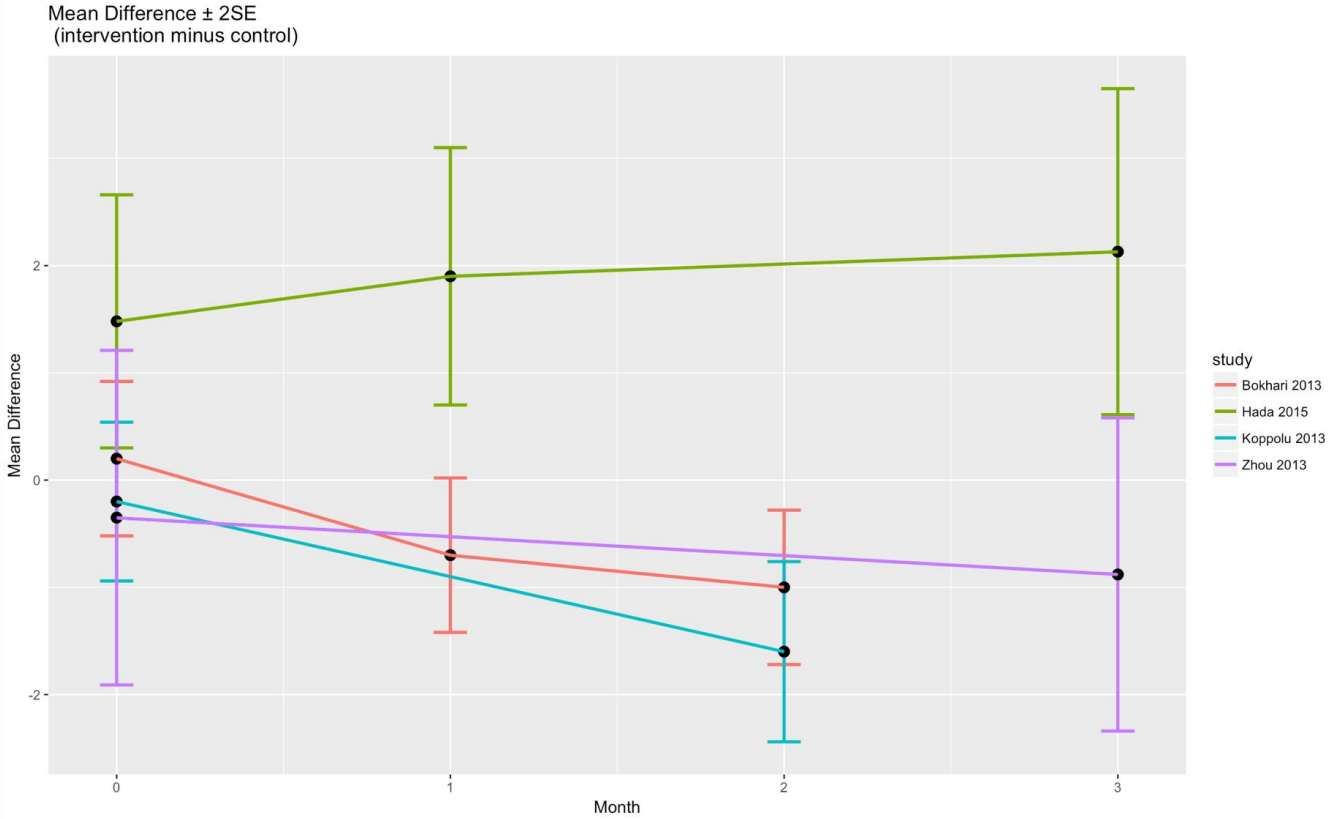
Effect of Intervention

Primary outcome

All included randomized clinical trials have considered C-reactive protein (CRP) as their primary outcome. At baseline, there was no significant difference found in the level of (CRP) between the intervention and control groups in three of the studies (Bokhari et al, 2012; Koppolu et al, 2013; Zhou et al, 2013). One study noted a statistically significant difference in the level of (CRP) between the treatment and control groups (intergroup) at baseline (Hada et al, 2015), which remarkably contributed to heterogeneity among the studies. In addition, C-reactive protein along with other studies parameters were assessed at baseline before the intervention and over variable follow up periods of 2 months (Bokhari et al, 2012; Koppolu et al, 2013), 3 months (Hada et al, 2015; Zhou et al, 2013), and 6 months (Hada et al, 2015). Heterogeneity was calculated at baseline using the I^2 statistics with 95% confidence interval, I^2= 53%, which considered a moderate heterogeneity. Due to lack of consistency, it was difficult to pool the overall effect of in one forest plot.

Three of the four RCTs showed a statistically significant reduction in the level of (CRP) in the intervention group compared to the control from baseline to follow up visits which ranged between 2 and 3 months (Bokhari et al, 2012; Koppolu et al, 2013; Zhou et al, 2013). Hada et al. (2015) observed statistically non-significant increase in the level of (CRP) in the intervention group compared with statistically significant increase in the control group at 6 months follow up (Table 4). Mean plot used to demonstrate IL- (Figure 2).

Figure 2: Mean plot: showing changes in mean differences over follow-up periods for C-reactive protein (CRP)



Secondary outcomes

Secondary outcomes of our review include interleukin-6, Tumor necrosis factor-α and Fibrinogen. There were variations between the included trials in considering the cardiovascular inflammatory risk markers being evaluated in each individual study. In regards to serum fibrinogen, only one study (Bokhari et al, 2012) have compared the change in its value between the intervention and the control group from baseline to 1 month and 2 months intervals. The study showed a significant reduction in the mean ±SE between baseline fibrinogen (367.1±10.4 mg/L) and at 1 month follow up visit (305.3±8.7 mg/L) and 2 months visit (299.3±8.0 mg/L) only for the intervention group with a statistically significant difference (*P* =0.01) in comparison with the control group at 2 months follow up (335.9±11.8 mg/L). Comparing the change in tumor necrosis factor-α (TNF-α) level between intervention and control group was evaluated by two studies (Koppolu et al, 2013; Zhou et al, 2013). Koppolu et al. (2013) found a statistically significant (*P* <0.001) reduction in the mean value of serum (TNF-α) in the intervention group from (22.14±1.46 to 20.2±1.61 pg/dl) compared to not statistically significant reduction in the control group (*P* >0.05) from (22.85±1.29 to 22.68 pg/dl) at 2 months follow up. Comparably, (Zhou et al, 2013) showed a reduction in the mean value of serum (TNF-α) at 3 months follow up from baseline in the intervention group (39.88±33.83 pg/ml) to (28.99±16.56 pg/ml) which was statistically significant (*P* =0.048), but not in the control group (49.61±69.60 pg/ml) to (50.64±86.33 pg/ml). Concerning serum interleukin-6 (IL-6), only one of the included trials had evaluated the reduction in its value from baseline to 3 months follow up visit (Zhou et al, 2013). The mean value of (IL-6) was statistically significantly reduced in the intervention group (*P* =0.049) from (38.61±21.87 pg/ml) to (31.40±20.32), but not in the control group, in which the value had increased (39.12±24.31 pg/ml) to (42.56±23.81 pg/ml).

Discussion

The aim of this study is to conduct a systematic review to investigate the effect of dental scaling and root planning on reducing the serum levels of inflammatory markers in patients with stable coronary heart disease. We summarized the current

literature of randomized clinical trials assessing the effect of routine non-surgical scaling and root planing on serum C-reactive protein, as the main outcome measure, fibrinogen, TNF-α and interleukin-6 in patients with history of coronary heart disease and are clinically stable at the time of investigation.

The main limitation of the present systematic review is that the changes in serum levels of the inflammatory markers were assessed at different follow up (sampling) periods that ranges between 2 months (Bokhari et al, 2012; Koppolu et al, 2013), 3 months (Hada et al, 2015; Zhou et al, 2013), and 6 months (Hada et al, 2015). This inconsistency makes it difficult to pool the results and to perform a meta-analysis. Additional limitations of this review include the small number of included studies and the small sample sizes except for (Bokhari et al, 2012). Moreover, there were variations in the consideration of the secondary outcome measures among the trials.

In general, the results of the included randomized clinical trials appear to support the effectiveness of scaling and root planing in reducing serum levels of inflammatory markers C-reactive protein, fibrinogen, TNF-α and interleukin-6 over a period of 2-3 months. However, random sequence generation was not clearly reported in one study (Koppolu et al, 2013) and in another study, the patients were given the option to be in the intervention group or the treatment group (Zhou et al, 2013). In Hada et al. (2015) study, there was a slight increase in level of CRP over the follow up period in both the intervention and the control groups, but the increase in the intervention group was less significant compared to the control group at 6 months. With the limited data on investigating the secondary outcomes, the studies indicate that scaling and root planing could have a positive effect on serum inflammatory markers fibrinogen, TNF-α and interleukin-6. All the included studies demonstrated improvement in periodontal parameters along with the reduction in systemic inflammatory markers.

Chronic periodontitis is caused by bacteria attached to teeth surfaces and is characterized by gingival erythema, bleeding, loss of tooth surrounding structures, mobility and eventually tooth loss. It contributes to systemic inflammation characterized by elevation of acute phase proteins, including inflammatory cytokines such as interleukin-6, coagulation factors such as fibrinogen, and CRP (Lockhart et al, 2012). Induction of CRP in hepatocytes in response to inflammation is mainly regulated by cytokines like interleukin-6, interleukin-1β (Black et al, 2004), and Tumor necrosis factor-α (Ebersole et al, 2000). C-reactive protein has been strongly associated with coronary heart disease. A meta-analysis found relative risk for incident coronary heart disease was 1.58 (95% CI, 1.37 to 1.83) for CRP levels > 3.0 mg/L compared with CRP levels <1.0 mg/L (Buckley et al, 2009). A Framingham Heart Study to assess the role of CRP on vascular risk, concluded that CRP levels help to estimate risk for

initial cardiovascular events and may be used most effectively in persons at intermediate risk for vascular events (Wilson et al, 2008). The American College of Cardiology/American Heart Association 2013 guidelines on the assessment of cardiovascular risk, recommend the use of additional risk markers including hs-CRP, when risk-based decisions about initiation of pharmacological therapy are uncertain, after quantitative risk assessment, with CRP with ≥2 mg/L support revising risk assessment (Goff et al, 2013).

Many pharmacological agents have been evaluated to suppress C-reactive protein. However, they have not been associated with atherosclerotic cardiovascular disease event reduction, or their predominant cardiovascular benefits could be attributed to another mechanism of action such as aspirin and statins (Martinez et al, 2018). Methotrexate suppresses systemic inflammation including serum CRP was associated with a 21% lower risk for total CVD (n = 10 studies, 95% confidence interval [CI] 0.73 to 0.87, p <0.001) and an 18% lower risk for myocardial infarction (n = 5, 95% CI 0.71 to 0.96, p = 0.01) in systematic review and meta-analysis on patients with rheumatoid arthritis, psoriasis, or polyarthritis (Micha et al, 2011).

With the limitations of the available evidence, it suggests that routine non-surgical periodontal therapy, which mainly consists of scaling and root planing of the dentition, may progressively reduce level of CRP and other serum inflammatory markers between periodontal maintenance visits in patients with stable coronary heart disease. Scaling and root planing considered a safe anti-inflammatory intervention (Achtari et al, 2012), in which the majority of cases do not require antimicrobial pharmacological agents and thus reducing the potential for adverse events and offering new treatment options for patients with contraindications for anti-inflammatory medications such as statins or aspirin (Demmer et al, 2013).

More prospective randomized clinical trials of longer follow up durations are required to sufficiently assess whether routine periodontal treatment with the maintenance of good oral hygiene would add a value in the prevention secondary vascular events by reducing systemic inflammatory burden in patient with stable coronary heart disease. However, it might be unethical to rely on RCTs to assess the effect of scaling and root planing over a long follow up duration, > 6 months, in which the participants in the control group need to be precluded from receiving prophylactic scaling and root planing for the maintenance of their oral health. Instead, well-designed observational studies, such as cohort or case-control designs may add a value in evaluating the effect of scaling and root planing on cardiovascular risk. Interpretation of the results obtained from both RCTs and observational

studies can help understand the efficacy/effectiveness and safety of a therapeutic option (Faraoni & Schaefer, 2016). Most of the observational studies were conducted to correlate coronary heart disease with periodontal disease, but not periodontal interventions. A retrospective cohort study used insurance claimed data from 338,891 individuals followed up from 2005 to 2009, investigated the effect of periodontal treatment on medical costs and hospitalization among individuals with type 2 diabetes, coronary heart disease, cerebral vascular disease, rheumatoid arthritis, and pregnancy. They found that patients with diabetes or cardiovascular disease showed a significant 20%-40% reductions in both outcomes relative to controls, which appeared to persist up to 3 years after initial periodontal therapy (Jeffcoat et al,2014).

Furthermore, testing biomarkers such as total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, serum creatinine (estimated glomerular filtration), and fasting blood glucose for the evaluation of modifiable risk factors for the progression of atherosclerosis is also fundamental to direct secondary preventive measures in patients with stable coronary heart disease (Morrow et al, 2010).

Conclusion

There is a low evidence from the current literature supporting the effect of scaling and root planing in reducing systemic inflammatory markers including C-reactive protein, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and fibrinogen in patients with coronary heart disease. Future research should include observational studies to assess the effect of scaling and root planing in reducing the inflammatory burden in this targeted population and the risk of secondary cardiovascular event.

Table 1: Characteristics of Included studies

Author(s), year	Study design	Sample size	Periodontal therapy	Diagnostic Criteria for Coronary heart disease	Diagnostic Criteria for Periodontal disease	Intervals between blood samples	Outcome measures	Conclusion
Bokhari et al, 2013	RCT	*n* = 317 Intervention group (*n* =212) Control group (*n* =105)	Non-surgical periodontal therapy included supra- and sub-gingival scaling and root planning and oral hygiene instructions in 2 to 4 visits within 10 days	Stable angiographically proven CHD; defined having > 50% stenosis of >1 coronary artery documented by angiography	≥ 4 teeth with ≥1 site with periodontal probing depth (PPD) ≥ 4 mm and clinical attachment level (CAL) ≥ 3 mm at same site, bleeding on Probing (BOP) >20%	Blood samples collected between 8 a.m.-12 p.m. (to control diurnal variations) at baseline, at 1 month and 2 months follow up visits.	**Primary outcome:** Change in CRP level at 1 and 2 months after completion of SRP **Secondary outcome:** Fibrinogen and WBCs level at 2 months after completion of SRP	**CRP baseline (mg/L):** Control: 4.2±0.3 Intervention: 4.4±0.2 **CRP at 1 month (mg/L):** Control: 4.1±0.3 Intervention: 3.4±0.2 **CRP at 2 months (mg/L):** Control: 4.1±0.3 Intervention: 3.1±0.2 **Fibrinogen baseline (mg/L):** Control: 339.6±10.5 Intervention:367.1±10.4 **Fibrinogen at 1 month (mg/L):** Control: 325.5±9.6 Intervention:305.3.3±8.7 **Fibrinogen at 2 months (mg/L):** Control: 335.9±11.8 Intervention:299.3 ±8.0
Hada et al, 2015	RCT	*n* = 70 Intervention group (*n* =35)	Non-surgical periodontal therapy included scaling and root planing and oral	Stable CHD, including stable angina, STEMI and non-STEMI and in which symptoms remained	Mild to moderate chronic periodontitis with ≥ 4 teeth with clinical attachment	Blood samples collected at baseline, and at 1, 3, and 6 months	**Primary outcome:** Change in CRP level at 1, 3, and 6 months after completion of SRP	**CRP baseline (mg/L):** Control: 3.62±2.31 Intervention: 5.10±2.00 **CRP at 1 month (mg/L):** Control: 4.31±2.43 Intervention: 6.21±1.92

		Control group (*n* =35)	hygiene instructions in 2 sittings with 24 hours interval	stable for at least 60 days and no evidence of recent myocardial damage	loss (CAL) ≤ 4 mm at ≥ 1 site	follow up visits	**Secondary outcome:** Changes in lipid profile, WBC profile, and systolic BP at 1, 3, and 6 months after completion of SRP	**CRP at 3 months (mg/L):** Control: 4.09±1.82 Intervention: 6.22±3.64 **CRP at 6 months (mg/L):** Control: 4.94±2.04 Intervention: 6.30±7.53
Koppolu et al, 2013	RCT	*n* = 40 Intervention group (*n* =20) Control group (*n* =20)	Non-surgical periodontal therapy included scaling and root planing performed once a week for 3 weeks	History of myocardial infarction	Probing depth of ≥ 5 mm evaluated at 4 sites per tooth	Blood samples collected at baseline and at 8 weeks follow up visit	**Primary outcome:** Change in CRP and TNF-alpha level at 8 weeks	**CRP baseline (µg/dl):** Control: 0.47±0.11 Intervention: 0.45±0.12 **CRP at week 8 (µg/dl):** Control: 0.45±0.14 Intervention: 0.29±0.12 **TNF-α at baseline (pg/dl):** Control: 22.85±1.29 Intervention: 22.14±1.46 **TNF-α at week 8 (pg/dl):** Control: 22.68±1.23 Intervention: 20.20±1.61
Zhou et al, 2013	RCT	*n* = 75 Intervention group (*n* =40) Control group (*n* =35)	Non-surgical periodontal therapy included supragingival scaling and four sessions of quadrant root debridement with oral hygiene instructions	Stable CHD with one of the following criteria: previous history of myocardial infarction, or angioplasty surgery more than 6 months previously, or proven coronary or left main stem vessel obstruction by more than 50% by angiography	More than 30% of teeth with probing depth (PD) ≥ 4 mm and clinical attachment loss (CAL) ≥ 3 mm, and with alveolar bone loss >30% of the root length shown on Panoramic radiograph. In addition, at least 2 teeth showed both (PD) ≥ 5 mm and (CAL) ≥ 3 mm distributed in different quadrants	Blood samples collected between 8 a.m.-10 a.m. at baseline and at 3 months follow up visit	**Primary outcome:** Change in CRP, TNF-alpha and IL-6 serum level at 3 months **Secondary outcomes:** Change in WBC counts, total cholesterol, triglyceride, HDL, LDL and blood glucose level at 3 months	**CRP baseline (mg/L):** Control: 2.96±3.55 Intervention: 2.61±3.16 **CRP 3 months (mg/L):** Control: 2.94±3.62 Intervention: 2.06±2.54 **TNF-α at baseline (pg/dl):** Control: 49.61±69.60 Intervention: 39.88±33.83 **TNF-α at 3 months (pg/dl):** Control: 50.64±86.33 Intervention: 28.99±16.56 **IL-6 at baseline (pg/dl):** Control: 39.12±24.31 Intervention: 38.61±21.87 **IL-6 at 3 months (pg/dl):** Control: 42.56±23.81 Intervention: 31.40±20.32

Table 2: Characteristic of Excluded Studies

Study	Reason for exclusion
Arrol et al. (2015). Relationship of root canal treatment to C-reactive protein as an inflammatory marker for cardiovascular disease	Root canal therapy is the only dental intervention
Arvanitidis et al. (2017) Reduced platelet hyper-reactivity and platelet-leukocyte aggregation after periodontal therapy	Controlled clinical trial and different outcome measures for the evaluation of cardiovascular risk
Beck et al. (2008). The Periodontitis and Vascular Events (PAVE) pilot study: adverse events	Pilot Study
Bresolin et al. (2013). Lipid profiles and inflammatory markers after periodontal treatment in children with congenital heart disease and at risk for atherosclerosis	Pediatric Population with variations in the diagnosis of congenital heart diseases
Caula et al. (2014). The effect of periodontal therapy on cardiovascular risk markers: A 6-month randomized clinical trial	Subjects with periodontits were not diagnosed with coronary heart disease
D'Aiuto et al. (2006). Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial.	Subjects with periodontitis were systemically healthy
D'Aiuto et al. (2005). Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol	Subjects with periodontitis were systemically healthy
D'Aiuto et al. (2004). Periodontitis and atherogenesis: Causal association or simple coincidence	Pilot Study Subjects with periodontitis were systemically healthy

D'Aiuto et al. (2007). Acute effects of periodontal therapy on bio-markers of vascular health	Subjects with periodontitis were systemically healthy Follow and up to 30 days
Gao et al. (2016). Effects of essential periodontal treatment on serum level of sCD40L and periodontal clinical parameters in patients with moderate to severe periodontitis at high risk of stroke	Different outcome measures Non- English literature (Chinese)
Ide et al. (2003). Effect of treatment of chronic periodontitis on levels of serum markers of acute-phase inflammatory and vascular responses	Subjects with periodontitis not coronary heart disease
Javed et al. (2016). Effect of Nd:YAG laser-assisted non-surgical periodontal therapy on clinical periodontal and serum biomarkers in patients with and without coronary artery disease: A short-term pilot study	Pilot study Intervention is laser assisted non-surgical periodontal therapy
Lapez et al. (2012). Effects of periodontal therapy on systemic markers of inflammation in patients with metabolic syndrome: A controlled clinical trial	Subjects with metabolic syndrome Controlled clinical trial
Leite et al. (2014). Effects of periodontal therapy on C-reactive protein and HDL in serum of subjects with periodontitis	Subjects with periodontitis were systemically healthy
Li et al. (2011). Effect of periodontal treatment on circulating CD34 + cells and peripheral vascular endothelial function: A randomized controlled trial	Subjects with periodontitis were systemically healthy Different outcome measures
Lobo et al. (2016). Treating Periodontal Disease in Patients With ST-Elevation Myocardial Infarction: A Randomized Clinical Trial	Missing Data
Lowe (2004) Dental Disease, Coronary Heart Disease and Stroke, and Inflammatory Markers: What Are the Associations, and What Do They Mean?	Review article

Merchant et al. (2017). Evaluating Periodontal Treatment to Prevent Cardiovascular Disease: challenges and Possible Solutions	Review article
Meuman et al. (2004). Oral health, atherosclerosis, and cardiovascular disease	Review article
Monteiro et al. (2012). Measurement of the nonlinear optical response of low-density lipoprotein solutions from patients with periodontitis before and after periodontal treatment: evaluation of cardiovascular risk markers	Study excluded patients with history of cardiovascular disease
Payne et al. (2011). The effect of subantimicrobial-dose-doxycycline periodontal therapy on serum biomarkers of systemic inflammation: a randomized, double-masked, placebo-controlled clinical trial	Periodontal therapy included use of doxycycline
Ramarez et al. (2014). Biomarkers of cardiovascular disease are increased in untreated chronic periodontitis: A case control study	Case control study
Renvert et al. (2009). Short-term effects of an anti-inflammatory treatment on clinical parameters and serum levels of C-reactive protein and proinflammatory cytokines in subjects with periodontitis	Intervention included a combination of dipyridamole and prednisolone (CRx-102)
Sharma et al. (2014). A study of C-reactive protein, lipid metabolism and peripheral blood to identify a link between periodontitis and cardiovascular disease	Subjects with periodontitis were systemically healthy
Skilton et al. (2011). The effect of a periodontal intervention on cardiovascular risk markers in Indigenous Australians with periodontal disease: The PerioCardio study	Study excluded patients with history of cardiovascular disease

Seymour et al. (1998). Is there a link between periodontal disease and coronary heart disease?	Meta-analysis
Tuter et al. (2007). Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease	Both intervention and control groups received periodontal therapy with/or without doxycycline respectively
Taylor et al. (2010). The effect of initial treatment of periodontitis on systemic markers of inflammation and cardiovascular risk: A randomized controlled trial	Participants not diagnosed with coronary heart disease
Thaker et al. (2010). Evaluation of the C-reactive protein serum levels in periodontitis patients with or without atherosclerosis	Case control study
Tonetti et al. (2007). Treatment of periodontitis and endothelial function	Study excluded patients with history of cardiovascular disease
Tonregeani et al. (2016). Evaluation of periodontitis treatment effects on carotid intima-media thickness and expression of laboratory markers related to atherosclerosis	Different outcome measures
Vidal et al. (2009). Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension	Participants not diagnosed with coronary heart disease

Table 3: Risk of Bias Assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Bokhari et al , 2013						
Hada et al, 2015						
Koppolu et al, 2013						
Zhou et al, 2013						

Key: Low risk High risk unclear

Standard Deviation: *, Standard Error: ^

Appendices:

Appendix 1:

PubMed=106: ((("Cardiovascular Diseases"[Mesh] OR Cardiovascular Diseases OR Cardiovascular Disease OR Cardiovascular OR arteriosclerosis OR atherosclerosis OR "Atherosclerosis"[Mesh] OR "Arteriosclerosis"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Acute Coronary Syndrome"[Mesh] OR Myocardial Ischemia OR ischemic heart disease OR ischemic heart diseases OR myocardial infarction OR myocardial infarctions OR "Myocardial Infarction"[Mesh] OR Myocardial Infarct OR coronary diseases OR coronary disease OR coronary heart diseases OR coronary heart disease OR "Coronary Disease"[Mesh])) AND (((alveolar bone OR "Alveolar Bone Loss"[Mesh] OR "Bone

Table 4: Changes in CRP level over follow up periods

Study	Sample Size	CRP at Baseline	CRP at 1 month	CRP at 2 months	CRP at 3 months	CRP at 6 months
Bokhari et al, 2013	Control group (n= 85) Intervention (n= 161) Total n= 246	Control: (4.2± 0.3 mg/L)^ (4.2± 2.8 mg/L)* Intervention: (4.4±0.2 mg/L)^ (4.4± 2.5 mg/L)*	Control: (4.1±0.3 mg/L)^ (4.1± 2.8 mg/L)* Intervention: (3.4±0.2 mg/L)^ (3.4± 2.5 mg/L)*	Control: (4.1±0.3 mg/L)^ (4.1± 2.8 mg/L)* Intervention: (3.1±0.2 mg/L)^ (3.1± 2.5 mg/L)*	Not Applicable	Not Applicable
Hada et al, 2015	Control group (n= 25) Intervention (n= 30) Total n= 55	Control: (3.62±2.31 mg/L)* Intervention: (5.10±2.00 mg/L)*	Control: (4.31±2.43 mg/L)* Intervention: (6.21±1.92 mg/L)*	Not Applicable	Control: (4.09±1.82 mg/L)* Intervention: (6.22±3.64 mg/L)*	Control: (4.94±2.04 mg/L)* Intervention: (6.30±7.53 mg/L)*
Koppolu et al, 2013	Control group (n= 19) Intervention (n= 20) Total n= 39	Control: (0.47±0.11 µg/dl)* Intervention: (0.45±0.12 µg/dl)*	Not Applicable	Control: (0.45±0.14 µg/dl)* Intervention: (0.29±0.12 µg/dl)*	Not Applicable	Not Applicable
Zhou et al, 2013	Control group (n= 35) Intervention (n= 40) Total n= 75	Control: (2.96±3.55 mg/L)* Intervention: (2.61±3.16 mg/L)*	Not Applicable	Not Applicable	Control: (2.94±3.62 mg/L)* Intervention: (2.06±2.54 mg/L)*	Not Applicable

Resorption"[Mesh] OR Alveolar bone loss OR "bone loss" OR periodontal attachment loss OR "Periodontal Attachment Loss"[Mesh] OR periodontitis OR periodontal disease

OR periodontal diseases OR "Periodontal Diseases"[Mesh] OR "Gingival Diseases"[Mesh] OR chronic periodontitis OR Gingival disease OR Gingival diseases OR "Chronic Periodontitis"[Mesh] OR periodontal index OR "Periodontal Index"[Mesh] OR "Gingival Pocket"[Mesh] OR "Periodontal Pocket"[Mesh])) OR (periodontal therapy OR periodontal treatment OR periodontal treatments OR periodontal index OR "Periodontal Index"[Mesh] OR dental prophylaxis OR "Dental Prophylaxis"[Mesh] OR periodontal debridement OR subgingival debridement OR subgingival curettage OR "Periodontal Debridement"[Mesh] OR "Subgingival Curettage"[Mesh] OR scaling OR "Dental Scaling"[Mesh] OR root planing OR "Root Planing"[Mesh] OR scaling root planing OR subgingival scaling OR supragingival scaling OR non-surgical dental OR non-surgical periodontal OR non-surgical dental therapy OR non-surgical periodontal therapy OR non-surgical periodontal treatment))) AND (Biomarkers OR "Biomarkers"[Mesh] OR Biomarker OR inflammatory markers OR serum markers OR biological markers OR plasma level OR inflammatory mediators OR Proinflammatory mediators OR Pro-inflammatory mediators OR Pro-inflammatory mediator OR Proinflammatory mediator OR inflammatory mediator OR inflammatory marker OR biomarker OR serum marker OR interleukin OR interleukins OR "Interleukins"[Mesh] OR IL6 OR IL-6 OR interleukin 6 OR "Interleukin-6"[Mesh] OR "IL6 protein, human" [Supplementary Concept] OR Tumor Necrosis Factor-alpha OR Tumour Necrosis Factor-alpha OR tumor necrosis-alpha OR tumor necrosis factor-α OR “Tumor Necrosis Factor-alpha"[Mesh] OR "TNF protein, human" [Supplementary Concept] OR tnf alpha OR tnf-alpha OR tnf-α OR c-reactive protein OR "C-Reactive Protein"[Mesh] OR C-reactive proteins OR cytokines OR cytokine OR "Cytokines"[Mesh] OR fibrinogen OR "Fibrinogen"[Mesh] OR fibrinogens OR "Gingival Crevicular Fluid/chemistry"[Mesh] OR "Gingiva/immunology"[Mesh]) Filters: Randomized Controlled Trial; Clinical Trial

Appendix 2:

Scopus=134: (TITLE-ABS-KEY (cardiovascular W/2 disease*) OR TITLE-ABS-KEY (cardiovascular) OR TITLE-ABS-KEY (arteriosclerosis) OR TITLE-ABS-KEY (atherosclerosis) OR TITLE-ABS-KEY (acute PRE/0 coronary PRE/0 syndrome*) OR TITLE-ABS-KEY ({Myocardial Ischemia}) OR TITLE-ABS-KEY (ischemic PRE/0 heart PRE/0 disease*) OR TITLE-ABS-KEY (myocardial PRE/0 infarct*) OR TITLE-ABS-KEY (coronary W/2 disease*)) AND (TITLE-ABS-KEY ({alveolar bone}) OR TITLE-ABS-KEY ({Alveolar Bone Loss}) OR TITLE-ABS-KEY (bone W/2 resorption) OR TITLE-ABS-KEY ({Periodontal attachment loss}) OR TITLE-ABS-KEY (periodontitis) OR TITLE-ABS-KEY (periodont* W/2 disease*) OR TITLE-ABS-KEY ({chronic periodontitis}) OR TITLE-ABS-KEY (gingiva* W/2 disease*) OR TITLE-ABS-KEY (periodontal PRE/0 ind*) OR TITLE-ABS-KEY (gingival PRE/0 pocket*) OR TITLE-ABS-KEY (periodontal PRE/0 pocket*)) OR (TITLE-ABS-KEY (periodont* W/2 therapy) OR TITLE-ABS-KEY (periodont* W/2 treatment*) OR TITLE-ABS-KEY (

periodontal PRE/0 ind*) OR TITLE-ABS-KEY ({dental prophylaxis}) OR TITLE-ABS-KEY (periodont* W/2 debridement*) OR TITLE-ABS-KEY (subgingival PRE/0 debridement*) OR TITLE-ABS-KEY (subgingival PRE/0 curettage) OR TITLE-ABS-KEY (scaling) OR TITLE-ABS-KEY (root PRE/0 planing) OR TITLE-ABS-KEY (scaling PRE/0 root PRE/0 planing) OR TITLE-ABS-KEY (subgingival PRE/0 scaling) OR TITLE-ABS-KEY (supragingival PRE/0 scaling) OR TITLE-ABS-KEY (non-surgical W/2 dental) OR TITLE-ABS-KEY (non-surgical W/2 periodont*) OR TITLE-ABS-KEY (non-surgical AND dental AND therapy) OR TITLE-ABS-KEY (non-surgical PRE/0 periodontal PRE/0 therapy) OR TITLE-ABS-KEY (non-surgical PRE/0 periodontal PRE/0 treatment)) AND (TITLE-ABS-KEY (biomarkers) OR TITLE-ABS-KEY (bio-marker) OR TITLE-ABS-KEY (inflammat* W/2 marker*) OR TITLE-ABS-KEY (serum W/2 marker*) OR TITLE-ABS-KEY (biological PRE/0 marker*) OR TITLE-ABS-KEY ({plasma level}) OR TITLE-ABS-KEY (inflammat* W/2 mediator*) OR TITLE-ABS-KEY (proinflammatory AND mediator*) OR TITLE-ABS-KEY (pro-inflammatory AND mediator*) OR TITLE-ABS-KEY (interleukin) OR TITLE-ABS-KEY (interleukins) OR TITLE-ABS-KEY (il6) OR TITLE-ABS-KEY (il-6) OR TITLE-ABS-KEY (interleukin 6) OR TITLE-ABS-KEY (tumor AND necrosis AND factor-alpha) OR TITLE-ABS-KEY (tumour AND necrosis AND factor-alpha) OR TITLE-ABS-KEY (tumor AND necrosis AND factor-α) OR TITLE-ABS-KEY (tnf PRE/0 alpha) OR TITLE-ABS-KEY (tnf-α) OR TITLE-ABS-KEY (c-reactive AND protein*) OR TITLE-ABS-KEY (cytokine*) OR TITLE-ABS-KEY (fibrinogen*) OR TITLE-ABS-KEY (gingiva* W/2 immunology)) AND (LIMIT-TO (EXACTKEYWORD , "Clinical Trial") OR LIMIT-TO (EXACTKEYWORD , "Randomized Controlled Trial"))

Appendix 3:

Cochrane Library=269 (113 Trials): ([mh "Cardiovascular Diseases"] OR Cardiovascular Diseases OR Cardiovascular Disease OR Cardiovascular OR arteriosclerosis OR atherosclerosis OR [mh "Atherosclerosis"] OR [mh "Arteriosclerosis"] OR [mh "Myocardial Ischemia"] OR [mh "Acute Coronary Syndrome"] OR Myocardial Ischemia OR ischemic heart disease OR ischemic heart diseases OR myocardial infarction OR myocardial infarctions OR [mh "Myocardial Infarction"] OR Myocardial Infarct OR coronary diseases OR coronary disease OR coronary heart diseases OR coronary heart disease OR [mh "Coronary Disease"]) AND (alveolar bone OR [mh "Alveolar Bone Loss"] OR [mh "Bone Resorption"] OR Alveolar bone loss OR "bone loss" OR periodontal attachment loss OR [mh "Periodontal Attachment Loss"] OR periodontitis OR periodontal disease OR periodontal diseases OR [mh "Periodontal Diseases"] OR [mh "Gingival Diseases"] OR chronic periodontitis OR Gingival disease OR Gingival diseases OR [mh "Chronic Periodontitis"] OR periodontal index OR [mh "Periodontal Index"] OR [mh "Gingival Pocket"] OR [mh "Periodontal Pocket"] OR periodontal therapy OR periodontal treatment OR periodontal treatments OR periodontal index OR [mh "Periodontal Index"] OR dental prophylaxis OR [mh "Dental Prophylaxis"] OR periodontal debridement OR subgingival

debridement OR subgingival curettage OR [mh "Periodontal Debridement"] OR [mh "Subgingival Curettage"] OR scaling OR [mh "Dental Scaling"] OR root planing OR [mh "Root Planing"] OR scaling root planing OR subgingival scaling OR supragingival scaling OR non-surgical dental OR non-surgical periodontal OR non-surgical dental therapy OR non-surgical periodontal therapy OR non-surgical periodontal treatment) AND (Biomarkers OR [mh "Biomarkers"] OR Bio-marker OR inflammatory markers OR serum markers OR biological markers OR plasma level OR inflammatory mediators OR Proinflammatory mediators OR Pro-inflammatory mediators OR Pro-inflammatory mediator OR Proinflammatory mediator OR inflammatory mediator OR inflammatory marker OR biomarker OR serum marker OR interleukin OR interleukins OR [mh "Interleukins"] OR IL6 OR IL-6 OR interleukin 6 OR [mh "Interleukin-6"] OR [mh"IL6 protein, human"] OR Tumor Necrosis Factor-alpha OR Tumour Necrosis Factor-alpha OR tumor necrosis-alpha OR tumor necrosis factor-α OR [mh "Tumor Necrosis Factor-alpha"] OR [mh "TNF protein, human"] OR tnf alpha OR tnf-alpha OR tnf-α OR c-reactive protein OR [mh "C-Reactive Protein"] OR C-reactive proteins OR cytokines OR cytokine OR [mh "Cytokines"] OR fibrinogen OR [mh "Fibrinogen"] OR fibrinogens OR [mh "Gingival Crevicular Fluid"/CH] OR [mh "Gingiva"/IM])

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