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Research Article

Troponins as a Major Cardiac Biomarkers and Periodontitis: Systematic Review

Alaa Moustafa Attia*

Department of Basic and Clinical Oral Sciences, Division of Periodontology, Faculty of Dentistry, Umm Al-Qura University (Makkah), Saudi Arabia, and Faculty of Dentistry, AL-Azhar University (Assiut), Egypt

***Corresponding Author:** Alaa Moustafa Attia, Department of Basic and Clinical Oral Sciences, Division of Periodontology, Faculty of Dentistry, Umm Al-Qura University (Makkah), Saudi Arabia, and Faculty of Dentistry, AL-Azhar University (Assiut), Egypt.

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Abstract

Background: The impact of periodontal infection on several systemic diseases and conditions have been a wide range of recent investigations. The association between periodontitis and cardiovascular diseases (CVD) become established and mostly studied. Thus, periodontal pathogens can cause bacteremia, increased expression of pro-inflammatory proteins leading to vascular infection and development of CVD.

Objectives: The present systematic review aimed to discuss the major ischemic cardiac biomarker; cardiac troponins (cTn) I and T in linking to systemically healthy and periodontitis subjects, and periodontally affected CVD patients.

Materials and Methods: A literature search was presented using two databases (PubMed and Medline), in addition to searching on original articles. The search policy used the combination of the terms: ''Troponin,'' ''Periodontitis,''. The result of searching obtained 21 studies, the interested selected studies are 8/21, the selection of these articles based on troponin levels (cTnI and cTnT) in clinical healthy individuals, chronic periodontitis (CP) and CVD patients with periodontitis.

Results: The selected research articles demonstrated that the troponin levels were significantly higher in the periodontitis groups compared to the controls. the troponin levels were highly significantly increased in coronary heart disease patients with periodontitis and the severity of myocardial problems are associated with severity of periodontitis. Moreover, The cTnI more studied in comparison to cTnT in different patient groups. Only one study revealed insignificant differences of cTnI in CP patients after periodontal therapy.

Conclusion: The current review concluded that a strong association between periodontitis and CVD and high troponin levels in periodontally affected CVD patients, and the relation in both diseases is association more than causation. Furthermore, the strategic plan for awareness and prevention of periodontal infections in CVD patients and the effectiveness of nonsurgical periodontal therapy on troponin levels are recommended.

Keywords: Troponins; Periodontitis; CVD; Periodontitis; Periodontal Therapy

Abbreviations

CVD: Cardiovascular Diseases; CHD: Coronary Heart Disease; CP: Chronic Periodontitis; AMI: Acute Myocardial Infarction; PISI: Periodontal Inflammatory Severity Index; cTnI: Cardiac Troponin I; TG: Test Group; CG: Control Group; cTnT: Cardiac Troponin T; PISA: Periodontal Inflammatory Surface Area; HD: Hemodialysis; hsTnT: High Sensitive Troponin T; CRP: C Reactive Protein; VLDL: Very Low-Density Lipoprotein

Introduction

Periodontal disease is a chronic inflammatory process precipitated by periodontal pathogens. Several etiological risk factors such as systemic, genetics, environmental, social, and other local factors which may affect and modify the expression and progression of inflammation in the periodontium. Numerous systemic diseases affect the development and progression of gingivitis and other forms of periodontitis. Immunological disorders that affect, macrophage/monocyte, lymphocyte and neutrophil functions re-

sult in altered activity or production of host cytokines and inflammatory mediators [1]. The previous effects manifested clinically as the early onset of periodontal destruction or as a high rate of alveolar bone resorption. Many recent suggestions have also observed the light on the opposing side of the relationship between systemic condition and oral health express the possible effects of inflammatory periodontal diseases on a wide range of systemic organs [2].

The impact of many systemic diseases on the periodontium is well documented, recently evidence recommends that periodontal infections may significantly increase the progression for certain systemic diseases or modify the progression of systemic diseases or conditions [3,4]. While more than 50 different systemic conditions have been associated with periodontal diseases, the new evidence are quite large for numerous of these diseases and small for others. Furthermore, conditions in which the impacts of periodontal infection are well recognized comprise coronary heart disease (CHD) and CHD-related events such as angina, atherosclerosis, myocardial infarction, and other vascular circumstances; diabetes mellitus, stroke, low birth-weight delivery, preterm labor, and preeclampsia, and respiratory conditions as acute and chronic obstructive pulmonary diseases [5].

A possible association between dental infections and cardiovascular diseases (CVD) was first described in literature by Matilla., *et al*. (1989) [6]. The precondition for CVD is endothelial dysfunction, which forms the potential basis for the disturbance of vascular functions [7]. Exciting supportive evidence for these mechanisms can be resulting from intervention clinical trials in which assaying the serum levels of inflammatory mediators and cardiac markers before and after periodontal therapy that is aimed at decreasing the inflammation of periodontal tissues. For clarification, in subjects with chronic periodontitis, serum levels of C-reactive protein (CRP) and IL-6 are reduced after nonsurgical periodontal therapy [8]. A systematic and metanalysis review on 25 intervention clinical studies evaluating the periodontitis patients with and without periodontal management established that periodontal therapy was correlated with a significant reduction in systemic levels of IL-6, CRP, TNF-α, and fibrinogen [9]. Chronic inflammatory periodontal disease is also associated with altered vascular endothelial function. After scaling and root planing with a subsequent decreasing of periodontal inflammation, and significantly improvement for markers of vascular health over time [10].

A case-control study established those clinical periodontal parameters and especially radiographic criteria for periodontitis very strong evidence of an association among periodontitis and risk for acute myocardial infarction (AMI). Also, in Korean population the periodontitis was associated with CVD. Therefore, those with periodontitis, especially young adults with advanced periodontitis, may be strictly observed for CVD. Also, Cardiac patients are characterized by elevated levels of several cardiac biomarkers especially the troponins [11].

Troponins are proteins that modify the relaxation and contraction of striated muscle, they are categorized of three forms: troponin C, I, T and T (TnC, TnI and TnT). Troponins are originated in cardiac and skeletal muscles, but not present in smooth muscles. About 7% of cardiac (cTnT) and 3.5% of cTnI release freely in the cytoplasm of cardiac myocytes. Assessments of cardiac troponins I and T are broadly used as diagnostic and prognostic indicators in the managing of acute coronary syndrome (ACS) and myocardial infarction. Serum level troponins used as a diagnostic marker for stroke or other myocardial injuries which is ongoing, although the sensitivity of this measurement is low [12]. Recently, high-sensitive cardiac troponin (hs-cTn), developed an essential role in the diagnosis process. The capability of hs-cTn to notice very small infarcts that otherwise would have not been considered myocardial infarction (MI) emphasizes the important clinical implications of this biomarker and the requirement of its correct assessment [13].

Some studies on levels of troponins in periodontitis patients were reported the strong relationship between the two diseases [14-18,26-29]. Mapping the link between cardiac biomarkers and chronic periodontitis was investigated by Boyapati., *et al*. (2020), they reported that statistically significant differences were seen not only in plaque and gingival indices, pocket depth (PD), Clinical attachment loss and periodontal inflammatory surface area (PISA) among both the groups, but also between several cardiac parameters of control and test groups. Positive correlations were seen in the diseased group between cardiac biomarkers as total cholesterol (TC), very low-density lipoprotein (VLDL), high-sensitive C reactive protein (Hs-CRP), and troponin T with periodontal parameters such as PISA and PD [14].

Kotorina., *et al.* (2021) interpreted the results of two studies in USA and UK on Poor oral health and inflammatory, cardiac, and hemostatic biomarkers in older adults. They documented that Poor oral health, chiefly tooth loss, was constantly associated with some inflammatory, hemostatic, and cardiac biomarkers [15]. For amazing, the degree and severity of periodontitis is associated with AMI size as examined by serum cTnI and myoglobin levels [16]. Additionally, levels of troponin I are significantly increased in smokers than non-smokers periodontitis patient [17].

The purpose of this systematic review article is to present the most characteristics of this biomarker (troponins levels) in rela-

tion to systemically healthy, periodontitis and CVD periodontitis patients, and to express the importance of oral and periodontal heath for the cardiac diseased individuals.

Materials and Methods

The inclusion criteria of researched articles were selected according to the following contents: periodontitis patient groups, mean levels of troponin I and/or T or both, and clinical studies.

The literature searching was conducting through using two electronic databases (PubMed and Medline), the electronic searching through writing two keywords (periodontitis and troponins), twenty-one studies were detected through the searching process. Eight articles only had the above inclusion criteria [14,16-18,26-28], the other articles were excluded due to not focused on troponins levels in different periodontitis patient groups. Consequently, the effectiveness of periodontal therapy on troponin levels is searched, only one study was detected [18].

Results

A total of 21 articles were retrieved from the selected databases, 13 articles were excluded according to the inclusion criteria, the clinical selected articles were summarized in (Table 1). The studies managed according to the following items: authors, type of study, patients, mean values of troponins I and T or both, and results. The studies were, cross sectional studies (6/8), prospective cohort study (1/8) and Case control study (1/8). Troponin I levels were detect in 7/8 of studies, whereas Troponin T levels were detected in 3/8 of studies. The collective results of the selected studies reveal an association of periodontitis severity with levels of troponin, and significantly increased in periodontitis for CHD periodontitis groups especially AMI patients. Furthermore, significantly decreased of troponin levels in healthy control patients in comparison to periodontitis and CHD patients with periodontitis.

Author	Study title	Patients	Troponin Mean levels ng/mL	Results
Boyapati., *et al.* 2020 (14)	Cross sectional study	32 CP with CHD 31 without CP	cTnI 2.22, cTnT 11.72 cTnl 5.58, cTnT 0.26	Significant differences were seen in TG versus CG, strong association between periodontitis and diseases of cardiovascular nature.
Marfil-Álvarez., *et al.* 2014 (16)	Cross sectional study	112 CP with AMI	cTnI 40.89	Level of cTnI and myocardial infarct size are higher and corelate with extent of CP severity
Ameen., *et al.* 2020 (17)	Cross sectional study	28 CP smokers 32 CP nonsmokers 20 healthy	cTnl 0.231 cTnl 0.224 cTnl 0.086	significant level of cTnI between CPS and CPNS versus to healthy. Non-Significant between CPS and CPNS
Scherbaum., *et al.* 2020 (18)	Prospective cohort study	147 CP 60 Healthy	cTnl 3.30 cTnl 3.00	cTnI significantly higher in the periodontitis group compared to the control. No significant levels after periodontal therapy
Goteiner., *et al.* 2008 (26)	Cross sectional study	194 with ACS or angina	cTnI 27.3	An association between endotoxin/LPS and levels of serum triglycerides, troponin, and HDL.
Loo., *et al.* 2011 (27)	Cross sectional study	108 controls44 CP 30 cancer pts. With CP	cTnI 0.19 cTnT 1.03 cTnI 1.88 cTnT 10.47 cTnI 3.44 cTnT 18.10	Troponin T, troponin I, pro-BNP, LDH and high sensitivity C-reactive protein may be used as markers to monitor cardiac lesions in chronic inflammatory patients.
Wojtkowska., *et al.* 2021 (28)	Case control study	71 AMI with CP 40 CP	cTnI 31.24 cTnI 0.19	Periodontitis is a risk factor for myocardial infarction and also affects the degree of post-infarction left ventricular damage.
Cotic., *et al.* 2017 (29)	Cross sectional study	All 111 CP HD 79 dentate 32 edentulous	cTnT 10.10 cTnT 10.10 cTnT 25.40	HD patients in Slovenia have compromised oral health and increased serum inflammatory and cardiac biomarkers.

Table 1: Selected studies which demonstrated the troponin levels in healthy, chronic periodontitis and CVD periodontist patients.

Subsequently, (Table 2) expressed the mean values of cTnI and cTnT levels (ng/ml) in different groups with CP and healthy control. The mean values of troponins were generally lowest decreased in healthy, CP and CP smoker's individuals versus other CVD groups patients. There was a one study revealed the efficacy of non-surgical periodontal therapy on cTnI in systemically healthy periodontitis patient, the level of cTnI was slightly decreased but the difference was insignificant.

Study	*cTN*	*Healthy*	*CP*	*CP smokers*	*AMI with CP*	*ACS with CP*	*CHD with CP*	*Cancer Pts. With CP*	*CHD with CP Dentate*	*CHD with CP Edentulous*
Boyapati., *et al*. 2014 (14)	cTnI	5.58	-----	--------	----------	----------	2.22	----------	----------	----------
	cTNT	0.26	-----	--------	----------	----------	11.72	----------	----------	----------
Marfil-Álvarez., *et al*. 2014 (16)	cTnI	---------	-----	--------	40.89	----------	----------	----------	----------	----------
	cTNT	---------	-----	--------	----------	----------	----------	----------	----------	----------
Ameen., *et al*. 2020 (17)	cTnI	0.086	0.224	0.231	----------	----------	----------	----------	----------	----------
	cTNT	---------	-----	--------	----------	----------	----------	----------	----------	----------
Scherbaum., *et al*. 2020 (18)	cTnI	3.00	3.30	--------	----------	----------	2.22	----------	----------	----------
	cTNT	---------	-----	--------	----------	----------	11.72	----------	----------	----------
Goteiner., *et al*. 2008 (26)	cTnI	---------	-----	--------	----------	27.3	----------	----------	----------	----------
	cTnT	---------	-----	--------	----------	----------	------ -----	----------	----------	----------
Loo., *et al*. 2011 (27)	cTnI	0.19	1.88	--------	----------	----------	----------	3.44	----------	----------
	cTNT	1.03	10.47	--------	----------	----------	----------	18.10	----------	----------
Wojtkowska., *et al*. 2021 (28)	cTnI	---------	0.19	--------	31.24	----------	----------	----------	----------	----------
	cTNT	---------	-----	--------	----------	----------	----------	----------	----------	----------
Cotic., *et al*. 2017 (29)	cTnI	---------	-----	--------	----------	----------	----------	----------	----------	----------
	cTnT	---------	-----	--------	----------	----------	----------	----------	10.10	25.40

Table 2: Mean values of cTnI and cTnT levels (ng/ml) in different groups with chronic periodontitis.

Discussion

The impact of periodontal infection on several systemic disorders and condition has a wide range of investigations especially the CHD and interrelationship between the two diseases has been stablished through many evidences, but the effects of periodontal infection is association more the causations [19].

Regarding to the hypothesis of focal infection which may impact several systemic organs; periodontitis is considered as localized infection. According to recent dental based evidence studies, periodontal infection through numerous direct and indirect mechanisms may affect the onset or progression of atherosclerosis and other CVD [3,11,20,21]. Periodontitis and CVD such as atherosclerosis, and ischemic heart disease have a multifactorial risk factor that include genetic and environmental influences, smoking and others [20,21].

The effect of periodontal and systemic infections on blood viscosity led to increasing of von-Willebrand factor, plasma fibrinogen and precipitate a hypercoagulability combined with an increased white blood cell count, LDL and VLDL thereby increasing the risk of ischemic heart diseases [14,22].

Periodontitis acts as a reservoir of endotoxins which produced by gram negative microorganisms, in moderate to severe periodontitis, the ulcerated sulcular epithelium increase the possibility of endotoxins to pass into the systemic circulation, thus making damage of the vascular endothelium and advancing many undesirable cardiovascular effects. Respectively, the concentration of endotoxin in the bloodstream of periodontitis patients more than fourfold in comparison of healthy subjects [19,23].

The possible role of periodontal infection in thrombogenesis can be precipitated through production of platelet aggregation–associated protein (PAAP) which produced by some strains of S*treptococcus sanguinis* and *Porphyromonas gingivalis* which involved in coronary thrombogenesis and adverse myocardial events [20,24,25].

Troponins are group of proteins that are produced in skeletal and cardiac muscle fibers, cTnI and cTnT regulates the cardiac muscle contraction. Consequently, they are specific biomarker to the heart muscle with a high sensitivity and specificity. [12] Several cross-sectional studies revealed the troponin levels in relation to periodontitis [14,16,17,26-29]. The mean values of cTnI and cTnT were significantly decreased in heathy controls individuals in comparison to systemically healthy CP patients [14,17,18,27]. These findings revealed that the troponin levels may be affected by impact of periodontitis on systemic inflammatory biomarkers which precipitated by endotoxins of periodontal pathogens. While the mean values of cTnI and cTnT were high significantly increased in CH diseased patients versus to CP patients and CH patients without periodontitis [14,16,26,27]. These reports indicated that CVD patient condition more affected by periodontal infections.

Compromised oral health and severe periodontal status were associated with high level of inflammatory and cardiac biomarkers especially CRP and troponins [15,28,29]. Dembowska., *et al.* (2022) studied the shared risk factors for acute coronary syndrome (ACS) and periodontitis and reveal the systemic impact of periodontitis on the incidence of ACS. They concluded that the patient with high risk of CVD associated with periodontitis managed at a prevention and treating plan of periodontitis may enhance both primary and secondary prevention of CVDs [30]. Smoking is considered a major environmental risk factor in development and progression of the periodontitis and CVDs, cTnI levels more increased in smokers versus nonsmokers CP patients. [17] Also, Influence of cigarette smoking on cardiac biomarkers was evaluated by Nadruz., *et al.* (2016). They recorded that cigarette smoking was related with biomarkers of myocardial stress and damage at baseline in addition to continued assessable increase in these biomarkers for 15 years of follow-up and concluded that cigarette smoking might be harmful to the heart beyond stimulating coronary artery disease (CAD), possibly by increasing ventricular wall stress and inducing subclinical myocardial damage [31].

The effect of nonsurgical periodontal therapy on CRP and TNF-α levels in CVD patients was investigated by Koppolu., *et al.* (2013). They concluded that the clinically successful therapy more beneficial to reduce concentration of circulating systemic inflammatory biomarkers (CRP, TNF-α) [32]. According to available knowledges, there is one study on the effect of periodontal therapy on the levels of troponin levels. Scherbaum., *et al*. (2020), they recorded that there was a high significantly increased of cTNI levels in periodontitis patients versus healthy subjects, after periodontal therapy of CP patients, the cTnI was slightly decreased than the baseline lev-

els and the statistically difference was insignificant. Therefore, recommendation to performing a clinical trial on the efficacy of periodontal treatment for systemically healthy periodontitis patients and CVD patients with periodontitis is very important to shed light on the possible causal role of periodontitis in developing and progressing the status of CVD.

Conclusions

The outcomes of this systematic review suggested the followings: (1)- The association between periodontitis and CVDs became documented. (2)- The levels of cardiac biomarkers especially troponins levels are high significantly increased in CVD with periodontitis patients in comparison to periodontitis patients and healthy individuals. (3)- Improvement of oral and periodontal health are more beneficial to decrease the risking of development and progression of the CH diseases. (4)- For recommendation, the effectiveness of nonsurgical periodontal therapy on systemic troponin levels recommended to determine the beneficial effects of periodontal health on ischemic heart complications.

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