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sTNF-R Levels: Apical Periodontitis Linked to Coronary Heart Disease

Rajnish K. Singhal[1*], Balwant Rai[2]

[1]Department of Conservative Dentistry and Endodontics, Maharana Pratap College of Dentistry and Research Centre, Gwalior (M.P), India; [2]World Dental Networks, Denmark, Chief, JBR Society, India; Director, KSI, USA

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***Correspondence:** Dr. Rajnish K Singhal, MDS. Prof. and Head, Dept of Conservative Dentistry and Endodontics, Maharana Pratap College of Dentistry and Research Centre, Gwalior (M.P), India. E-mail: rajnishksinghal@gmail.com

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Abstract

BACKGROUND: Different studies have implicated the exposure to systemic conditions in the aetiology of cardiovascular diseases like chronic inflammation including chronic periodontitis.

AIM: The present study has been conducted to examine whether biomarker sTNF-R was elevated in apical periodontitis as sTNF-R is a systemic marker of inflammation and has been identified as risk factors for cardiovascular diseases.

MATERIAL AND METHODS: sTNF-R levels were measured in 52 patients with apical periodontitis (M:F::25:27), aged 20-45 years and in 20 control patients without periodontitis (M:F::10:10, aged 20-48 years). Measurement of sTNF-R1 and sTNF-R2 was carried out in duplicate with standardised, commercially available enzyme immunoassays (R&D Systems Europe, Abingdon, UK).

RESULTS: The mean sTNF-R1 and sTNF-R2 levels in periodontitis were 820 (240) pg/ml (413 – 1620 pg/ml) and 1309 (403) pg/ml (540 – 2430 pg/ml), while in normal sTNF-R1 and sTNF – R2 levels were 740 (340) pg/ml (407-1240 pg/ml) and 1283 (414) pg (480 – 2340 pg/ml) respectively. Results indicated a positive high relationship between cardiovascular markers such as sTNF-R1 and sTNF – R2 and apical periodontitis.

CONCLUSION: Elevated levels of sTNF-R1 and sTNF – R2 in apical periodontitis patients indicate an increased independent risk of coronary heart disease.

Introduction

Periodontal disease is a chronic infection of periodontal tissue characterised by the loss of attachment between tooth and bone, and by the bone loss. Epidemiological associations between periodontitis and cardiovascular disease have been reported [1, 2]. This association could be attributed to the direct action of periodontal pathogens or their products on endothelial cells through transient bacteremia or ultimately due to products of the inflammatory response [3-5]. Advanced stages of dental caries lead to apical periodontitis.

Periodontitis and atherosclerosis have complex etiologies, genetic and gender pre-dispositions and might share pathogenic mechanisms as well as general risk factors. Also, increased levels of chronic inflammatory marker CRP, serum LDL-C and t-PA (a parameter of endothelial function) have been related to increased cardiovascular risk [6-8].

Tumour necrosis factor (TNF-alpha) plays a key role in the initiation of the inflammatory response [9]. TNF-alpha has been linked with CVD risk factors, and with carotid intima – media thickness [10]. TNF receptors ($sTNFR_1$ and $sTNF\text{-}R_2$) are markers of TNF activity [11]. TNF has also been implicated in the pathogenesis of some cardiovascular diseases, including atherosclerosis, heart failure, myocardial infarction, myocarditis and cardiac allograft rejection, and vascular endothelial cell responses to TNF might underlie the vascular pathology in many of these conditions. This might be because TNFR1 and TNFR2 differentially regulate cardiac responses to TNF. In transgenic mice with TNF-induced cardiomyopathy, ablation of the TNFR2 gene aggravates heart failure and reduces survival, whereas ablation of TNFR1 blunts heart failure and improves survival [12, 13]. In cardiac allografts either TNF receptor is capable of mediating a response that will culminate in graft arterial disease [14]. Patients with chronic inflammatory conditions such as rheumatoid arthritis have the higher incidence of cardiovascular disease. Inflammatory mediators, including TNF, have been concerned with higher cardiovascular risk, and there is some evidence that anti-TNF therapy ameliorates this risk in patients with rheumatoid arthritis [15-20].

A good correlation has been observed between saliva and serum concentrations of biomarkers [21]. Therefore sampling of saliva is advantageous since non-invasive, stress-free, easy and frequent collections are possible [21]. Hence, if periodontal disease is found to be associated with $sTNFR_1$ and $sTNF\text{-}R_2$, it might be a potential mediator for the association between apical periodontitis and CVD (Cardiovascular diseases).

Our study aimed to assess whether serum $sTNFR_1$ and $sTNF\text{-}R_2$ was elevated in apical periodontitis as sTNF-R is a systemic marker of inflammation and has been identified as risk factors for cardiovascular diseases.

Material and Methods

The total sample of 72 patients was quantified into two groups. Out of 72 patients, fifty-two patients were diagnosed with apical periodontitis (M: F::25:27, aged 20-45 years. Twenty (M: F::10:10, aged 20-48 years) subjects with in normal periodontal condition were selected for control. One or more apical lesions due to dental caries in teeth with non-vital pulp were taken as diagnostic criteria of apical periodontitis [16]. Periodontal parameters such probing depth and clinical loss attachment were measured by William probe. Subjects were excluded from the study if they were the chronic alcoholic or chronic smoker since they are known predisposing factors for periodontitis. None of the subjects selected had any history of a chronic inflammatory disease, diabetes, hypertension or use of steroids or drugs.

From all subjects, 10 ml EDTA blood was sampled at before treatment. After cooling centrifugation (10 min at 4°C and 3000 revs/min), the plasma was frozen at -80°C in 250 ml aliquots for up to 30 days. sTNF-R1 and sTNF-R2 were analysed by ELISA kit. Measurement of sTNF-R1 and sTNF-R2 was carried out in duplicate with standardised, commercially available enzyme immunoassays (R&D Systems Europe, Abingdon, UK). The data was statistically analysed using SPSS version 11.0, and Student t-test was applied.

Results

There was no significant difference in socio-demographic status between two groups (Table 1).

Table 1: Socio-demographic characteristics of periodontitis and normal healthy

Variables	Number in %		P value
	Periodontitis subjects	Normal (control) subjects	
Age in years			0.076
17-25	33	30.1	
26-32	29.1	28.9	
More than 32	37.9	41	
Mean (SD)	29.45 (6.34)	29.34 (5.62)	
Education Status			0.726
Less than high school	41.6	45.9	
High school	31	27.4	
More than high school	27.4	26.7	
Job status.			0.789
Not employed	90.2	89.2	
Employed	9.8	10.8	

sTNF-R1 and sTNF–R2 levels and clinical periodontal profile were significantly higher in apical periodontitis patients as compared to normal patients without periodontitis (Table 2). The mean intra-observer agreement was 96.4%, and the mean inter-observer agreement was 94.2%.

Table 2: Different clinical parameters of periodontal profile and sTNF-R1 and sTNF-R2 levels in periodontitis and normal healthy control

	Periodontitis	Normal	P value
Average number of periodontal involved site	9.2 ± 1.2	2.0 ± 1.8	0.001
Average probing pocket Depth (in mm) (William probe)	6.3 ± 1.2	1.3 ± 1.2	0.001
Average clinical loss of attachment (in mm)	5.2 ± 1.3	1.7 ± 1.5	0.001
$sTNF\text{-}R_1$ (pg/ml)	820 ± 240	740 ± 340	0.03
sTNF R_2 (pg/ml)	1309 ± 403	1283 ± 414	0.04

Data observed that a positive significant relationship between sTNF-R1 and sTNF – R2 cardiovascular disease markers and periodontal disease clinical parameters markers such as an average number of periodontally involved site, probing depth and clinical loss of attachment (Table 3).

Table 3: Bivariate correlations between cardiovascular markers and Markers of periodontal in periodontitis patients (after adjusting the age and gender)

Variables	$sTNF\text{-}R_1$	$sTNF\text{-}R_2$
Average number of periodontal involved site	0.49	0.42
Average probing pocket (Depth)	0.49	0.43
Average clinical loss of attachment (in mm)	0.69	0.66

Discussion

Our study showed the correlation between apical periodontitis and cardiovascular marker TNF receptors. The $sTNF\text{-}R_1$ and $sTNF\text{-}R_2$ levels were considerably higher in periodontitis patients as compared to normal patients without periodontitis. TNFα is one of the major pro-inflammatory cytokines [10-13]. It's role in the pathogenesis of chronic inflammatory diseases has been long established, and serves as a source for the novel anti-cytokine therapies lately introduced [10]. An increased TNF secretion without corresponding higher levels in sTNFR shedding advocates a relative deficiency in sTNFR and an increase in the bioavailable TNF. This secretion disproportion between TNF and its soluble receptor had been detected in some chronic inflammatory disorders and had been implicated in their pathogenesis [10-11]. Previous studies reported that no associations between periodontal disease and TNF receptors [10]. This might be due to small sample size or less inflammation observed in the studies.

TNF-alpha has been associated with CVD risk factors, and with carotid intima-media thickness [11]. It has been observed that genetic variation at gene locus for TNF-alpha affect the risk of preterm birth independently and as interacting factors [12-15]. Many Studies found that levels of these biomarkers during acute infection revealed levels of sTNF-R ten-fold or greater than those reported in the present study. While differences were statistically significant [13-17], but the clinical significance of these differences was not observable. This could be attributed to the fact that periodontal infection was not so acute and severe as compared to the cardiovascular disease.

TNF-α is a potent inflammatory cytokine. The main source of TNF-α is activated mononuclear leukocytes, though it is concealed by a broad variety of other immune and nonimmune cell types, including fibroblasts, smooth muscle cells, astrocytes, and neurones [15]. TNF receptor 1 (also known as p55) and TNF receptor 2 (also known as p75) are both soluble receptors discard by different cell types on which they reside [15, 16, 18]. Elevation of TNF-α and TNF receptor levels occurs in a variety of infectious, autoimmune, inflammatory, and neoplastic diseases. Elevated levels of TNF receptor might be a reflection of the inflammatory mechanisms operative in the atherosclerotic plaque. Macrophages and T-lymphocytes are important in human atheromas, still at the earliest stages of the disease process [16, 17], suggesting that immune processes might play an early role in the development of the lesion in human beings. Our data provides evidence for at least a partial role for activated leukocytes in the chronic process of periodontitis. It has been demonstrated that patients with advanced CHF had increased concentrations of circulating TNF, especially those who were cachectic. Numerous studies have confirmed that CHF is a state of inflammatory cytokine activation [18]. It has been speculated that the association between elevated levels of inflammatory markers and periodontitis reflects chronic subclinical infection, although this hypothesis awaits confirmation. Several observational epidemiological studies [18-20], have suggested an association between chronic infections such as Chlamydia pneumonia and periodontitis and stroke risk or carotid atherosclerosis. Nonetheless, the elevations in TNF receptor levels seen here could also be related to the presence of other noninfectious stimulants of inflammation. Further prospective studies of the relationship between TNF receptors and other inflammatory and infectious markers are needed. While many investigators have examined the relationship between inflammation, infection, periodontitis and atherosclerotic heart disease, these may not reflect the relationship between these processes and stroke. Further study is required on a large scale while considering the risk factors and effect of apical periodontitis treatment on TNF receptor levels.

In conclusion, elevated levels of sTNF-R1 and sTNF–R2 in apical periodontitis patients indicate an increased independent risk of coronary heart disease.

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