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RESEARCH

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To evaluate the relationship of obstructive sleep apnea with chronic periodontitis and its association with coronary artery disease by assessing serum tumor necrosis factor-α

Shilpi Gupta[1*], Nand Lal[1], Wahid Ali[2], Akshyaya Pradhan[3], Ajay Kumar Verma[4], Prashant Gupta[5], Neeraj Kumar[6], Balendra Pratap Singh[7] and Neeraj Sinha[8]

Abstract

The periodontal tissue initiates an immune-inflammatory response against bacteria and their products at the site of periodontal infection, and systemic attack by these pathogens triggers an acute phase response that contributes to the systemic inflammatory burden. Obstructive sleep apnea (OSA) and periodontal diseases share many common risk factors and are therefore disorders associated with, and possibly related to, systemic inflammation.

Objectives 1.) To evaluate the severity of infection-causing chronic periodontitis subjects leading to Coronary Artery Disease (CAD) risk.

2.) To evaluate specific Inflammatory marker TNF-α in coronary artery disease (CAD) subjects with chronic periodontitis and obstructive sleep apnea.

Methods A total of 5 ml of the venous blood was collected from each participant which was separated out by centrifugation at 3000 rpm for 5–10 min at room temperature for the estimation of inflammatory markers. Collected samples were labeled and stored at − 20 °C in a deep freezer. The estimation of human TNF-α (tumor necrosis factor-alpha) levels was determined using an ELISA kit based on the Sandwich-ELISA principle.

Conclusion TNF-α may serve as important markers for the diagnosis of chronic periodontitis and obstructive sleep apnea and the prediction of the severity of cardiovascular diseases. Cardiovascular disease can be efficiently circumvented with a biomarker-based approach to treatment, which also benefits patients' quality of life.

Results The result of our study showed that TNF-α is involved in the onset and progression of obstructive sleep apnea leading to coronary artery disease since the expression levels of TNF in the case group were considerably higher than those in the control group.

*Correspondence:
Shilpi Gupta
drshilpigupta16@gmail.com
Full list of author information is available at the end of the article

Introduction

Periodontitis is a disease of the tissue surrounding the tooth structure and alveolar bone. It results from abnormal host responses to oral and dental plaque microorganisms [1, 2]. Host responses to a greater extent are impaired by unfavorable lifestyles including smoking and systemic conditions such as diabetes. Without diagnosis and treatment of periodontitis, chronic periodontitis can persist for years. Tissue deterioration progresses, and the tooth may become mobile and eventually fall out. Periodontal disease is linked with many imminence, including smoking, diabetes, obesity, genetics, and anxiety. Therefore, successful treatment of periodontitis requires not only mechanical removal of plaque biofilms but also control or elimination of various associated risks and environmental factors. Periodontitis is now a feature of some systemic conditions including atherosclerosis and diabetes mellitus and has been shown to affect more than 40% of healthcare around the globe [3, 4].

Cardiovascular disease (CVD) is a spectrum of disorders that encompasses stroke, valvular heart disease, atherosclerosis, coronary artery disease, congestive heart failure, cardiac arrhythmias, and myocardial infarction. Of these, a significant factor in cardiovascular disease is atherosclerosis which is characterised by the formation of atherosclerotic plaques in the innermost wall layers of big and medium-sized arteries. Myocardial infarction, stroke, and coronary artery thrombosis are among the terminal consequences of atherosclerosis. Age, male sex, low socioeconomic status, smoking, and psychosocial factors like stress are all chronic, complex diseases that both CVD and periodontitis share as risk factors [5].

Recently, periodontal diseases (PD) have been investigated as a potential factor in the development and pathogenesis of CVD. Additionally, a chronic multifactorial respiratory condition called obstructive sleep apnea (OSA) which causes breathing to temporarily stop for less than 10 s lowers blood oxygen saturation by more than 3% to 4%, and/or awakens the nervous system. It has been established that OSA has systemic effects on humans. OSA affects the upper respiratory tract. Recently, there has been speculation that periodontitis, another chronic multifactorial disease, may be connected to OSA [6].

Furthermore, interleukins, metalloproteinases, and tumor necrosis factor (TNF-) are common inflammatory mediators involved in these systemic inflammatory responses [7]. It has been established that these problems can lead to the onset of systemic diseases including diabetes and cardiovascular diseases. A connection between these conditions might also have an impact on how dentistry and medicine are practiced. The question of whether there is a causal link between chronic periodontitis and OSA leading to cardiovascular disease is the current focus of research in order to advise healthcare professionals on diagnostic procedures, risk factors, and therapies. This would promote more complete dental treatment and help build a working relationship between the dentist and the physician.

Methodology

In this case–control study, a total of 300 case groups with Chronic Periodontitis and Coronary heart disease (CHD) were recruited from OPD, Department of Cardiology, King George's Medical University, Lucknow, of subjects having different types of vessel blockage, stroke or myocardial infarction and obstructive sleep apnea. Obstructive sleep apnea subjects underwent polysomnography. Further, the control group ($n=300$) enrolled in the study was a healthy population with chronic periodontitis and was recruited from OPD, Department of Periodontology, King George's Medical University, Lucknow. The study was approved by the institutional ethical committee of King George's Medical University, Lucknow, Uttar Pradesh, India. All the participants were personally interviewed to obtain written informed consent. Information regarding gender, age, occupation history, smoking, and alcohol history, as well as anthropometrical, clinical, and pathological investigations, were recorded in a custom-designed questionnaire.

Inclusion criteria

All the subjects aged between 30 and 80 years were included in the study, which were further divided into-

Periodontal criteria

1) 30% of sites with clinical attachment loss
2) Periodontal pocket depth ≥ 4 mm and presence of bleeding on probing
3) Gingival Inflammation
4) Bleeding on probing

Cardiovascular disease criteria

1) Previous history of Acute Coronary Syndrome which has been proven angiographically.

2) Previous history of Stroke and Transient Ischemic Attack (TIA).

Exclusion criteria

1) Subjects who regularly use mouthwashes like chlorhexidine mouthwash etc.
2) Undergone any periodontal treatment for at least 6 months prior to sampling.
3) Lactating mothers
4) Pregnant women

Laboratory analysis

Of the 5 ml blood collected, 3 ml was taken in plain vials for serum, which was separated out by centrifugation at 3000 rpm for 5–10 min at room temperature within 30 min of blood collection for the estimation of lipid profile and inflammatory markers. Collected samples were labeled and stored at − 20 °C in a deep freezer. The estimation of human TNF-α (tumor necrosis factor-alpha) levels was determined using an ELISA kit based on the Sandwich-ELISA principle.

Enzyme-linked immunosorbent assay KITs

TNF-α was detected using a high-sensitivity ELISA kit. This sandwich kit is for the accurate quantitative detection of human tumor necrosis factor-alpha, in serum, plasma, cell culture supernates, ascites, tissue homogenates, or other biological fluids.

Statistical analysis

Descriptive statistics was performed by calculating the mean and standard deviation for continuous variables. The software used for the statistical analysis was SPSS (Statistical Package for Social Sciences) version 19.0.

Results

General information

There was no remarkable difference in sex and age ratio. Thus, the mean of both the groups were comparable and no statistical difference was found in the case and control groups (Figs. 1 and 2).

Distribution of tumor necrosis factor-α (TNF-α) marker in case and control groups

Table 1 depicts the tumor necrosis factor-α of case and control group subjects was 41.99 ± 54.34 and 41.19 ± 38.13 respectively. The mean tumor necrosis factor-α of both groups was not comparable (Fig. 3); however, there was a significant difference between these groups ($p = 0.007$).

Correlation between probing pocket depth (PPD)

The Spearman correlation rho coefficient showed a linear correlation in the case group and control group between PPD and tumor necrosis factor-α (TNF-α). In the case group, there was a significant positive correlation between PPD with TNF-α having a correlation coefficient of 0.159 ($p = 0.006$) respectively. However, in the control group, there was no significant correlation between PPD and TNF-α.

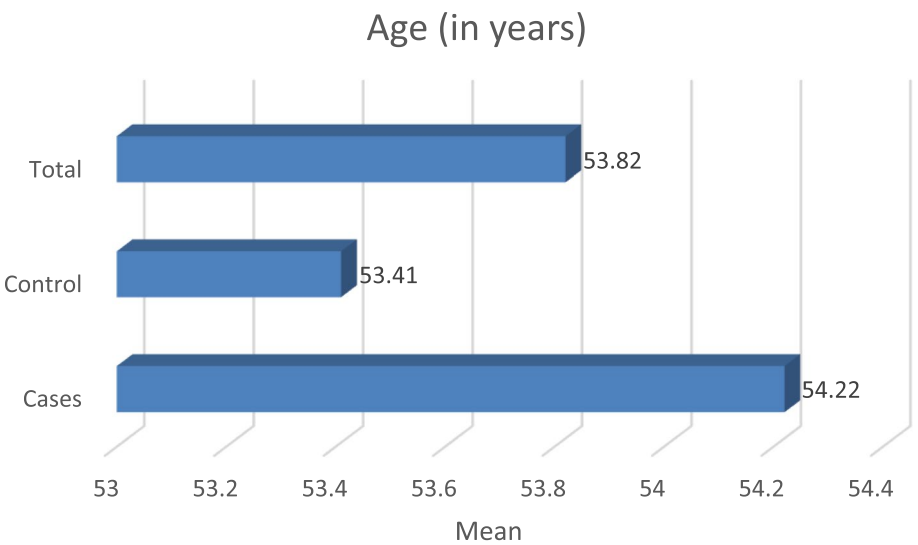

Fig. 1 The mean of both the groups—age (in years)

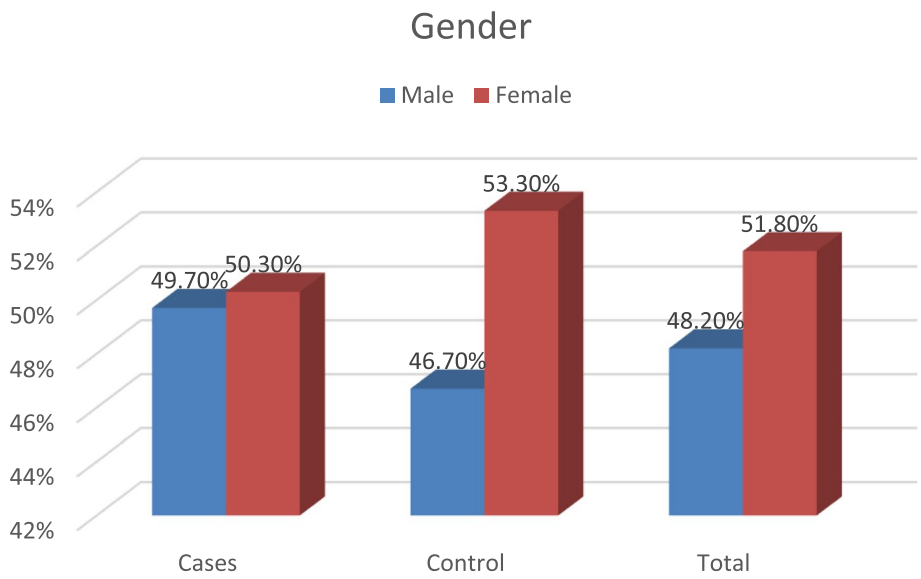

Fig. 2 The mean of both the groups—gender

Table 1 Distribution of tumor necrosis factor-α (TNF-α) marker in case and control groups

	Groups						Z value	*p* value
	Case group		Control group		Total			
	Mean	SD	Mean	SD	Mean	SD		
Tumor necrosis factor-α	41.99	54.34	41.19	38.13	41.59	46.90	−2.69	**0.007**

Applied Mann–Whitney *U* test for significance

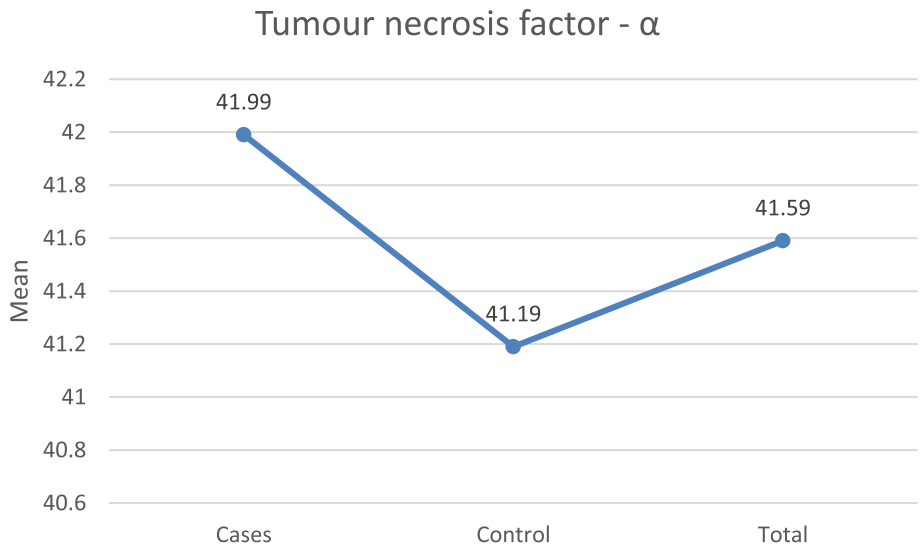

Fig. 3 The mean tumor necrosis factor-α of both groups

Correlation between clinical attachment level (CAL)

The Spearman correlation rho coefficient showed that there was no significant correlation between CAL and TNF-α in the case group and control group.

Discussion

The primary role of cytokines, which are highly significant peptide mediators, is cell signaling and communication. Cytokines serve a variety of purposes, including regulating immunological reactions, inflammatory reactions, cell proliferation, and cell differentiation. The term "cytokines" refers to soluble tiny proteins (5 − 20 kDa) that attach to certain receptors on particular cells, initiate some internal cellular changes, and affect numerous chemical and genetic processes. Cytokines are produced by specific cells and affect the behavior of many other cells [8].

Certain cytokines have a range of functions, including autocrine, endocrine, and paracrine activity. They carry out their functions by attaching to certain receptors and eliciting various reactions based on the target cell and even the cytokine itself [9]. They include chemokines which promote chemotaxis, interleukins which regulate the communication between white blood cells, interferons which regulate innate immunity, and lymphokines and tumor necrosis factor which have a pro-inflammatory activity [10].

There are different common forms of inflammation and as we know every inflammatory process is driven by a series of inflammatory mediators. As periodontitis, obstructive sleep apnea, and coronary artery disease are inflammatory processes, they are related to inflammatory mediators too.

The findings of our study revealed a substantial positive connection between serum TNF- and probing pocket depth ($p = 0.006$) which was in accordance with a study done by Varghese et al. [11] (2015), to estimate the TNF-α in chronic and aggressive periodontitis and control participants. Nevertheless, TNF- demonstrated a strong positive connection with attachment loss but not probing depth in a prior work by Engebretson et al. [12]. The link between TNF and periodontitis severity was shown to be severity-dependent. Our findings suggested that TNF may be involved in the onset and progression of obstructive sleep apnea leading to coronary artery disease since the expression levels of TNF in the case group were considerably higher than those in the control group. When the association between obstructive sleep apnea and periodontitis was investigated, the results revealed that periodontal inflammation is related to circulating TNF- in terms of tissue destruction and vascular reaction in individuals with cardiovascular disease [13, 14].

TNF- is another protein generated from monocytes that affects a variety of cell types in a pro-inflammatory and immunomodulatory manner. In addition to stimulating bone resorption, TNF- may stimulate fibroblasts, including gingival fibroblasts, to create collagenase, an enzyme thought to be responsible for periodontal disease-related tissue damage [15–18]. TNF- activates monocytes and promotes the synthesis of prostaglandins, IL-1b, and platelet-activating factor. Lipopolysaccharide stimulates monocytes to produce more TNF-, which has been demonstrated to cause collagenase release and bone resorption in vivo (Erdemir EO) [19–22]. TNF-α and IL-1 are pro-inflammatory cytokines required to start an efficient inflammatory response against infection. TNF-α also activates osteoclasts and thus induces bone resorption and has synergistic effects with the bone-resorptive actions of IL-1 β [23].

TNF-α has a variety of inflammatory biological functions [24], and the majority of OSAHS patients experience throat inflammation, which can influence the levels of a number of inflammatory mediators, including an increased production of TNF-α [25]. Increased TNF-α production can lead to cell delipidation, procoagulant activity, and fibrin deposition, all of which increase peroxide production and impair the cardiovascular system [26]. In OSAHS patients, TNF-α may also encourage neovascularization and the development of atherosclerosis [27], which can result in cardiovascular complications and heart failure. Moreover, TNF increases the expression of adhesion molecules on leukocytes and vascular endothelial cells, which produce an accelerated activation of lymphocytes and induce severe inflammatory reactions in the area of the lesion [28]. Strengthen cell adhesion between endothelium and other cells may result in microcirculation channel blockage, which may reduce blood flow to tissues and induce severe hypoxia in obstructive sleep apnea [29].

TNF-α in patients with obstructive sleep apnea and chronic periodontitis are related to the activation of inflammatory reactions and abnormal production, and accumulation of these two factors may induce chemotactic infiltration of inflammatory cells and endothelial cell injury, which is an important risk factor for atherosclerosis.

Conclusion

Traditional diagnostic tools, such as probing depth and attachment loss, have been shown to be insufficient in the current era of periodontal treatments due to their difficulty in identifying active disease and the continuous degradation of periodontal tissue. Researchers have been experimenting with and discovering novel molecules in the search for a biomarker for periodontitis, which can help a clinician make numerous decisions about the patient's situation.

TNF-α may serve as an important maker for the diagnosis of chronic periodontitis and obstructive sleep apnea and the prediction of the severity of cardiovascular diseases. Cardiovascular disease can be efficiently circumvented with a biomarker-based approach to treatment, which also benefits patients' quality of life.

Abbreviations

CAD	Coronary artery disease
OSA	Obstructive sleep apnea
CVD	Cardiovascular disease
TNF	Tumor necrosis factor
OPD	Outpatient department
TIA	Transient ischemic attack
PPD	Probing pocket depth
CAL	Clinical attachment level
IL	Interleukin
PD	Periodontal disease
ELISA	Enzyme-linked immunosorbent assay
OSAHS	Obstructive sleep apnea/hypopnea syndrome

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Authors' contributions
All the authors made the same contribution to this study. The authors read and approved the final manuscript.

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Availability of data and materials
The data of this study are available upon reasonable request.

Declarations

Ethics approval and consent to participate
Informed written consent was obtained from all the patients and or their caregivers. This study protocol was approved by the Institutional Ethics Committee, U.P. (Ref number: 104th ECM II B-Ph.D/PI) on 27/02/2021.

Consent for publication
Participants provided consent for the study findings to be published.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [2]Department of Pathology, Faculty of Medical Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [3]Department of Cardiology, Faculty of Medical Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [4]Department of Respiratory Medicine, Faculty of Medical Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [5]Department of Microbiology, Faculty of Medical Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [6]Department of Neurology, Faculty of Medical Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [7]Department of Prosthodontics, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh, India. [8]C.B.M.R, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Uttar Pradesh, Lucknow, India.

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