INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 12; Issue 04(A); April 2023; Page No. 1916-1920
DOI: http://dx.doi.org/10.24327/ijcar.2023.1920.1421

Research Article

SERUM LEVELS OF CARDIAC BIOMARKERS SOLUBLE ST2 AND C - REACTIVE PROTEIN IN PATIENTS WITH PERIODONTITIS

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A R T I C L E I N F O

Article History:
Received 4th January, 2023
Received in revised form 25th February, 2023
Accepted 18th March, 2022
Published online 28th April, 2023

Key words:

Serum, ST2, C-reactive protein, periodontitis, enzyme-linked immunosorbent assay

A B S T R A C T

Background: Soluble ST2 (sST2) is an emerging prognostic biomarker in patients with periodontitis and cardiovascular disease. There is a proposed pathophysiological mechanism that links periodontitis with cardiovascular disease. Early detection of periodontitis patients with cardiovascular disease events helps in accurate diagnosis and better treatment plan. But there are limited studies in the literature on serum sST2 in periodontitis patients.

Aim: This observational study aimed to investigate the associations between periodontitis severity and the serum levels of cardiac biomarkers sST2 and CRP in comparison with healthy and periodontitis group.

Materials & Methodology: A total of 30 patients who were divided into two groups of study and control group consists of 15 patients in each group. Patients were selected based on inclusion and exclusion criteria. Blood sample collection was done by trained professional and serum samples were stored at -80 degree Celsius. The sST2 levels and C-reactive protein levels were measured using a high-sensitivity enzyme-linked immunosorbent assay.

Results: The mean of 2894.546 in soluble suppression of tumerogenesis-2 (sST2) serum levels in (control group) gingivitis group with the standard deviation of 1185.891 was obtained. With the p value of 0.01. The mean of 3279.115 in soluble suppression of tumerogenesis-2 (sST2) serum levels in periodontitis group with the standard deviation of 566.2393 was obtained. With the p value of 0.01. Serum C-reactive protein levels showed statistically significant results when compared between the control and study group. The serum sST2 levels showed weekly significant statistical value when compared to the control and study group.

Conclusion: There is a pathophysiological mechanism that links the cardiovascular diseases with periodontitis, the serum C-reactive protein levels are higher in periodontitis patients and the serum cardiac biomarker—soluble ST2 (sST2) showed weekly significant difference in periodontitis patients which is comparable to the serum CRP levels and may be used as a cardiac biomarker in periodontitis patients.

INTRODUCTION

Periodontal disease is an inflammatory disease primarily initiated in response to a specific group of bacteria and characterized by a complex host-biofilm interaction, *Sanz M et al*. According to the World Health Organization, the severe form of periodontitis causes tooth loss in about 5–15% of the population worldwide with a prevalence rate of up to approximately 90% collectively. and it is considered the sixth most common disease affecting humans. Aberrant immune–inflammatory responses determine a patient's susceptibility to developing periodontitis, which may be modified by a range of risk factors *Seymour GJ* et al. Cardiovascular disease is the second most common cause of death worldwide.

Epidemiological studies suggest that periodontitis is independently associated with an increased risk of atherosclerotic cardiovascular disease (CVD). Given increasing data suggesting that chronic inflammatory conditions can increase the risk of CVD, attention has been turned to periodontitis and its potential link to CVD. While a possible association between periodontitis and atherosclerotic CVD has been more recently recognized, the link between dental procedures and bacteremia, and the implications on valvular heart disease, dates as far back as the early 1900s. This ultimately led to guidelines for antibiotic prophylaxis prior to dental procedures and was the impetus for dental evaluation or "dental clearance" prior to heart valve surgery. It is challenging to prove that periodontitis is the source of inflammation resulting in CVD, largely because those with significant periodontitis often have other potential causes of increased inflammation, such as diabetes and tobacco use, that can confound findings While a direct causal relationship

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between periodontitis and atherosclerotic CVD has not been established, it is hypothesized that periodontitis, which can trigger an inflammatory cascade in the oral cavity, could, in moderate to severe cases, trigger a similar systemic cascade as a result of transient bacteremia.

At least, two mechanisms have been proposed to explain the associations between these two diseases. First, subgingival plaque bacteria can translocate into the circulation and promote an inflammatory or immune response within the atherosclerotic plaque. Additionally, pro-inflammatory cytokines locally produced in periodontitis lesions can enter the bloodstream, resulting in systemic inflammation, which is characterized by elevated levels of inflammatory biomarkers, such as C-reactive protein (CRP).

CRP and inflammation plays a fundamental role in the atherosclerosis process in the pathophysiology of coronary artery disease may lead to novel therapies that target aspects of the inflammatory process smoldering within the atheroma. CRP reflects activation of the inflammatory system and play a role in the prediction of first coronary events in combination with other risk profile factors. Moderately elevated serum CRP (>2 mg/l) concentration is a systemic marker of inflammation and a documented risk factor for CVD in otherwise healthy persons. Elevated CRP values have also been associated with other diseases.

C-Reactive Protein as a biomarker provides a reflection of the underlying atherosclerotic burden or activity useful for reliable, accurate, and cost-effective information; and to predict future events and blood levels of CRP are now commonly used in clinical practice to improve vascular risk prediction in primary and secondary prevention in cardiovascular disease.

ST2 is a member of the interleukin-1 receptor family and exists as two isoforms: ST2L, a trans-membrane form, and soluble ST2 (sST2), a secreted form, sST2 acts as a decoy receptor for interleukin-33, thus preventing interleukin-33 from binding to ST2L.

Clinically, sST2 is elevated in individuals with heart disease, hypertension, or diabetes, as well as in those suffering from systemic infection or inflammation, such as sepsis, acute lung inflammation and active systemic lupus erythematosus. sST2 is a strong predictor of future cardiovascular events, independent of traditional risk factors and other cardiac biomarkers. There are limited studies in the literature on serum levels of sST2 and C-Reactive Protein in periodontitis patients. So, aim of the study is to investigate the associations between periodontitis severity and the serum levels of cardiac biomarkers sST2 and CRP in comparison with healthy and periodontitis group.

METHODS AND METHODOLOGY

30 patients reporting to the outpatient of Periodontology and Implantology, Faculty of dental sciences, RUAS. The ethical clearance for this study was obtained from the ethical committee of the institution and informed consent were taken from the patient. The study was conducted in the Dept. of Periodontology and Implantology, Faculty of dental sciences, Ramaiah university of applied sciences. The present study is an observational study design.

Subjects with age 18 to 65 yrs. Patients with periodontitis should have at least 20 teeth having pocket depth ≥5 mm and at least three sites in each quadrant with clinical attachment loss ≥4 mm (CAL) and radiographic evidence of bone loss. Patient with diabetes mellitus, Smokers, patients with autoimmune diseases or osteoporosis, users of antibiotics or non- steroidal anti- inflammatory drugs within the last 3 months and patients who were subjected to any periodontal therapy during the last year were excluded from the study

Sample Collection

Periodontal examinations were performed using mouth mirror and UNC 15 probe. Individuals with at least six teeth present in the selected quadrants were included for periodontal examination.

Blood samples were obtained by trained personal. Briefly 2 ml of venous blood was collected from the antecubital fossa by venipuncture using a 20gauze needle with a 2 ml syringe. Blood sample were allowed to clot at room temperature and, after 1 hour, serum was separated from blood by centrifugation and 0.5 ml of extracted serum was transferred to 1.5 ml aliquots. Each aliquot was stored at -80 degree Celsius until required for analysis. Serum samples were assayed for sST2 and C-Reactive Protein levels using a commercially available ELISA kit (GENLISA^{TM}LISA, KRISHGEN BioSystems).

sST2 Measurements

Serum sST2 and CRP levels were measured using frozen serum. The sST2 levels were measured using a high-sensitivity enzyme-linked immunosorbent assay (GENLISA^{TM}LISA, KRISHGEN BioSystems) (cat No#KB1120, Ver2.0). The detection limit was less than 20 pg/ml. The within-run and total coefficients of variation were <5.8%.

CRP Measurements

CRP levels were determined using a high-sensitivity enzyme-linked immunosorbent assay (GENLISA^{TM}LISA, KRISHGEN BioSystems) (cat No#KBH1798, Ver3.0) with a detection limit of less than 20 pg/ml.

Statistical Analysis

Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp., were used to perform statistical analyses. Descriptive analysis of all the explanatory and outcome parameters will be done using mean and standard deviation for quantitative variables, frequency and proportions for categorical variables. Independent Student t Test were used to compare the expression of Cardiac biomarkers soluble ST2 and C-Reactive Protein between the groups. Pearson's correlation test was used to estimate the relationship between ST2 and C-Reactive Protein and the clinical parameters in each study group. The level of significance [P-Value] was set at P<0.01

RESULTS

This observational study comprises study population of 30 patients, control group of 15 patients, study group of 15 patients of gingivitis and periodontitis respectively with mean (±SD) age of 48.7 ± 4.4 years (age range: 35–65) and with 65% of males and 35% of females.

Table 1 Serum sST2 levels in gingivitis group

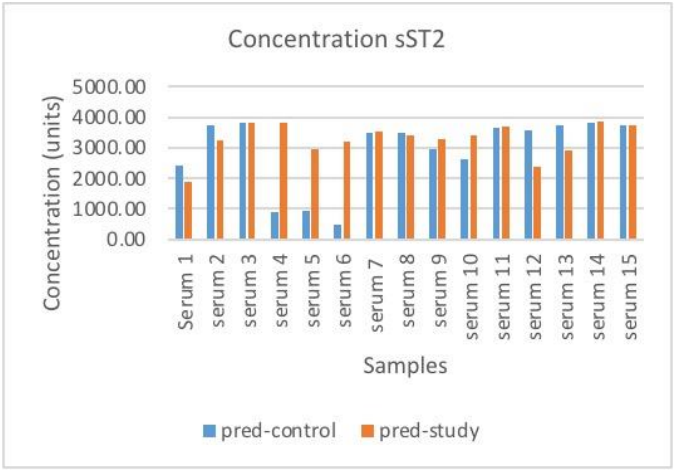
Serum sST2 levels in control group														
Serum 1	Serum 2	Serum 3	Serum 4	Serum 5	Serum 6	Serum 7	Serum 8	Serum 9	Serum 10	Serum 11	Serum 12	Serum 13	Serum 14	Serum 15
2.501	3.818	3.876	0.972	1.008	0.57	3.575	3.545	3.031	2.68	3.721	3.642	3.818	3.876	3.818
p value- 0.24*														

Table 2 Serum sST2 levels in periodontitis group

Serum sST2 levels in study group														
Serum 1	Serum 2	Serum 3	Serum 4	Serum 5	Serum 6	Serum 7	Serum 8	Serum 9	Serum 10	Serum 11	Serum 12	Serum 13	Serum 14	Serum 15
1.955	3.323	3.876	3.876	3.025	3.259	3.607	3.491	3.359	3.466	3.667	2.438	2.979	3.994	3.818
p value- 0.24*														

Table 3 Showing various parameters to compare the CRP and sST2 values

Comparison of parameters of CRP and sST2				
Measurements	**CRP**		**sST2**	
	Control	**Study**	**Control**	**Study**
Mean	12923.41	3994.86	2894.546	3279.115
Standard deviation	10272.22	5110.81	1185.891	566.2393
p Value	0.01*		0.24	



Graph 1 Showing various parameters to compare the CRP and sST2 values

The C-reactive protein (CRP) serum levels in gingivitis group of 15 patients the highest concentration of 3.243 µg/L and the lowest concentration of 2.007 µg/L was obtained. The mean of 12923.41 in C-reactive protein (CRP) serum levels in (control group) gingivitis group with the standard deviation of 10272.22 was obtained. With the p value of 0.01.The C-reactive protein (CRP) serum levels in periodontitis group in the total of 15 patients the highest concentration of 3.041 µg/L and the lowest concentration of 1.346 µg/L was obtained. The mean of 3994.86 in C-reactive protein (CRP) serum levels in (study group) periodontitis group with the standard deviation of 5110.81 was obtained. With the p value of 0.01.

The soluble suppression of tumerogenesis-2 (sST2) serum levels in gingivitis group is shown in the (Table:1). In the total of 15 patients the highest concentration of 3.818 µg/L and the lowest concentration of 0.57 µg/L was obtained. The mean of 2894.546 in soluble suppression of tumerogenesis-2 (sST2) serum levels in (control group) gingivitis group with the standard deviation of 1185.891 was obtained. With the p value of 0.01.

The soluble suppression of tumerogenesis-2 (sST2) serum levels in periodontitis group is shown in the (Table:2). In the total of 15 patients the highest concentration of 3.943 µg/L and the lowest concentration of 1.955 µg/L was obtained. The mean of 3279.115 in soluble suppression of tumerogenesis-2 (sST2) serum levels in (study group) periodontitis group with the standard deviation of 566.2393 was obtained. With the p value of 0.01.

The soluble suppression of tumerogenesis-2 (sST2) serum levels serum levels in gingivitis and soluble suppression of tumerogenesis-2 (sST2) serum levels in periodontitis showed weekly significant difference with the p value of 0.24

The concentration of soluble suppression of tumerogenesis-2 (sST2) serum levels in (control group) gingivitis and (study group) periodontitis was colour coded. Gingivitis group (control group) was indicated by colour blue, whereas periodontitis group (study group) was indicated by colour orange. Y-axis was plotted with serum samples of both control and study group, x-axis was plotted with the serum concentrations ranging from 0 to 4500 units.

When comparing between the C-reactive protein (CRP) serum levels and soluble suppression of tumerogenesis-2 (sST2) serum levels, CRP in gingivitis group showed less serum concentration than any other group in both C-reactive protein and soluble suppression of tumerogenesis-2 (sST2) serum levels. C-reactive protein serum concentration showed statistically significant results with the p value of 0.01, whereas soluble suppression of tumerogenesis-2 (sST2) serum levels had showed weekly significant difference with the p value of 0.24. (Table:3 , Graph:1)

Study group (periodontitis group) patients of serum levels of soluble suppression of tumerogenesis-2 (sST2) when compared to the serum levels of C-reactive protein levels in periodontitis patients, 5 patients showed positive corelation with the serum C-reactive protein levels and serum levels of soluble suppression of tumerogenesis-2 (sST2). A total of 33% patients showed positive corelation between the serum C-reactive protein levels and serum levels of soluble suppression of tumerogenesis-2 (sST2).

DISCUSSION

This observational study with 30 total sample size, divided into 15 patients of control group, 15 patients of study group assessed the cardiac biomarkers sST2 and CRP levels in serum. Although periodontitis is a chronic inflammatory disease but some factors of acute inflammation phase are involved in this disease among which is the C-Reactive protein (CRP). CRP can also be used for the prediction and early detection of periodontal disease.

Majid feredyoni golpasha et al conducted a study to compare the amount of salivary C-Reactive protein (CRP) in healthy subjects and patients with periodontal disease. The statistical analysis showed a significant difference in salivary CRP concentrations between the periodontitis patients and healthy

subjects (P=0.045) which is in accordance with our study results.

Epidemiological studies have demonstrated that elevated CRP is associated with an increased risk for future cardiovascular events *Kaptoge et al.,* 2010., evidence suggests that CRP may be involved in several events of atherogenesis, such as endothelial dysfunction, oxidized low-density lipoprotein uptake by macrophages, and vascular smooth muscle cell proliferation *Devaraj, Singh, & Jialal*., Study done by in group of Thai adults.

In one meta-analysis the findings resulted in a conclusion that periodontitis and poor oral health overall indeed contribute to the pathogenesis of cardiovascular disease *Meurman et al.*

Serum levels of CRP in periodontitis patients when compared with the serum levels of CRP in gingivitis showed statistically significant difference. This is in accordance with the one more study done by *Kitti Torrungruang et al.,* where cross-sectional study examined the associations between periodontitis and the serum cardiac biomarkers-soluble ST2 (sST2) and C-reactive protein (CRP)-in systemically healthy adults.

Demonstrated that periodontitis and poor oral hygiene were associated with increased serum levels of sST2 and CRP in otherwise healthy individuals. Showed that the participants with poor oral hygiene, as indicated by higher plaque scores, were twofold more likely to have elevated serum sST2 and CRP levels, compared to those with good oral hygiene.

Interleukin-33 is the ligand of the ST2 receptor, a member of the Toll-like receptor/IL-1R superfamily, *da Luz FA et al*. IL-33 is now known as a dual function cytokine acting both as an anti-inflammatory intracellular and as a proinflammatory extracellular cytokine.

Levent Savran et al in Turkey had conducted a clinical study is to comparatively investigate the interleukin-33 (IL-33) levels in gingival crevicular fluid (GCF), saliva and plasma of patients with periodontal disease as well as periodontally healthy subjects and the association between these levels and clinical parameters. They found that that the total amounts of GCF IL-33 were higher in periodontal disease compared to the periodontal healthy condition.

But we found the contrasting results in serum soluble suppression of tumerogenesis-2 (sST2) levels in both gingivitis patients and periodontitis patients, there is no statistically significant levels of serum soluble suppression of tumerogenesis-2 (sST2) when compared between the gingivitis and periodontitis patients. This could be because of intraoperative variability, methodological errors, wide age range of patients and also because of procedural errors in ELISA running etc.

Future studies assessing the association between periodontitis and cardiovascular diseases must also consider the prevalence of both disease entities. Available studies suggest that periodontitis prevalence in older subjects is high *Terpenning et al., Persson et al., HolmPedersen et al., Krustrup & Petersen*. The aspect of aging as factor in the link between periodontitis and cardiovascular diseases including stroke must be considered in future studies.

The research on serum markers of inflammation in both cardiovascular and periodontal research is extensive. The literature clearly demonstrates that elevated proinflammatory cytokines are present in both cardiovascular diseases as well as in periodontitis. It appears that Il-6, PA-1, and WBC counts are closely related to periodontitis whereas the levels of serum CRP are not conclusive, *Persson & Persson et al.*

Limitations of our study is that it includes wide age range of patients and also grading of periodontal disease severity was not done. To overcome this discrete age range of patients along with large sample size and future prospective interventional studies and randomized controlled clinical trials are suggested.

CONCLUSIONS

This observational study showed that there is a pathophysiological mechanism that links the cardiovascular diseases with periodontitis, the serum cardiac biomarkers—soluble ST2 (sST2) showed weekly significant difference when compared between the gingivitis and periodontitis patients. Serum C-reactive protein (CRP) showed significant difference when compared between the gingivitis and periodontitis patients. Hence to conclude that human serum soluble suppression of tumerogenesis-2 (sST2) may be used as cardiac biomarker in periodontitis patients. But further long-term studies with larger sample size is required to validate our results.

Suggestions for future directions

Further studies with larger sample size and considering various risk factors are recommended. Longitudinal studies with longer follow up period are suggested in this field. Multi-centric clinical studies with comparing different cardiovascular biomarkers with sST2 should also be carried out, to reaffirm the pathological link between periodontitis and cardiovascular disease.

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How to cite this article:

Kranti Konuganti and Daedeepya (2023) 'Serum Levels of Cardiac Biomarkers Soluble St2 And C - Reactive Protein In Patients With Periodontitis', *International Journal of Current Advanced Research*, 12(04), pp. 1916-1920.
DOI: http://dx.doi.org/10.24327/ijcar.2023.1920.1421

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