Association of Periodontal Disease with Serum Uric Acid and CRP in Patients Treated for Acute Coronary Syndrome: A Comparative Study

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Abstract

Background: Periodontal diseases (PED) are a widespread, complicated, long-lasting inflammation of the gum. In recent years, lots of lines of evidence have confirmed the existence of an interrelated link between PED and systemic illnesses including acute coronary syndrome (ACS). In the pathogenesis of ACS, the persuasive inflammatory role of coronary vessels is well documented. An increasing body of evidence highlights the impact of UA in inflammation. C-reactive protein (CRP) is an acute phase reactant well-known as a nonspecific marker for systemic and vascular inflammation. The study intended to evaluate the associations of PED with SUA and CRP in patients treated for ACS in a comparative study.

Methodology: 136-patients registered in this comparative study labeled as ACS besides 74-controls. The blood analysis of creatinine, urea, SUA and CRP had done for the applicants. Oral examination for grades and severity of PED had performed, and the candidates were grouped accordingly. Statistical studies had attained using SPSS software (IBM), with a significance-value calculated at <0.05.

Results: There was a significantly higher HSCRP levels with a higher nonsignificant SUA levels among the ACS group. Risk factors in terms of incidence of DM, hypertension, and smoking (except the BMI) were significantly higher among patients. More than 3/4th of the patients' group was suffering from generalized PED (74.3%), while 15.4% had a localized PED and only 9% had healthy periodontium. Meanwhile, about 2/3rd of the controls has normal periodontium. 18.4% vs. 75% had a mild, 25.7% vs. 4% had a moderate, and 21.3% vs. zero had a severe form of PED, in patients and control respectively. There was a significant worsening of PED in terms of severity and grading (p-0.001) with the increase of HSCRP levels, which is not the case for increased SUA.

Conclusion: HSCRP levels were significantly higher among patients with ACS compared to healthy control. There was a significant worsening of PED in terms of severity and grading with the increase of HSCRP levels. This is not the case for increased SUA, which is not associated with poor periodontal status.

Key Words: C-reactive Protein, Uric Acid, SUA, Periodontitis, Periodontal Diseases, Acute Coronary Syndrome.

DOI Number: 10.14704/nq.2021.19.8.NQ21106 **NeuroQuantology 2021; 19(8):07-12**

Introduction

Periodontal diseases (PED) are a widespread, complicated, long-lasting inflammation of the gum. PED usually, activated by bacterial biofilm but progressed essentially by unbalanced local immunity, progressive injury of attaching gingiva, and dental bone resorption and loss (Liccardo, 2019, Samer MM., 2020). In recent years, lots of lines of evidence have confirmed the existence of an interrelated link between PED and systemic illnesses.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 28 May 2021 **Accepted:** 02 July 2021

For example, both PED and acute coronary syndrome (ACS) interrelates within the corresponding inflammatory panel (Amir Al-Mumin, 2020a). There have been studies that show elevated cardiac biomarkers in the samples of both saliva and blood in patients with ACS (Hayder M., 2016). It is well-known that ACS is a worldwide disorder that might cause serious morbidity & mortality among different societies (Dhul Fuqar A. et al., 2020, Asseel K. et al., 2020, Amir Al-Mumin, 2020b). In the pathogenesis of ACS, the persuasive inflammatory role of coronary vessels is well documented (Hajir K., 2020).

Urate or uric acid (UA) is the breakdown of purine, revealed to promote inflammation, and vascular endothelial dysfunction (Hayder A., 2019a, Amir Al-Mumin, 2020a). An increasing body of evidence highlights the impact of UA in inflammatory renal or hepatic disorders, hypertension, diabetes mellitus, AMI, and others (Hajir K., 2020). As an effective antioxidant, around 50% of the circulatory antioxidant capacity is of UA origin (Hayder A., 2019a). Likewise, UA has a critical antioxidant (protective) role in PED.

C-reactive protein (CRP) is an ''acute phase reactant'' hepatic product; well-known as a nonspecific marker for systemic and vascular inflammation (Hayder AA., 2019b, Qasim AL-Daami, 2020). The latter effect may be attributed to the local synthesis by vascular atheroma and smooth muscle cells (Theodora B. 2018). Several preclinical studies have shown CRP association with the severity of PED and ACS (Hayder A., 2019b, Al-Saad, et al. 2020).

Aim of the study: to evaluate the associations of PED with SUA and CRP in patients treated for ACS in a comparative study.

Patients and Methods

Study Setting and Patients

One hundred thirty-six patients registered in this comparative study labeled as ACS in addition to 74 healthy controls without overt cardiac diseases. Candidates were recruited from those attending the cardiac center of Al-Imam Al-Sadiq teaching hospital in Babylon. All study participants accomplished clinical examination and mouth inspection while signing a well-informed permission formula. The blood analysis of creatinine, urea, SUA and CRP had done at the main hospital labs. All study procedures are approved by the ''Ethical Committee'' of the local health authorities and are consistent with the Helsinki-Declaration principles.

Evaluation of Periodontal Diseases

Mouth inspection had achieved by a skillful examiner, using a precise mirror and tooth-explorer. Grades of PED were calculated based on ''a new classification outline for periodontal and preimplant diseases: Introduction and key changes from the 1999-classification'' (Caton J, 2018, Samer MM., 2020). Meanwhile, the PED severity completed using a classical-prob to estimate ''clinical-attachment-loss (CAL)'' separates the gum from the alveolar edge in millimeters (Papapanou, 2018, Samer MM., 2020).

Study Grouping

Three grades of PED in participants were planned: normal gum, localized PED, and generalized PED. Likewise, the PED severity was divided based on CAL into 4 stages: healthy (less than 2mm), mild PED (2-3mm), moderate PED (4-5mm), and severe PED when CAL was more than 5mm.

Biochemical Analyses

Biochemical analyses of creatinine, urea, SUA, and C-RP were scrutinized at admission day and were assessed according to existing conventional methods, and a ''high sensitivity immunoturbidometric assay'' using immunology analyzer (Roche Diagnostics®), Cobas c111- USA for C-RP analysis (HSCRP).

Statistical Analyses

The categorical variables were shown as (frequencies and percentages), while the continuous variables as mean±SD. The presence/absence of risk factors crosswise the groups were completed by using the *chi-square* test. Relations between SUA and HSCRP levels with PED (grades and/or stages) were inspected by *ANOVA* test. Statistical studies had attained using SPSS software (IBM), with a significance-value calculated at <0.05.

Results

Characteristics of Study Parameters (Table-1)

The mean ages of patients were higher than control [63.3 vis 37.9 years], respectively; with males' predominance. The mean sera concentrations of creatinine and urea were analogous among the groups. There was a significantly higher HSCRP

concentration (p-0.05) with a higher nonsignificant SUA concentration among the ACS group (p-0.51). Risk factors in terms of incidence of DM, hypertension, and smoking (except the BMI) were significantly higher among patients. More than 3/4th of the patients' group was suffering from generalized PED (74.3%), while 15.4% had a localized PED and only 9% (11) had healthy periodontium. Meanwhile, virtually 2/3rd of the controls has normal periodontium and only 27% (20) suffered from generalized PED. For the grading of PED, 18.4% (25) vs. 75% (56) had a mild, 25.7% (35) vs. 4% (3) had a moderate, and 21.3% (29) vs. zero had a severe form of PED, in patients and control respectively. The rest 34.6% (47) of patients and 20.3% (15) of the controls had normal periodontium.

Table 1. Basic group characteristics differences between 136 patients with acute myocardial infarction and 74 healthy control

Characteristics	**Total (210)**	**ACS patients (N=136)**	**Healthy control (N=74)**	Significance
Age	56.3±10.7	63.3±9.8	37.9±8.1	0.05
Female sex (No %)	78 (36.9)	60 (76.3%)	18 (23.7%)	NS
BMI (Kg/m2)	29.7±7.0	28.1±4.1	27.3±1.6	NS
Smoking (No %)	72 (34.3)	54 (39.7%)	18 (24%)	0.05
Grades of Periodontal diseases				
Normal (No %)	62 (29.5)	47 (34.6)	15 (20.3)	0.001
Mild (No %)	81 (38.6)	25 (18.4)	56 (75.7)	0.001
Moderate (No %)	38 (18.0)	35 (25.7)	3 (4.0)	0.001
Sever (No %)	29 (13.8)	29 (21.3)	0	0.001
Stages of Periodontal Diseases				
Normal (No %)	62 (29.5)	14 (10.3)	48 (64.9)	0.001
Localized (No %)	27 (12.9)	21 (15.4)	6 (8.1)	0.001
Generalized (No %)	121 (57.6)	101 (74.3)	20 (27.0)	0.001
HSCRP (mg/l)	4.7±6.1	8.2±6.7	1.1±0.7	0.05
Serum Uric Acid (mg/l)	5.43±1.7	5.6±1.8	4.9±1.9	NS
S. Creatinine (mg/l)	0.7±0.7	0.7±0.7	0.6±0.6	NS
B. Urea Nitrogen (mg/l)	7.6±3.4	7.6±3.4	8.1±1.7	NS
Diabetes mellitus (No %)	67 (31.9	59 (88.1)	8 (11.9)	0.05
Hypertension (No %)	73 (34.7)	68 (93.2)	5 (6.8)	0.05

Gender Variations (Table-2)

The gender exhibited no influence on all the study parameters, apart from the frequency of smoking-habit, hypertension, and concentrations of HSCRP and SUA, which were higher significantly among the patients. Notably, no gender impact on both severity and stages of PED among studied participants was observed (results not shown).

Table 2. Sex differences of the study characteristics and their significance among the study participants

Characteristics	**Sex**	**Mean**	**Significance**
Age (Mean±SD)	M	52.4 ± (15.4)	NS
	F	58.2 ± (18.4)	
Smoking (No %)	M	48 ± (90.6)	0.05
	F	5 (9.4)	
Diabetes Mellitus (No %)	M	49 (80.3)	NS
	F	12 (19.7)	
Hypertension (No %)	M	45 (67.2)	0.02
	F	5 (32.8)	
BMI (Mean±SD)	M	27.5 ± (5.2)	NS
	F	26.2 ± (4.7)	
HSCRP (Mean±SD)	M	4.8 ± (4.8)	NS
	F	7.9 ± (10.4)	
Uric Acid (Mean±SD)	M	5.4±1.6	0.05
	F	5.7 ± 2.2	
Creatinine (Mean±SD)	M	0.8 ± 0.7	NS
	F	0.7 ± 0.5	
B. Urea Nitrogen (Mean±SD)	M	7.9 ± 3.7	NS
	F	6.7 ± 2.2	

HSCRP and SUA with Periodontal Status (Table-3)

There was a significant worsening of PED in terms of severity and grading (p-0.001) with the increase of HSCRP levels. This is not the case for increased SUA, which is not associated with poor periodontal status (p> 0.05), (table-3).

Table 3. Relationship of HSCRP and SUA with periodontal status among study participants

	Severity of PED	**Mean± SD**	**P-value**	**Grades of PED**	**Mean± SD**	**P-value**
HSCRP	Mild	1.9±2.7	0.001	Normal	3.4±0.9	0.001
	Moderate	5.9±6.1		Localized	6.9±1.2	
	Severe	6.5±4.8		Generalized	9.4±2.2	
SUA	Mild	5.2±1.7	0.4	Normal	5.2±1.4	0.1
	Moderate	5.5±1.5		Localized	5.9±1.8	
	Severe	5.8±1.9		Generalized	5.7±1.4	

Relationships of Uric Acid and HSCRP with Diabetes Mellitus and Hypertension (Table-4)

In comparison to the controls, a positively high-significant correlation has been noticed among HSCRP and DM (*p*-0.024) among the patients. Meantime, a positive association between HSCRP and hypertension did not reach a significant value (p-0.24). Contrariwise, a positive correlation has been noticed among SUA levels with hypertension and DM that does not reach a significant value (0.059 and 0.26), individually.

Table 4. Correlation of highly-sensitive CRP and uric acid with diabetes mellitus and hypertension in acute coronary syndrome and healthy control

Characteristics	Acute coronary syndrome				Healthy control			
	Classes of HSCRP			Significance	Classes of HSCRP			Significance
	Low	Moderate	High		Low	Moderate	High	
Diabetic (no %)	6 (10.0)	8 (13.3)	45 (76.7)	0.024	3 (37.5)	5 (62.5)	0	0.28
Non-diabetic (no %)	2 (2.2)	2 (2.2)	73 (95.6)		39 (59.1)	25 (37.9)	2 (3)	
Hypertensive (no %)	2 (2.9)	4 (5.9)	62 (91.2)	0.26	4 (80)	1 (20)	0	0.26
Non-hypertensive (no %)	3 (7.3)	3 (7.3)	35 (85.4)		39 (55.1)	30 (42.0)	2 (2.9)	
	Classes of SUA				Classes of SUA			
	Normouricemic	Hyperuricemic			Normouricemic	Hyperuricemic		
Diabetic (no %)	45 (77.1)	14 (22.9)		0.56	5 (68.3)	3 (31.7)		0.49
Non-diabetic (no %)	53 (76.3)	16 (23.7)			47 (71.9)	19 (28.1)		
Hypertensive (no %)	45 (66.7)	23 (33.3)		0.059	4 (72.4)	1 (27.6)		0.08
Non-hypertensive (no %)	56 (81.9)	12 (18.1)			53 (73.5)	19 (26.5)		

Discussion

In this paper, the discussion centers on the association of higher levels of HSCRP and SUA with PED among patients with ACS. There is ample support for the concept of a significant link between oral health and ACS (Amir Al-Mumin, 2020a, Samer MM., 2020, Al-Saad, 2020). In earlier reports, the scientists exhibited no association between dental loss and ACS (Vedin et al., 2015). Though still controversial, the impact of SUA on the pathogenesis of cardiovascular disorders has been supported by a wide range of clinical studies (Hayder A., 2019a, Hajir K., 2020, Amir Al-Mumin, 2020a). Similarly, previous reports from tertiary referral clinics verified elevated serum levels of CRP among patients with ACS associated with unhealthy oral status (Asseel K., et al., 2020, Hayder A., 2019b, Samer MM., 2020). The inflammatory background might epitomize the most significant shared path, linking ACS and oral health. Owing to individual hygiene negligence, bacteria colonize the cervical parts of the tooth, creating dental plaque (biofilm) that establishes a source of a natural niche, defending them from antiseptics and antimicrobial agents (Aarabi et al., 2017). Among a few agreeing premises, there are two most important entities. Either bacteria or their toxic products have a direct vascular injury or inflammatory mediators released through periodontal inflammation that indirectly could harm the vessels (Wojtkowska et al., 2021).

The data generated by this work appears to suggest that SUA has no direct association with PED. This finding is consistent with Germany's study that failed to show any differences between ACS patients and control groups regarding PED (Dirk Ziebolz, 2012) and the same outcomes reported by earlier another study (Colditz G, 2004). As an inflammation mediator, urates might arouse vascular endothelial dysfunction with smooth muscle cell proliferation. In this manner; it will enhance coronary sclerosis. Added, irregular teeth brush promotes calculus formation induced by urate salts. High urate concentrations in a healthy tooth, can increase ammonia synthesis that supports mineralization-demineralization steadiness, contribute to plaque-pH homeostasis. Also, urate acts to hamper cariogenic microbes and hence delay the evolution of dental caries (Amir Al-Mumin, 2020a).

The significant correlation of HSCRP with PED among ACS patients in this study is consistent with several current surveys (Samer MM., 2020, Al-Saad, 2020). The prevailing records offer positive evidence that the periodontium is one of the utmost vital sites of CRP synthesis (Theodora B. 2018). In ACS subjects, PED may confound the usual evolution of the arteriosclerotic event thus increases the risk for plaque friability that is typically insecure for increased risk of rupture (Hamilton JA, 2017).

A closer look at our data indicates that DM has an impact on periodontal health, a finding that concord with the study published by Swathi, et al. (2018). Diabetic persons are classically found to have more

periodontal attachment loss than normal subjects. Even after adjusting for probable confounding factors (K., 2012). Xerostomia is common amongst diabetics. Moreover, diabetic patients had lesser saliva flow rates than normal people, which in part owing to autonomic and sensory neuropathy (López-Pintor et al., 2016). Lower immunity of diabetic patients is a well-known sequel of DM. Along a similar vein, significant pieces of evidence claim independent links that DM is one of the numerous risk factors sharing PED and ACS (Preshaw et al., 2012, Al-Saad, 2020). As well, the risk had described as being related to the duration of DM and the degree of its control (Tervonen and Knuuttila, 1986).

Quite a lot of academics submit the view that few growth factors (GF) intricate in the inflammatory element of arteriosclerosis possibly persuaded by CRP effect including transforming growth factor-beta (TGF-β) besides platelets derived GF (PDGF). TGF-β belongs to ''TGF-β superfamily'' had various cell activities (Hayder AA., 2020, Fouad S., 2020, Mazin J., 2020). C-RP may persuade incitement and cross-talk among toll-like receptor-4 and ''NF-κB/TGF-β1 signaling-pathway'' (which has a critical inflammatory contribution) in cardiocytes (Sun W. et al., 2019). PDGF classified within the GF family, has a strong mitogenic activity for multicellular activities (Hayder AA., 2020, Fouad S., 2020). The endogenic C-RP can induce the expression of ''PDGF-receptors and PDGF-mediated chemotaxis''. Consequently, arouse the smooth muscle cells migration that had a well-recognized atherogenic contribution (Ho K. et al., 2008). Inline, C-RP binds to ''phosphatidylcholine-generating long-chain acylcarnitines and lysophosphatidylcholines'' with the existence of Ca^{++} and finally causing apoptotic death that could further exaggerate inflammation (Galea et al., 2014). Dentists share the main role in both management and control of ACS patients, thereby promoting their life quality. Good oral hygiene is vital not just to avoid oral disease, but also to preserve better general wellbeing. The oral health experts and the physicians should work hand-in-hand to expand the planning of prevention strategy.

Conclusion

HSCRP levels were significantly higher among patients with ACS compared to healthy control. There was a significant worsening of PED in terms of severity and grading with the increase of HSCRP levels. This is not the case for increased SUA, which is not associated with poor periodontal status. Additional future researches are desirable to explain this association (and related confounders) and other systemic biomarkers could be more specific to PED.

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*e*ISSN 1303-5150