

# Caries Burden is associated with serum uric acid and CRP in Patients Treated for Acute Coronary Syndrome

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## Abstract

Background: Dental caries is an ongoing, widespread multifactorial disorder and is considered one of the topmost worries of WHO about oral hygiene. Of late, lots of lines of evidence have confirmed the existence of a consistent link between oral health and systemic illnesses. For example, both oral health and acute coronary syndrome (ACS) interrelate within the corresponding inflammatory panel. Uric acid (UA) is the breakdown of purine, revealed to promote inflammation and vascular endothelial dysfunction. An increasing body of evidence highlights the impact of UA on inflammatory diseases. UA has a critical antioxidant (protective) role orally. C-reactive protein (C-RP) is an "acute phase reactant", well-known as a nonspecific indicator for systemic and vaso-inflammation. Several preclinical studies have shown C-RP association with oral health and ACS. This study aimed to investigate the association of SUA and C-RP with CB in ACS patients. Methodology: This is a case-control study, including 136 ACS patients and 74 controls free from any cardiac diseases, recruited from those attending the cardiac center. All participants accomplished clinical and mouth inspections with blood analyses of SUA and C-RP. The oral inspection utilized the WHO-agreed dental (DMF-T) index. Frequencies and percentages had used to express the categorical variables, whereas the mean±SD had used to express the continuous variables. The presence/absence of risk factors crosswise the groups had completed by using the chi-square test. Relations between SUA and C-RP levels with DMF-T had inspected by linear regression. Statistical studies had attained using SPSS software V25, with a significance value calculated at <0.05. Results: There was a significantly worse CB among ACS patients compared to control [DMF-T scores were 13.7±9.8 vis 5.1±4.8, p=0.00], respectively. As well, all DMF-T components were higher among the patients' group. The classes of DMF-T were of inferior quality also among patients. There was a significantly higher C-RP level with a higher, but not significant SUA level among patients (p=0.51). Gender revealed no impact regarding variation in the study variables. The exception is in the incidence of smoking, hypertension, mean sera levels of UA, and blood urea among studied subjects (p=0.05). There was a worsened CB with incremental SUA and C-RP values among all studied participants. Conclusions: Patients with ACS had significantly higher CB compared to controls. The patients with ACS have significantly higher C-RP levels and higher nonsignificant SUA levels. In terms of DMF-T score and missing teeth, there was a worsened CB with incremental SUA and C-RP values. These findings confirm the influence of both hyperuricemia and inflammation have a deleterious impact on CB.

**Keywords:** acute coronary syndrome, ACS, DMFT, dental caries, C-reactive protein, SUA, uric acid, oral hygiene.

## 1. Introduction

Caries burden (CB) is an ongoing, widespread multifactorial disorder and is considered one of the topmost worries of WHO about oral hygiene [1]. In the face of undue worldwide achievements in oral hygiene, uncertainties remain in various societies, mostly among deprived communities of developing countries. Of late, lots of lines of evidence have confirmed the existence of a consistent link between oral health and systemic illnesses [2]. For example, both caries burden (CB) and acute coronary syndrome (ACS) interrelate within the equivalent inflammatory panel [3]. It is well-known that ACS is a

global disorder that might cause crucial morbidity and mortality among different societies [4, 5]. In ACS pathogenesis, the persuasive inflammatory contribution is well-documented [6].

Uric acid (UA) is the purine breakdown, known to promote inflammation and endothelium dysfunction [7, 8]. An increasing body of evidence highlights the impact of serum UA (SUA) in many illnesses like hypertension, diabetes mellitus, ACS, and others [8]. As an effective antioxidant, around 50% of the antioxidant capacity is of UA origin [7]. Likewise, UA has a critical antioxidant (protective) role orally [3, 9]. C-reactive protein (C-RP) is an "acute phase reactant" hepatic product well-known as a

nonspecific indicator for systemic and vaso-inflammation [10-12]. The latter effect may attribute to the vascular synthesis by atheroma and smooth muscle cells (SMCs) [13]. Several preclinical studies have shown C-RP association with oral health and ACS mutually [6, 12].

This study aimed to investigate the association of SUA and C-RP with CB in ACS patients.

## 2. Patients and Methods

### Study Setting and Patients

There were one hundred thirty-six patients registered in this case-control study labeled as ACS besides 74 healthy controls free from any cardiac diseases. Candidates were recruited from the cardiac center attendants of Alimam-Alsadiq teaching hospital in Babylon. All participants accomplished clinical and mouth inspections while signing a well-informed permission formula. The analyses of SUA and C-RP had directed at the hospital labs. The study procedures are approved by the "Ethical Committee" of the local health authorities and are consistent with the Helsinki Declaration principles.

### Evaluation of Caries Burden

A skillful examiner carried out the oral inspection utilizing the WHO-agreed dental (DMF-T) index [14]. The outsides of occluded teeth have been managed with a soft brush, dried, and checked with a tooth-explorer and mirror. The DMF-T values were interpreted based on DMF-T scoring. The candidates are classified into 3 classes: a DMF-T value of 1-4 indicates low, 5-9 moderate, and >9 as high CB [15].

### Biochemical Analyses

Biochemical analyses of both SUA and C-RP were scrutinized and assessed on admission day. The blood UA, creatinine, and urea examination had performed according to existing conventional methods. The high-sensitive C-RP had analyzed

using "immunoturbidometric-assay" by an immunology analyzer (Roche Diagnostics®), Cobas c111-USA. The participants were divided according to their SUA levels into hyperuricemic and normouricemic (>6.5 and <6.5), respectively.

## 3. Statistical Analyses

Frequencies/percentages had used to express the categorical units, whereas the mean± SD had been used to express the continuous units. The risk factors' presence/absence crosswise the groups had completed by using the *chi-square*. Relations among SUA and C-RP levels with DMF-T classes had inspected by *linear regression*. A statistical investigation had achieved using SPSS software V25, with a significance-value calculated at <5%.

## 4. Results

### Characteristics of Study Parameters (table 1)

The mean ages of patients were higher than the control [63.3 vis 37.9 years], respectively. Out of 210 candidates included in this study, males' numbers were dominant. The global caries index of all participants was 11.4±9.6, which was significantly worse among ACS patients compared to control [DMF-T scores were 13.7±9.8 vis 5.1±4.8, *p*-0.00], correspondingly. As well, the measures of all DMF-T components were higher among the patients. All the DMF-T classes were of inferior quality among the ACS patients compared to the control: <1 (11.6 vis 23.7), 1-4 (23.2 vis 20.7), 5-9 (18.6 vis 20.7), and >9 (82.6 vis 8.9), respectively. The mean blood levels of creatinine, urea, and mean BMI was comparable between the two groups. There were significantly higher C-RP levels (*p*-0.05) with higher, not significant SUA levels among the patients (*p*-0.51). Risk factors in terms of incidence of DM, hypertension, and smoking (except the BMI) were significantly higher among the patients.

Table 1: Basic group characteristics differences between 136 patients with acute coronary syndrome and 74 healthy control

P-value	Healthy control (N=74)	ACS patients (N=136)	Total (210)	Characteristics
0.05	37.9±8.1	63.3±9.8	56.3±10.7	Age
NS	18 (24.3)	33 (24.3)	51 (24.3)	Female Sex
				<b>Caries Burden</b>
0.05	5.1±4.8	13.7±9.8	11.4±9.6	DMF-T
0.05	3.3±3.3	10.9±8.9	9.1±8.6	Missing
NS	1.7±2.9	2.4±2.5	2.2±2.6	Decayed
0.05	0.3±0.7	0.7±1.7	0.5±1.3	Filled
				<b>Classes of DMF-T</b>
0.05	23.7 (32.0)	11.6 (8.5)	32.6 (15.6)	DMF-T (< 1) No (%)
0.05	20.7 (28.0)	23.2 (17.1)	42.8 (20.4)	DMF-T (1-4) No (%)
0.05	20.7 (28.0)	18.6 (13.7)	37.8 (18.0)	DMF-T (5-9) No (%)
0.05	8.9 (12.0)	82.6 (60.7)	96.6 (46.0)	DMF-T (>9) No (%)
				<b>Biochemical Analyses</b>
0.05	1.1±0.7	8.2±6.7	4.7±6.1	C-RP (mg/l)
NS	4.9±1.9	5.6±1.8	5.4±1.7	Serum Uric Acid (mg/l)
NS	0.6±0.6	0.7±0.7	0.7±0.7	S. Creatinine (mg/l)
NS	8.1±1.7	7.6±3.4	7.6±3.4	B. Urea Nitrogen (mg/l)
				<b>Risk Factors</b>
0.05	8 (10.8)	59 (43.3)	67 (31)	Diabetes mellitus (No %)
0.05	5 (6.7)	68 (50.0)	73 (34.7)	Hypertension (No %)
NS	27.3±1.6	28.1±4.1	29.7±7.0	BMI (Kg/m <sup>2</sup> )
0.05	9 (12.2)	44 (32.3)	53 (25.2)	Smoking

### Gender Variations (table 2)

Gender revealed no impact on the study variables, apart from its effect on the incidence of smoking,

hypertension, and levels of C-RP, which were higher among the patients compared to the control group ( $p=0.05$ ). Likewise, the number of filled teeth was significantly higher in males (results not appeared).

**Table 2: Sex differences of the study characteristics and their significance among all study participants**

Characteristics	Sex	Mean	P-Value
Age (Mean± SD)	M	51.8 ± 15.3	NS
	F	54.1 ± 18.3	
Smoking (No %)	M	48 (47.6)	0.05
	F	5 (9.3)	
Diabetes Mellitus (No %)	M	51 (24.3)	NS
	F	16 (23.9)	
Hypertension (No %)	M	47 (22.4)	0.02
	F	26 (12.4)	
BMI (Mean± SD)	M	27.5 ± 5.2	NS
	F	26.2 ± 4.7	
DMF-T Index (Mean± SD)	M	11.2 ± 9.4	NS
	F	8.9 ± 9.2	
C-RP (Mean± SD)	M	4.3 ± 4.7	0.05
	F	7.9 ± 10.4	
Uric Acid (Mean± SD)	M	5.4 ± 1.6	NS
	F	5.5 ± 2.1	
Creatinine (Mean± SD)	M	0.8 ± 0.7	NS
	F	0.7 ± 0.5	
Urea Nitrogen (Mean± SD)	M	7.9 ± 3.7	NS
	F	6.7 ± 2.3	

### Correlation of Uric Acid and C-RP with Diabetes Mellitus and Hypertension (table-3)

Compared to the control group, a positive association has been detected between SUA with hypertension but not with diabetes, in which the

positive association did not reach a significant level. Conversely, a positive high significant association has been detected between C-RP and the incidence of diabetes ( $p=0.024$ ) among the ACS group. In the interim, a positive correlation between C-RP and hypertension does not reach a significant level ( $p=0.24$ ).

**Table 3: Correlation of highly-sensitive C-RP and serum uric acid to diabetes mellitus and hypertension in acute coronary syndrome and healthy control**

Characteristics	Acute coronary syndrome				Healthy control			
	Classes of C-RP			Significance	Classes of C-RP			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)		

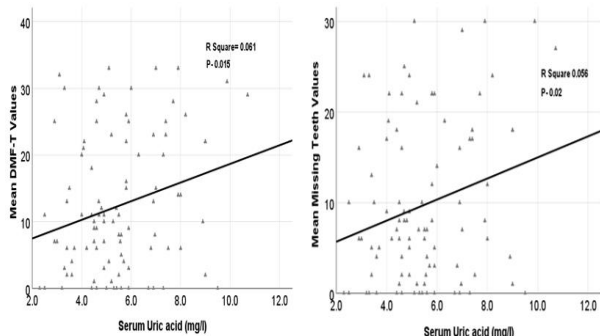


Figure-1: Correlation of mean DMF-T and missing teeth values with uric acid levels among ACS patients

### Correlation of Serum Uric Acid and C-RP with Caries Burdens

Figure (1) exposed a worsened CB with incremental SUA values among all studied subjects reflecting a toxic effect of hyperuricemia on the dental state. It had been observed that the DMF-T index had worsened also with increasing C-RP levels in both groups reflecting a significant rise of caries with incremental C-RP levels (figure-2).

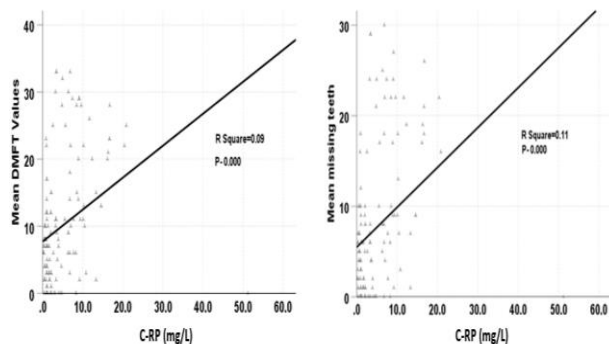


Figure-2: Correlation of mean DMFT and missing teeth values with C-RP levels among ACS patients

## 5. Discussion

The global caries index of all enrolled participants was  $11.4 \pm 9.6$ , which is within the average documented for South-East Asia [16]. In this article, similar to some of the current works supporting poor oral hygiene in patients with ACS [17, 18], I put forward the claim that all DMFT elements aside from decayed teeth were significantly inferior among ACS. Research issued last year revealed raised ACS severity with the increasing number of missing teeth, but not any of the other dental indices [19]. Meantime, another study reported an overall score of 5 oropathologies had significantly correlated to ACS [20].

Our study exposed a relationship between high SUA and CB among patients. Our finding of higher CB among ACS subjects corresponds to the results of Leng et al., who reported a significant relationship between oral infection and ACS [21]. Numerous studies have demonstrated an association between CB and the risk of ACS [6]. However, it is still unclear how exactly ACS and caries are related. This could be explained by the transmission of bacteria from dental caries that cause endothelial inflammation, in addition to the possibility that CB will exacerbate metabolic-related cardiovascular risk factors [22]. One of the significant bacteria that is responsible for caries is *Streptococcus Mutans*, which originates in the plaques of the coronary wall [23], representing a proatherogenic role of dental caries [24]. There have been studies that show SUA promotes the multiplication of vascular SMCs with the production of molecules that promote inflammation, oxidation, and vasospasm [25]. It was found in some plaques that UA induces platelet buildup [26, 27] along with its endothelial oxidative role [28].

Based on the evidence that presently exists, it looks fair to recommend the presence of a significant correlation between inflammations, poor oral hygiene, and ACS [13]. Though the scholars are consistent, the accurate pathway underlying such associations remains debatable [19]. Nonetheless, inflammation might be one of the most imperative common etiopathology between ACS and CB [17]. C-RP is a marker of systemic inflammation [5, 10]. Mutually hyperlipidemia, the action of oral microbiota in arteriosclerosis, and stimulated "protease-activated receptors" might be added

probable clarification [3, 7]. The current two works in Babylon, also show such a correlation [3, 12].

Lack of teeth brushing and poor oral health are connected to vascular endothelial dysfunction. [29]. On other hand, a current work revealed nonsignificant variations in the CB between ACS and control groups [18]. Additionally, Lockhart PB. Et al, exposed that patients with acute myocardial infarction displayed worsened CB after adjustment of cofounders, and nonsignificant relation between C-RP with the apical-lesions on X-rays [30].

This article develops the claim that gender shows no impact on the research variables, aside from incidences of smoking, hypertension, and levels of C-RP. As anticipated, males tend to have smoked at a growing rate more than females [31]. Besides, the hypertensive females were far less compared to males [32]. Finally, significant gender discrepancies are present in the CRP levels amongst the common people [33].

The data appear to suggest a high incidence of risk factors in this work like hypertension, diabetes (DM), and smoking among ACS patients. This may indicate the relationship between high SUA and C-RP with cardiovascular risk factors, which is also observed by a few scholars [8, 34].

A closer look at the data indicates a positive significant association between C-RP and diabetes among ACS patients. In this regard, our results agree with some other works [18, 19]. Diabetes had an impact on both oral health and C-RP [35]. Although, C-RP is shown to be higher among diabetics than in controls in one study [36]. Alternatively, a study found no relation between C-RP and diabetes [37]. Somewhat, the raised C-RP levels in diabetes were due to obesity and elevated BMI [38], or owing to the vulnerability of diabetics to infections and/or diabetic sequelae [39]. Notable, diabetics are at higher risk for ACS; hence, higher C-RP levels could reflect partly, the inflammatory portion of the thrombosis that is so prevalent among diabetes [40]. The data generated by the study display a positive SUA correlation with CB among the participants. Several factors affect oral health like the mouth microflora that has a vibrant protective role though it is affected by oral pH. In hyperuricemia, high salivary UA secretion decreases pH and exacerbates oral pathology [41]. Bacteria could enter the blood and excite innate and adaptive immunity [42]. Additional bacterial kinds like *Streptococcus Anginosus* are also found in caries, particularly in the saliva of hyperuricemic patients [43].

The outcomes yielded by this study offers conclusive evidence that C-RP concentrations are related linearly with DMFT and missed teeth consistent with numerous earlier revision [44]. Tooth infections may provoke a systemic inflammation that contributes to ACS [19]. Moreover, chronic gum inflammation may induce destructive bony changes with ensuing tooth loss [45]. Meantime, no oral parameters significantly correlated with means of C-RP verified by a current study held by Beatriz G. et al. [18]. Another study

inspected the association of oral variables with ACS and found that the CB was not expressively varied compared to controls [46]. Such incongruity in the last couple of papers can be attributed to the younger age of the cohorts and/or associated comorbidities.

It is worth noting that links are correlating SUA, C-RP, ACS, and CB with specific growth factors, namely transforming growth factor- $\beta$  (TGF- $\beta$ ) and platelet-derived growth factor (PDGF). Although much remains to learn about their precise role in the risk of ACS, a large body of evidence supports their dynamic influences. TGF- $\beta$  is primarily a pro-fibrotic cytokine that has many-sided cell activities [47-49]. An increased TGF- $\beta$  expression in odontoblasts and tertiary dentine, suggests a modified role in dental reaction to injury [50]. There is a significant association between ACS and levels of TGF- $\beta$ 1, SMAD3, and SUA [51], and TGF- $\beta$ 1 has a recognized anti-inflammatory effect in arteriosclerosis [52]. Instead, C-RP induces stimulation and cross-talk among "TLR4 and NF- $\kappa$ B/TGF- $\beta$ 1 signaling-path" in a cardiocytes model [53]. Surprisingly, the effects of TGF- $\beta$ , released in the post-ischemic attack, are the initiation of apoptosis, hypertrophy, and fibrosis [54] [58, 59].

PDGF is a member of the "growth-factor family" and has a potent-multicellular "mitogenic activity" [55]. Studies have shown that its levels increased significantly in ACS [56]. The PDGF-BB-isoform has potent action in the motivation of "odontoblast tissue regeneration" [57]. Of note, clinically appropriate C-RP values can activate SMCs migration probably via upregulation of PDGF receptors [58].

Based on the foregoing evidence, hyperuricemic patients must pay attention to their oral hygiene to reduce the risk of ACS. The authors recommend concern "tooth-care" parallel to other cardiovascular risk factors and the worsening CB can be considered as a poor sign for ACS.

## 6. Conclusions

Patients with ACS had significantly higher CB compared to controls. The patients with ACS have significantly higher C-RP levels and higher nonsignificant SUA levels. In terms of DMF-T score and missing teeth, there was a worsened CB with incremental SUA and C-RP values. These findings confirm the influence of both hyperuricemia and inflammation have a deleterious impact on CB.

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