ASSOCIATION BETWEEN HYPERURICEMIA AND GUM DISEASES IN ADULTS WITH CORONARY HEART DISEASES

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ABSTRACT

Gum diseases (GmD) are chronic inflammation of the teeth supporting tissue. Concurrent years exposed a lot of lines of evidence that reinforced the presence of bi-directional linkage between GmD and systemic illnesses. Coronary heart diseases (CHD) are one of these illnesses, and both GmD and CHD sharing several risk factors like age, dyslipidemia, diabetes mellitus, and hypertension. The role of uric acid (UA) in inflammation has well recognized besides its crucial role as an antioxidant agent, both these effects have interacted in GmD and CHD. This work is an attempt to evaluate the relation between SUA and GmD in adult patients with CHD in Babylon province.

Known cases of CHD underwent oral examination for gum diseases (GmD). The severity of GmD performed by using distinct standardized periodontal-prob to measure clinical-attachment-loss between the gum and the dental edge in millimeters. Whereas grading of GmD was implemented according to "a new classification outline for periodontal and preimplant diseases: Introduction and key changes from the 1999-classification". All participants investigated for serum levels of UA, creatinine, urea, and serum UA/creatinine ratio had been calculated. Then again, studied subjects divided into normouricemic and hyperuricemic, using a cutoff level of 7.0mg/dl for males and 6.0mg/dl for females were assigned. The statistics were processed and investigated using SPSS V-25.

Most of the patients were hyperuricemic (71%). More than three-quarters of all patients were suffering from generalized GmD (77%), while 14% had a localized GmD and only 9% had normal gum hygiene. About 37% patients had mild grading GmD, (30%) had moderate, and (23%) patients had a severe form of GmD. The rest grade-0 or normal gum. The mean SUA/creatinine ratio was 2.7. The normouricemic patients were significantly affected by GmD with increased severity and stages than hyperuricemic patients [(p=0.026) (OR=3.6, 95%CI is 2.43-5.47)] and [(p=0.026) (OR=2.9, 95%CI is 1.9-5.29)] sequentially. The means of SUA/creatinine ratios have a non-significant negative correlation with increasing severity and staging of GmD in patients with CHD.

Hyperuricemic is associated with CHD patients. CHD is associated with increased severity and staging of GmD. The normouricemic patients were significantly affected by GmD with increased severity and stages than hyperuricemic patients. The means of SUA/creatinine ratios have a non-significant negative correlation with increasing severity and staging of GmD in patients with CHD.
INTRODUCTION

Gum diseases (GmD) are a widespread, multifaceted, chronic inflammation of the teeth supporting tissue, began by bacterial biofilm but proceeded basically by dysregulated host immunity and progressive loss of gingival attachment, alveolar bone resorption and loss \(^{[1,2]}\). In the current decades, lots of lines of evidence have reinforced the presence of bi-directional linkage between GmD and systemic illnesses. For instance, both GmD and coronary heart diseases (CHD) interacts within the equivalent inflammatory-model. It is well-known that CHD is a worldwide disorder that might cause serious morbidity & mortality among different societies \(^{[3]}\).

Uric acid (UA) is the purine end breakdown, shown to facilitate inflammation, and endothelial dysfunction \(^{[4,5]}\). A cumulative body of evidence highpoints the role of UA in inflammatory diseases of renal, hepatic diseases, hypertension, diabetes, and CHD, and others \(^{[6,7]}\). As a potent antioxidant, over half the plasma antioxidant capability initiates from UA. Similarly, UA has a crucial role as an antioxidant agent in GmD \(^{[8]}\).

Aim of the study

This work is an attempt to evaluate the biochemical association between SUA and GmD in adult patients with CHD in Babylon province.

MATERIALS AND METHODS

Source of Data

This survey was conducted in Al-Imam Al-Sadiq Teaching Hospital, during the period from the 1st of May to the 20th of October 2019. We had examined 118 patients known to be CHD clinically evaluated by physicians.

Settings and Design

This was a cross-sectional survey, intended to guesstimate and connect the SUA values with GmD in patients with CHD. All the applicants were tolerant about the aim of this observational analysis in local dialectal and their informed permission was gotten and the whole study policy was permitted officially by Babylon Health Directorate ethical-committee.

Assessment of Gum Diseases Status (Grading & Severity)

Gum inspection by using a dental-mirror and explorer. Grading of GmD was implemented according to "a new classification outline for periodontal and preimplant diseases: Introduction and key changes from the 1999-classification" \(^{[9]}\). Whereas the severity of GmD judged by using distinct standardized periodontal-prob to measure clinical-attachment-loss (CAL) between the gum and the dental edge in millimeters (mm) \(^{[10,12]}\).
Grouping of Study Participants

Patients were divided into three grades of GmD: a grade-0 (normal gum), grade-1 (localized GmD), and grade-2 (generalized GmD). Localized versus generalized GmD: categorized as localized ≤30% of locations intricated and generalized >30% of locations intricated [12,13]. Additionally, the severity of GmD in CHD patients was divided based on CAL into 4 stages: normal (CAL<2 mm), mild (CAL=2-3 mm), moderate (CAL=4-5mm) and sever (CAL>5mm). Then again, for the division of studied subjects into normouricemic and hyperuricemic, a cutoff SUA level of 7.0mg/dl for males and 6.0mg/dl for females were assigned [14].

Statistical Study:

One-way ANOVA tests were conducted to intercorrelate SUA levels with subgroups of GmD. Results are displayed in means± SD. The variation and relationship among variables were assigned significant for all the tests, once p-value=0.05. The Cronbach’s Alpha reliability test for study parameters was =0.90. The data was processed and analyzed using SPSS25 IBM-compatible.

RESULTS

Characteristics of Studied Variables

The main characteristics of studied patients had been displayed in table-1. The mean age of patients was 59.48 with a predominance of the male sex (77.1%). Most of the patients were hyperuricemic 84 (71%) vis normouricemic 34 patients (29%). The mean BMI of the patients was 27.2, of the 48% (57) were hypertensive, 42% (50) were diabetic while the active smokers represent 40% (48 patients). The mean R/FBS of the ischemic patients was high (10.9 mmol) with WBCs mean count of 10.3. The mean blood urea nitrogen was 15.9 mg/dl, mean serum creatinine was 0.9 mg/dl while the mean SUA was (5.6 mg/dl).

Grading and Severity of Gum Diseases

More than three-quarters of all patients were suffering from generalized GmD (77%), while 14% (16) had a localized GmD and only 9% (11) had normal gum hygiene. For the grading of GmD, 37% (44) patients had mild, 30% (35) had moderate, and 23% (27) patients had a severe form of GmD. The rest 12% (10) of 118 had grade-0 or normal. The mean SUA/creatinine ratio was 2.7 (table-1).
Chi-square tests of SUA with the severity of gum diseases (table-2) revealed that normouricemic ischemic patients were significantly (p-0.026) affected by GmD (either localized or generalized) with increased severity 3.6 times more than hyperuricemic patients (95%CI is 2.43-5.47).

Similarly, Chi-square tests of SUA with the stages of gum diseases (table-3) revealed that those ischemic patients with normouricemia had significantly (p-0.026) advanced stages of GmD 2.9 times more than ischemic patients with hyperuricemic (95%CI is 1.9-5.29).
Table 3: Chi-Square Tests of Serum Uric Acid with the Staging of Gum Diseases

<table>
<thead>
<tr>
<th>Grades of Gum Diseases</th>
<th>Serum Uric Acid (No &amp; %)</th>
<th>Total</th>
<th>P-value</th>
<th>Risk Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normouricemic</td>
<td>Hyperuricemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (Grade 0)</td>
<td>2 (1.7%)</td>
<td>7 (5.9%)</td>
<td>9 (7.6%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Abnormal (Grades 1-3)</td>
<td>79 (66.9%)</td>
<td>30 (25.4%)</td>
<td>109 (92.3%)</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>81 (68.6%)</td>
<td>37 (31.3%)</td>
<td>118</td>
<td></td>
</tr>
</tbody>
</table>

In this study the gender showed no significant impact on the association between SUA and GmD in CHD patients (table not shown in the results).

Table 4: Correlation of SUA/Creatinine ratio with Severity and Stages of Gum Diseases

<table>
<thead>
<tr>
<th></th>
<th>Severity of Gum Diseases</th>
<th>Stages of Gum Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Correlation</td>
<td>-0.12</td>
<td>-0.15</td>
</tr>
<tr>
<td>Significance</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table-4 displayed that means of SUA/creatinine ratios have a non-significant negative correlation with increasing severity and staging of GmD in patients with CHD.

**DISCUSSION**

Gum diseases are a progressive non-communicable illness with a high incidence, being severe form, affecting 11.2% of the general public, the sixth utmost common human disorder [15]. Based on the "National-Health and Nutrition-Examination Survey 1999–2004 data", the frequency of moderate-severe periodontal infection in the USA was 5% among those aged 35-49 years, 11% among those aged 50-64 years, 14% among those aged 65-74 years, and 20% among those aged 75 years [16]. The prevalence of GmD in CHD is around (74.2%) [17, 18] which is moderately similar to the prevalence of GmD in our patients (77%). Based on the evidence currently available, it seems fair to suggest that both GmD and CHD sharing several etiopathophysiological factors like smoking, age, and diabetes mellitus [19]. GmD is consociated with activation of local and systemic inflammatory cytokines, including IL-1, IL-6, IL-8, and tumor necrosis factor [20]. Periodontal pathogens potentially enhance the atherosclerotic process [21]. There is strong evidence to suggest that low-grade inflammation that is typical of GmD, has unfavorable impacts on the endothelial function [22], possibly resulting in vascular stiffness and higher blood pressure [23].

Vascular endothelial-cells have numerous dynamic functions, like antithrombotic effect, adjusting of both vascular tone through mediators besides nitrous oxide (NO), and interactions among vascular wall with thrombocytes, leukocytes, and monocytes. Endothelial dysfunction may be the earliest vascular manifestation of atherosclerosis [22]. Inflammation, and the immune response, in turn, increases atherosclerotic risk [24-26] even in those without vascular risk-factors, through a reduced in NO levels in which systemic inflammation maybe, a cause of endothelial dysfunction, leading to cardiovascular diseases [27]. Numerous surveys evaluating the bacterial association of GmD with vascular inflammation revealed the same microbes in gum samples and samples taken from cardiac valves and aorta [28].
Dietrich et al., 2013 identified in a systematic-review an overall of 6 case-control and cohort studies, a higher risk of an initial coronary event in those with severe GmD compared to those without or mild GmD [29].

**Hyperuricemia, Gum Diseases and Coronary Heart Diseases**

Our results revealed a high prevalence of hyperuricemia among CHD patients (71%), which is rather similar to several other studies [5, 7, 30]. Inflammation is one of the features of atherosclerosis [25, 31]. The release of SUA from cellular storing causes the formation of UA crystals in the dying cells that may induce inflammatory responses [7, 32, 33]. For the moment, a systemic metanalysis that estimated the correlation between higher SUA levels with the risk for CHD; had uncovered much controversy [5, 34]. To some extent, this contradiction in the SUA results among CHD patients might be due to the individual gap in SUA values that approaches the variation among people, which may have reduced the strength of the association seen among studies. Added clarification is that such reviews were restricted by heterogeneity in the viewpoint of sample size [5].

**High Prevalence of Gum Diseases in Coronary Heart Diseases**

There is ample support for the claim that GmD is prevalent among CHD patients [3, 35, 36]. Inconsistent with these reports our results showed that 77% of CHD patients had experienced a generalized form and 14% experienced local forms of GmD, while only 9% had no GmD. Then again, about 90% suffered from (mild-sever) grades of GmD versus 10% had normal gum hygiene. Along similar lines, the association of GmD and CHD is an issue that has been broadly reviewed elsewhere [29, 37, 38].

**Gender, Gum Diseases and Coronary Heart Diseases**

No impact of gender on study variables in our work. As a rebuttal to this point, it might be credibly argued that that the degree of atherosclerosis assessed by intravascular ultrasound in females is less (severity and prevalence) independent of other classical vascular risk factors [39], or only after adjustment of other confounders in another survey [36]. In contrast, Desvarieux et al. (2004) have reported that measures of poor oral hygiene correlated to subclinical coronary-sclerosis in males only [40]. Nevertheless, sex-related risk factors and outcomes of CHD concerning GmD remain mostly indefinite [41].

**Hypertension, Gum Diseases and Coronary Heart Diseases**

Pietropaoli D., et al. 2019, pronounce an association of GmD and hypertension and explained their observation by the influence of local inflammation to the systemic inflammatory load [42]. A higher odds of hypertensive therapy failure in the presence of GmD was also reported elsewhere [43] and explained by the inflamed exterior periodontium [44]. Inconsistent with our results, an association of hypertension with GmD and CHD was well-recognized in other reports [15, 45, 46]. Contrary to these studies, there was no clear causal-relationship in a study published a few years ago [47, 48]. Further studies are looked-for to approve these inter-relationships and to understand the precise influence of GmD therapy on the incidence of hypertension and CHD vice-versa.

**Diabetes Mellitus, Gum Diseases and Coronary Heart Diseases**

There was a high prevalence of DM in our study (42.4%). Likewise, are significant shreds of evidence to claim independent associations between that DM is one of several risk-factors sharing GmD and CHD [15, 49, 51]. Indeed, there is a reciprocal inter-relationship between DM (or glycemic control) and GmD, [51]. Additionally, the risk was reported to be associated with the duration of DM and the degree of its control for both types I and II DM [52, 53].
Smoking, Gum Diseases and Coronary heart Diseases

The link between smoking & CHD had been demonstrated by many recent pieces of research [3, 54]. Observational statistics derived from large population analyses have verified an independent association between GlmD and CHD from the probable confounding effect of cigarette-smoke [46]. Likewise, in our study 40% of CHD patients were smokers. Supplementary studies are desirable for better recognize the smoking rule in the potential relation between GlmD and CHD.

Antioxidant Role of Uric Acid in Gum Diseases and Coronary heart Diseases

Uric acid is a nonprotein catabolic purine end-product [5, 7]. Body responses to GlmD occur normally in dual-mechanisms, either oxidative or nonoxidative, nevertheless, the overriding pathway is nonoxidative (70-85% of the total antioxidative capacity) owing to the anaerobic environment [55, 56], which can be present in plasma and saliva [57]. Of note, UA conferring protection in conditions characterized by high atherosclerotic risk and oxidative stress; given that its antioxidant abilities [58].

Oxidative stress has a strong reciprocal relationship with GlmD. Gum inflammation increases the levels of oxidative stress biomarkers, and then again, it tends to potentiate aspects of periodontal destruction [59]. Meanwhile, the antioxidant property of high SUA empowers for scavenging free radicals away from the body tissues including the gum, with the final decrease extent of GlmD [60]. In contrast, high SUA levels could aggravate gum inflammation and damage directly via xanthine-oxidase activity or indirectly via xanthine-oxidase-mediated stimulation of purine catabolism [61].

Our results revealed that hyperuricemic patients have lower severity and grades of GlmD [3.6 folds and 2.9 folds in sequence] than normouricemic patients. Lower levels of the total antioxidant is an issue that has been broadly reviewed elsewhere in GlmD patients compared to controls [62, 63]. A small part of studies found no change [64] or reverse change of blood UA levels in GlmD [64-66]. It appears that chronic GlmD is associated with hepatic-dysfunction [67]; that in turn, besides prolonged high SUA levels, could induce UA precipitation in the synovium of the temporomandibular joint and periodontal material [68].

Concentration of Uric Acid/Creatinine Ratio

Because the daily volume of creatinine production is moderately stable, both UA and urea to creatinine ratio mutually are better to elucidate the fluctuations of this compound concentration in plasma [69]. Our results exposed that SUA/creatinine ratios decreasing with incremental deteriorating in GlmD. The link between the SUA/creatinine ratio with other clinical conditions is an issue that has been far reviewed elsewhere [70-74]. The underlying mechanism is still not well reasonable though few explanations can be forwarded here to clarify the negative correlation of SUA/creatinine ratio with GlmD and CHD. First, decreased SUA is associated with a reduced antioxidative protective effect of UA which is a potential risk factor for both GlmD and CHD [55, 58, 60]. Second, the SUA/creatinine ratio has a negative correlation with diabetes [71] and 42% of our patients were diabetics. Third, SUA/creatinine ratio is associated

With entire metabolic syndrome or its distinct elements [72] that are shared impart, to GlmD and CHD [75, 76], as well as the effect of dyslipidemia on SUA levels, can be one of the explanations [77]. Moreover, 40% of CHD enrolled in our study were smokers, and it was well-known that antioxidants (like UA) are reduced in smokers owing to chronic exposure to smoke, which is a significant source of oxidative stress [58]. To finish, some of the therapies that are commonly encountered in cardiovascular diseases are calcium-channel blockers that can induce gingival overgrowth [78] and can be associated with decreased SUA [79].
Patients with CHD must be alert that GmD is a chronic condition, which may worsen their coronary problem and necessitates lifetime attention and skilled care. On the other hand, this association needs support and the establishment of a causal relationship by evidence-based clinical decisions regarding the use of antioxidants. Further complementary studies regarding other lipid parameters are needed to confirm the accurate association between dyslipidemia and SUA levels.

CONCLUSION

Hyperuricemic is associated with CHD patients. CHD is associated with increased severity and staging of GmD. The normouricemic patients were significantly affected by GmD with increased severity and stages than hyperuricemic patients. The means of SUA/creatinine ratios have a non-significant negative correlation with increasing severity and staging of GmD in patients with CHD.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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