Original Article

Association between fasting plasma glucose and highly sensitive C-reactive protein in a Sudanese population

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Abstract
Highly sensitive C-reactive protein (hs-CRP) is an acute phase reactant and a sensitive marker of inflammation. Hyperglycaemia can potentially promote the production of hs-CRP. The aim of this study was to determine whether increased fasting plasma glucose (FPG) levels are associated with elevated hs-CRP concentrations.

Methods
A total of 482 subjects (282 women and 200 men), aging between 22 and 77 years, 282 diabetic and 200 non diabetic were included in this study. Fasting blood sugar and hs-CRP in serum were determined, glycated hemoglobin (HbA1c) in whole blood was also determined.

Results
Highly sensitive C-reactive protein is higher in diabetic patients in comparison with non diabetic individuals, this elevation is directly correlated with fasting blood sugar level (r 0.567 P. value <0.001). HbA1c was significantly associated with an increased hs-CRP (r 0.623 P. value <0.001).

Conclusions
The results of this study indicated that there was a significant correlation between hs-CRP and FPG, and also significant correlation with glycaemic control indicated by HbA1c.

Keywords: hs-CRP, HbA1c, FPG, Diabetes

Introduction
Highly sensitive C-reactive protein (CRP) is an acute-phase reactant of systemic inflammation. It may be an independent predictor that reflects early stage cardiovascular disease. To date, many studies have confirmed that hs-CRP is a predictor of cardiovascular disease, diabetes and the metabolic syndrome (MetS)(1). Markers of inflammation such as (CRP) can identify individuals at high risk of developing coronary events (2).

Hyperglycaemia is known to stimulate the release of the inflammatory cytokines TNF-α
and IL-6 from various cell types, and hyperglycaemia can result in the induction and secretion of acute-phase reactants by the liver in response to factors released by fat cells (adipocytes)\(^3,4\). Due to that, elevated FPG is associated with elevated concentrations of CRP\(^5\).

Although hyperglycaemic can potentially promote production of inflammatory mediators, the relation between glycaemic status indicated by glycated hemoglobin (HbA1c) and markers of subclinical inflammation is controversial\(^6\), and few studies have directly examined the association between fasting plasma glucose and plasma concentrations of hs-CRP\(^7\).

The gender differences have been reported to be consistent across all ethnic subgroups even after multivariable adjustment; previous studies reported that C-reactive protein levels were higher in women compared with men\(^8\).

The objective of this study was to explore the relations between hs-CRP, FPG and HBA1c is a Sudanese population.

**Materials and methods**

**Subjects**

This is a cross-sectional study, participants were selected through a community-based process in Khartoum state (Khartoum center), Sudan, during the period between April 2011 to February 2012. Information on medical history, present conditions, and drugs were obtained by interview. Other characteristics, such as smoking and alcohol habits, and medication, were investigated by individual interviews using a structured questionnaire.

The sample population included 200 men and 282 women.

Subjects were classified as having diabetes based on self-reported physician diagnosed diabetes mellitus or treatment with insulin or oral agents. Those with glucose concentrations < 6.1 mmol / l (< 110 mg/dl) were classified as normal, and those with fasting glucose concentration between 6.1 and 6.9 mmol / l (110–125 mg/dl) were considered to have impaired fasting glucose\(^6\). People who had used anti-inflammatory drugs or cholesterol-lowering drugs within the previous 30 days were excluded from the analysis, due to the possible effects the drugs might have on hs-CRP levels\(^9\).

The Ethics Committee of AlNeelain University, Faculty of Medical Laboratory Sciences approved all the procedures and each subject gave informed consent to sign and participate.

**Laboratory data**

Blood samples were taken from each subject after an overnight fast, for estimation of serum concentrations of glucose and hs-CRP. Glucose in serum was estimated by enzymatic method based on glucose oxidase/peroxidase method performed using Mindray 200 (Shenzhen, China). HbA1c was measured by a boronate affinity assay method using NycoCard reader (Rodelokka, Norway). hs-CRP in serum was measured using immunotubidmetric method performed using Mindray 200 (Shenzhen, China). Biochemical analysis was performed in the laboratory of Modern Medical Center-Khartoum.

**Statistical Analysis**

Statistical analysis was performed using SPSS Statistics 17.0 (Statistical Package for Social Science). Data are presented as the mean ± standard deviation (SD). ANCOVA was performed using a general linear model approach to determine the association between FPG and CRP. In these analyses, CRP was the dependent variable, the levels of FPG, and confounding factors including HbA1c, gender, body mass index (BMI), hypertension, and smoking status were added as covariates. A P.value < 0.05 was considered significant.

**Results**

The clinical and biochemical characteristics in relation to CRP of the study are shown on the Table 1.
Table 1: Clinical and biochemical characteristics of 482 Sudanese subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All subjects</th>
<th>Subjects with DM</th>
<th>Subjects without DM</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>46 ± 9.0</td>
<td>50 ± 9.0</td>
<td>45 ± 11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>142 ± 50</td>
<td>192 ± 53</td>
<td>92 ± 15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.2 ± 3.0</td>
<td>8.0 ± 2.3</td>
<td>4.5 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>2.0 ± 1.2</td>
<td>2.6 ± 1.1</td>
<td>1.6 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

In comparison with non-diabetic subjects, the diabetic subjects were older, and have higher levels of hs-CRP (means 2.6 mg/l and 1.6 mg/dl respectively) (P < 0.001).

Table 2 presents the results of the Pearson’s correlation analysis of hs-CRP with age, FPG, and HbA1c.

CRP showed highly significant correlation with FPG and HbA1c, and not correlated with age P value <0.001 and 0.647, respectively.

Table 2: Pearson’s correlation coefficients and regression coefficients between variables of interest and C-reactive protein.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>0.023</td>
<td>0.647</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>0.567</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.623</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Figure 1 shows the 3 groups of FPG levels, it is clear that the mean hs-CRP levels significantly higher in diabetic patients compared with the other two groups (impaired fasting glucose tolerance and normal individuals).

Fig 1: High-sensitivity C-reactive protein (CRP) levels according to fasting plasma glucose levels.

Hs-CRP levels were higher in female than male (2.65 and 2.24 respectively) as shown in Table 3.

Table 3: Relationship between CRP in mg/L and gender.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Mean</th>
<th>N</th>
<th>Standard Deviation</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2.65</td>
<td>282</td>
<td>1.163</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.24</td>
<td>200</td>
<td>1.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>2.54</td>
<td>482</td>
<td>1.135</td>
<td></td>
</tr>
</tbody>
</table>

After adjustment for confounding factors in a stepwise multivariate linear regression analysis, fasting glucose remained significantly and independently related to hs-CRP levels as shown in Table 4.

Table 4: Multiple linear regression analysis with C-reactive protein as the dependent variable.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression Coefficient</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mg/dl)</td>
<td>0.090</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.100</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes = 0, no = 1)</td>
<td>0.250</td>
<td>0.020</td>
</tr>
<tr>
<td>Gender (men = 0, Women = 1)</td>
<td>0.025</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.080</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.280</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Discussion

C-reactive protein progressively increased as fasting glucose levels increased. These relationships did not show threshold effects, and hs-CRP levels apparently rose even with the fasting glucose levels corresponding to the normal range of the fasting glucose category (75-115 mg/dl, 4.1-6.3 mmol/l). This results was in agreement with what previously reported by Doi Y et al (2005). The present study showed a significance increase of hs-CRP in subjects with diabetes.
Studies on western populations have shown low grade systemic inflammation indicated by elevated hs-CRP to be one of the mechanisms by which hyperglycaemia and other known risk factors such as obesity, smoking and hypertension contribute to cardiovascular disease in diabetes mellitus (Pradhan et al. 2001(11); Pfortzner and Forst 2006(12)). The present study showed that in diabetic subjects hs-CRP was positively correlated with HbA1c, the same finding was reported by Li et al. 2004, P.value <0.001.

The stepwise multiple linear regression analysis using hs-CRP as dependent variable, adjusted for confounding factors as independent variables, showed that FPG as well as gender, BMI, smoking, and hypertension significantly associated with hs-CRP. This finding is in agreement with results reported by Fukuhara M et al (2007)13.

Mendall et al (1996)14 also found an association between hs-CRP levels and fasting glucose, but in several other studies CRP levels were not associated with fasting glucose concentrations15.

Wu et al (2002)16, found an association of CRP with fasting glucose only among women. However, in this study, hs-CRP was significantly higher in all patients with high blood sugar regardless of their gender and CRP is higher in female than male. Kawamoto et al (2011) reported that in women only, CRP increased significantly and progressively with increasing FPG (r = 0.169, P < 0.001)17.

A potential limitation of the current study is the fact that much of the data were by self-report, including the diagnosis of diabetes, use of anti-inflammatory medications, and smoking status.

In conclusion, the current study demonstrates that higher FPG and poor glycaemic control is significantly associated with elevation of CRP. Other studies with larger sample size should be conducted in normal individuals to confirm these findings.

Acknowledgment
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References


