White blood cell count and insulin resistance in patients with coronary artery disease

G. Piédrola (1), E. Novo (2), F. Escobar (3), R. García-Robles (1)

(1) Department of Endocrinology, Hospital Ramón y Cajal, 28034 Madrid, Spain.
(2) Department of Cardiology, Hospital Ramón y Cajal, 28034 Madrid, Spain.
(3) Department of Endocrinology, University of Granada, 18012 Granada, Spain.

 e-mail : gpiedrol@teleline.es

INTRODUCTION

A few studies have related an elevated leukocyte or white blood cell (WBC) count with the development of cardiovascular disease [4]; in particular an increased WBC count has been shown as an independent risk factor for cardiovascular disease [3, 17]; however, the pathogenic relationship between these two entities remains unclear.

Resistance to insulin stimulated glucose uptake is a common phenomenon and plays a central role in the pathogenesis of some well known risk factors for coronary artery disease, such as arterial hypertension, glucose intolerance, dyslipidemia and obesity [2, 13]. Decreased insulin sensitivity has been suggested as the possible link between increased WBC count and coronary artery disease [8, 16].

In the present study we have evaluated the relationship between insulin resistance and WBC count, as well as other biochemical parameters, in a group of patients with coronary artery disease and without previous history of metabolic disorders.

PATIENTS AND METHODS

Experimental design

We have assessed insulin sensitivity by performing 83 insulin suppression
platelets, fibrinogen, microalbuminuria, creatinine, urea and HbA1c were also assessed. Simple and multiple correlation analysis were carried out between insulin sensitivity parameters and the other variables measured.

There were significant correlation between SSPG and WBC count (r = 0.32 : p = 0.003) and microalbuminuria (r = 0.28 : p = 0.012). We also found statistically significant correlation between ISI and WBC count (r = 0.27 : p = 0.015) and microalbuminuria (r = 0.24 : p = 0.029). No correlation could be detected between either SSPG or ISI and the other variables measured.

In multiple regression analysis, WBC count was found to be an independent predictor of both SSPG (p < 0.01) and ISI (p < 0.05).

Our data show the existence of a significant relationship between decreased insulin sensitivity and WBC count in patients with coronary artery disease. The results of this study suggest that an elevated WBC count could be postulated as part of the insulin resistant syndrome.

**Key words :** Insulin resistance, white blood cell count, coronary artery disease, atherosclerosis, insulin suppression test.

**Assays**

Fasting blood samples were taken for measurements of plasma glucose (by the glucose oxidase method, Beckman Glucose Analyzer, Beckman Instruments, Fullerton, Ca, USA), creatinine and urea (by Hitachi Autoanalyzers, mods. 747 and 704, Hitachi Corp. Tokyo, Japan, with reactives provided by Boehringer Mannheim, GmbH, Germany), insulin (by a commercial radioimmunoassay, SORIN BIOMEDICA SpA, Saluggia, Vc, Italy), hemoglobin A1c (by high-performance liquid chromatography) and WBC count, blood platelets and fibrinogen (by automated standard procedures, Coulter Counter, Coulter Electronics, Hialeah, Fl, USA, with reactives provided by Boehringer Mannheim, GmbH, Germany). Albuminuria was measured by radioimmunoassay (Diagnostic Procedures Corporation, Los Angeles, Ca, USA) in three timed overnight urine collections (expressed as µg/min).

**Statistical analysis**

Correlation coefficients between each set of two variables were assessed by Pearson correlation analysis. A multiple regression analysis was carried out to see the independent effects of variables which were significant in bivariate analysis. P < 0.05 was considered significant. The results are expressed as mean ± SD.

**RESULTS**

The mean SSPG was 196.62 ± 66.15 mg/dL, and the mean ISI was 35.76 ± 17.04 dL/kg · min. The simple correlation coefficients between these insulin sensitivity parameters and the other variables measured were as shown in Table I. It is apparent from these results that SSPG was significantly correlated with WBC count (fig. 1) and microalbuminuria; the correlation coefficients obtained from the ISI were similar. However, no significant correlation could be found between either SSPG or ISI and any of the other variables studied. It should be specially noted that correlation coefficients...
Insulin sensitivity, WBC count and CAD

between HbA1c and insulin sensitivity parameters were borderline for significance in these patients (in whom fasting plasma glucose > 140 mg/dL and glucose intolerance were considered as exclusion criteria). No correlations could be found between different types of white cell and both SSPG and ISI.

The two variables significantly correlated with SSPG and ISI (WBC count and microalbuminuria) and the other one that showed borderline significance (HbA1c) were reanalyzed by multiple regression analysis in order to identify independent predictor variables of insulin sensitivity parameters. The results of this re-analysis (table II) displayed that WBC count was significantly associated with both SSPG and ISI, and that microalbuminuria and, mainly, HbA1c had no independent relationship with insulin sensitivity parameters.

DISCUSSION

Our data point out the existence of a relationship between decreased insulin sensitivity and WBC count and microalbuminuria in patients with coronary artery disease when simple correlation coefficients are used. However, after multiple regression analysis, only WBC count is found to be significantly related with both SSPG and ISI.

This study consists of patients with clearly diagnosed coronary artery disease but without classical cardiovascular risk factors (as they were considered exclusion criteria); an even stronger association between insulin sensitivity and WBC count could be postulated in case ischaemic patients with an abnormal metabolic profile had been included in the study (diabetes mellitus, arterial hypertension, obesity). In fact, in the Framingham Study, where patients with metabolic abnormalities were not excluded, WBC count was shown as a very powerful predictor of cardiovascular disease [9].

It has been hypothesized that the possible missing link between coronary artery disease and WBC count might be decreased insulin sensitivity. There have been a few recent reports [7, 14], including one of our own [12], that have demonstrated that ischaemic patients are truly insulin resistant, even when confounding risk factors are excluded. It has been attempted to explain the existing relationship between these abnormalities through, either the compensatory hyperinsulinemia (associated to the development of macrovascular disease [15]), or by other cardiovascular risk factors epidemiologically associated to insulin resistance such as arterial hypertension.

Table I
Simple correlation coefficients between insulin sensitivity parameters (SSPG and ISI) and other variables measured.

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>p Value</th>
<th>r</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>0.32</td>
<td>0.003</td>
<td>-0.27</td>
<td>0.015</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>0.28</td>
<td>0.012</td>
<td>-0.24</td>
<td>0.029</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.12</td>
<td>0.098</td>
<td>-0.11</td>
<td>0.029</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.15</td>
<td>0.115</td>
<td>-0.10</td>
<td>0.383</td>
</tr>
<tr>
<td>Urea</td>
<td>0.06</td>
<td>0.576</td>
<td>-0.05</td>
<td>0.681</td>
</tr>
<tr>
<td>Blood Platelets</td>
<td>0.06</td>
<td>0.607</td>
<td>-0.02</td>
<td>0.851</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.00</td>
<td>0.976</td>
<td>0.02</td>
<td>0.837</td>
</tr>
</tbody>
</table>

Table II
Regression coefficients from multiple regression analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficients</th>
<th>p Value</th>
<th>Regression Coefficients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count</td>
<td>0.01</td>
<td>0.008</td>
<td>-0.00</td>
<td>0.037</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>10.80</td>
<td>0.210</td>
<td>-2.41</td>
<td>0.289</td>
</tr>
<tr>
<td>HbA1c</td>
<td>2.15</td>
<td>0.088</td>
<td>-0.51</td>
<td>0.128</td>
</tr>
</tbody>
</table>

Figure 1: Relation between White Blood Cell (WBC) Count and Steady-State Plasma Glucose (SSPG, proportional to insulin resistance) in patients with coronary artery disease.

Figure 1: Rapport entre le nombre total de leucocytes et la glycémie moyenne (SSPG proportionnelle à la résistance à l'insuline) dans le groupe de malades ayant une maladie coronarienne.
Increased WBC count has also been associated with the development of coronary artery disease [4]. In fact, it has been proposed as an independent risk factor for cardiovascular disease [3, 17]. Elevated WBC count has also been related with other cardiovascular risk factors which have been described as part of the insulin resistance syndrome [5, 16]. In our study, we have found the existing relationship between increased WBC count and decreased insulin sensitivity, suggesting a potential role for the latter not only in the pathogenesis of coronary artery disease through the classical cardiovascular risk factors but also through an increase in WBC count.

In summary, we have provided new data on the pathogenetic relationship between WBC count and decreased insulin sensitivity in coronary artery disease patients; the results of this study suggest that the scope of insulin resistant disorders might be expanded to include elevated WBC count.

GRANTS : Clinical Investigation Grant from the Hospital Ramón y Cajal, Madrid, Spain (G.P.) and Research Project Grant # 93/1 (BMS) from Plan Nacional de Fomento a la Investigación, Spain.

REFERENCES