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

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Nombre total de leucocytes et insulinorésistance chez les patients ayant une maladie coronarienne

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Il a déjà été démontré que le nombre total de leucocytes (white blood cell count, WBC) est un véritable facteur de risque dans les maladies cardio-vasculaires. Peut être, est-ce la diminution de la sensibilité à l’insuline qui unit ces deux éléments. C’est pour ça que notre objectif a été de pouvoir étudier la possible relation qui existe entre l’insuline et le WBC dans un groupe de malades avec une maladie coronarienne.

Nous avons réalisé 83 tests de supression de l’insuline pour étudier sa sensibilité dans un groupe de 50 malades avant et après avoir fait un traitement. Précédemment nous avons écarté les malades avec intolérance au glucose, hypertension artérielle et obésité. Comme test de tolérance à l’insuline nous avons considéré la glycémie moyenne observée en cours d’épreuve (SSPG) et l’index de sensibilité à l’insuline (ISI). Nous avons aussi fait une étude quantitative des WBC, plaquettes, fibrinogène, microalbuminurie, créatinine, urée et HbA1c et des analyses de simple et multiple corrélation entre les différents paramètres.

Nous avons trouvé une corrélation entre SSPG et WBC (r = 0,32 ; p = 0,003) et microalbuminurie (r = 0,28 ; p = 0,012) ; et aussi entre ISI et WBC (r = 0,27 ; p = 0,015) et microalbuminurie (r = 0,24 ; p = 0,029), mais non avec les autres variables. Dans les analyses de multiple régression, WBC parait être un prédicteur indépendant de SSPG (p < 0,01) et ISI (p < 0,05).

Pour ces résultats, nous croyons qu’il existe une relation statistique entre la diminution de la sensibilité à l’insuline et le WBC chez les malades coronariennes, et que l’accroissement de WBC peut être considéré comme une partie du syndrome de résistance à l’insuline.

Mots-clés : Résistance à l’insuline, numération formule sanguine, maladie coronarienne, athérosclérose, test de suppression d’insuline.

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 740, 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, Fla, 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 \(\mu\)g/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

- Tests before and 6 months after conventional antischæmic therapy (nitrates, beta-blokers, calcium channel blockers or ACE inhibitors) in 50 patients with coronary artery disease (aged 60 ± 7 years, 40 men and 10 women, with a body mass index (BMI) of 26.1 ± 2.5 kg/m²). Clinical characteristics of the patients and their evolution of insulin sensitivity with the therapy have been previously reported [11].

This test [6] involve the suppression of endogenous insulin secretion with a sustained infusion of somatostatin (125 \(\mu\)g in bolus, followed by a constant infusion of 350 \(\mu\)g/h). Simultaneously, exogenous crystalline insulin is infused at a constant rate \((0.77 mUI/kg · min)\) to achieve a steady state plasma insulin (SSPI), and then the resultant steady state of plasma glucose (SSPG) in response to a constant glucose infusion \((6 mg/kg · min)\) is determined. The test has been explained in detail elsewhere [12]. The main results of the test are SSPG (mean of the plasma glucose measurements during the steady state of the test, which is inversely proportional to the insulin sensitivity) and ISI (glucose infusion rate / SSPG) · 10³, which is directly proportional to the insulin sensitivity).

The diagnosis of coronary artery disease was established on the basis of a typical history of exertional chest pain, associated with electrocardiographic changes during a treadmill exercise test (ST segment depression > 0.1 mV) and/or significant coronary stenosis on coronary angiography. Patients were excluded if they had a previous history of glucose intolerance or arterial hypertension, BMI > 30 kg/m², or fasting plasma glucose > 140 mg/dL. Subjects who had signs or symptoms of cardiac failure, renal failure, liver disease, or other chronic or intercurrent illness were also excluded from the study. None of the patients were taking any medication with potential effects on insulin sensitivity except that required for their coronary artery disease.

The protocol was approved by the Ramón y Cajal Hospital Ethic Committee, and informed consent was obtained from all patients.
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,
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.

REFERENCES