Emerging risk factors and early atherosclerosis indices in subjects with impaired glucose tolerance

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SUMMARY

Aim: To evaluate the response to an oral lipid overload, inflammatory markers and carotid intima-media thickness in subjects with impaired glucose tolerance.

Methods: 54 subjects, both sexes, 58 y-old average were submitted to 1) Clinical evaluation 2) Glucose tolerance test with 75 g glucose; classified as normal (2 h plasma glucose < 140 mg/dl, n = 37) or IGT (2 h G 140-200 mg/dl, n = 17), 3) 12 h fasting sample (plasma glucose, lipids, C-reactive protein, fibrinogen and HOMA-IR calculation); 4 and 6 h after the oral lipid overload (1000 kcal, lipids 65 g) glycemia, fibrinogen and triglycerides were reevaluated. Intima-media thickness was calculated by the average of 6 measurements (3 highest of each carotid) evaluated by ultrasonography (7 MHZ transducer).

Results: The IGT group had higher (P < 0.001) fasting plasma glucose (89.4 ± 13 vs 104.4 ± 8 mg/dl), HOMA-IR (1.69 ± 1.2 vs 2.93 ± 2.2) and waist (91 ± 14 vs 101 ± 9 cm), similar fasting lipids, intima-media thickness (P = 0.58) and post-oral lipid overload triglycerides (P = 0.74), but higher fibrinogen (284.3 ± 6 and 305 ± 10 mg/dl, P = 0.05) and C-reactive protein (2.11 ± 0.33 and 4.19 ± 0.65 mg/l, P = 0.003). C-reactive protein was positively correlated with HOMA-IR (r = 0.45, P = 0.001), fasting plasma glucose (r = 0.43, P = 0.002) and waist (r = 0.45, P = 0.0006), but not with postprandial lipids.

Conclusion: A higher C-reactive protein in IGT, and its positive correlation with insulin resistance indices, but not with postprandial lipaemia, suggests that the clustering of these factors, characteristic of the metabolic syndrome, occurs earlier than postprandial lipid abnormalities.

Key-words: Impaired glucose tolerance - Postprandial lipaemia - C-reactive protein - Glucose - Triglycerides - Fibrinogen - HOMA-IR.

RESUMÉ

Facteurs de risque émergents et indices d’athérosclérose précoce chez des sujets intolérants au glucose

Objectif: Analyser la réponse à une charge lipidique, les marqueurs inflammatoires et l’épaisseur intime-média carotidienne chez des sujets intolérants au glucose.

Méthodes: Chez 54 sujets, hommes et femmes, d’âge moyen 58 ans ont été réalisés : 1) une évaluation clinique; 2) une hyperglycémie provoquée orale avec 75 g de glucose classée soit normale (glycémie 2 h < 1,40 g/l, n = 37), soit intolérance au glucose (IGT) (glycémie 2 h comprise entre 1,40 et 2 g/l, n = 17); 3) un prélèvement sanguin obtenu après 12 heures de jeûne (glycémie, lipides, insuline, protéine-C réactive, fibrinogène), et permettant le calcul de l’indice HOMA-IR. En outre, la glycémie, le fibrinogène et les triglycérides ont été dosés 4 et 6 heures après charge lipidique (1 000 kcal, lipides 65 g). L’épaisseur intima-média de la carotide a été calculée à partir de la moyenne de 6 mesures (les trois plus élevées de chaque carotide) évaluées par ultrasonographie (transducteur de 7 MHZ).

Résultats: Nous avons observé dans le groupe des sujets intolérants au glucose une élévation significative (P < 0.001) de la glycémie (0.89 ± 0.01 vs 1.04 ± 0.08 g/l), de l’indice HOMA-IR (1.69 ± 1.2 vs 2.93 ± 2.2) et du tour de taille (91 ± 14 vs 101 ± 9 cm). En revanche, alors qu’il n’y avait pas de différences entre les deux groupes en ce qui concernait les paramètres lipidiques du sérum à jeun, l’épaisseur intima-média carotidienne (P = 0.58) et les triglycérides après charge lipidique (P = 0.74), les concentrations plasmatiques de fibrinogène (2.84 ± 0.06 et 3.05 ± 0.01 g/l, P = 0.04) et de protéine C-réactive (2.11 ± 0.33 et 4.19 ± 0.65 mg/l, P = 0.003) étaient plus élevées chez les intolérants au glucose. Une corrélation positive a été observée entre les taux de protéine C-réactive et l’indice HOMA-IR (r = 0.45, P = 0.001), la glycémie à jeun (r = 0.43, P = 0.002) et le tour de taille (r = 0.45, P = 0.0006), mais non pas avec les lipides sériques après charge lipidique.

Conclusion: L’existence chez les sujets intolérants au glucose d’une élévation de la protéine C-réactive, en corrélation positive avec les indices de résistance à l’insuline, mais non avec les paramètres lipidiques du sérum dosés après surcharge lipidique, suggère que ces anomalies caractéristiques du syndrome métabolique apparaissent avant les anomalies postprandiales des lipides.

Mots-clés: Intolérance au glucose - Lipémie post-prandiale - Protéine-C réactive - Triglycérides - Fibrinogène - HOMA-IR.

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Introduction

Atherosclerosis is a complex and multifactorial disease, which determines clinical events that cause significant morbi-mortality. Recent investigation of the mechanisms which cause atherosclerotic disease suggest an important role for inflammation in its development, progression and clinical endpoints [1]. Fasting hypertriglyceridaemia also has an established role in the genesis of atherosclerosis [2]. In the postprandial state, however, sustained high levels of triglyceride–rich lipoprotein can cause endothelial dysfunction [3], nitric oxide is less available and higher levels of oxidative stress are generated [4], all important changes in the development of atherosclerosis. High sensitive C-reactive protein (CRP), an inflammatory marker [5] and postprandial hyperlipaemia, an early marker of metabolic abnormalities not observed in the fasting state are not yet recognized as risk factors to be treated [6–8].

Impaired glucose tolerance is associated with a higher risk of developing diabetes [9,10], atherosclerosis [11], mortality and cardiovascular disease [12,13]. Diabetic macroangiopathy may develop earlier than microangiopathy, in a phase where plasma glucose levels are not yet obviously high, and there is no clinical diagnosis of the disease [14]. Early glucose homeostasis abnormalities (dysglycaemia) [15] or metabolic derangements that are usually associated (central obesity, arterial hypertension, dyslipidaemia, insulin resistance, ie, the metabolic syndrome) [16] are involved in the atherogenic profile presented by these individuals previous to the diagnosis of diabetes [17].

Recently, new data was reported showing the predictive value of low-grade inflammation for the development of diabetes [18], and subjects with impaired glucose tolerance also have higher levels of inflammatory markers [19,20]. C-reactive protein is associated with high carotid intima-media thickness (IMT) in individuals with no glucose metabolic abnormalities [21,22], and in diabetic individuals [23], but this relationship was not studied in impaired glucose tolerance. Fibrinogen, an acute-phase reactant, has an important role in platelet adhesion and aggregability [24]; their levels were associated with cardiovascular disease [25,26] and with diabetes, insulinemia and leukocyte count [27].

Postprandial triglycerides are associated with higher IMT in normal subjects, a relationship which is independent of other coronary artery disease risk factors and fasting triglyceride levels [28]. We [29] and others reported that in DM, the postprandial triglyceride excursion is high and prolonged [3,30]. However, a case-control study could not show an association between postprandial lipids and established coronary artery disease [30], and other authors described its association with high IMT [8]. Axelsen et al. demonstrated a postprandial lipid intolerance in healthy family members of diabetic individuals [7], but Henkel et al. [31] and Higashi et al. [32] did not observe higher postprandial lipaemia in individuals with impaired glucose tolerance.

Few studies evaluated individuals with impaired glucose tolerance concerning the emerging risk factors for atherosclerosis. The aim of the present study was to evaluate CRP, fibrinogen and postprandial triglyceride response to an oral lipid overload and to relate them to IMT in individuals with impaired glucose tolerance.

Methods

A group of 309 subjects was recruited by means of announcements, and those who fulfilled the inclusion criteria and who did not present the exclusion criteria were selected. Normal individuals with no personal history of diabetes, older than 40 years, both male and female, who presented triglycerides (TG) lower than 150 mg/dl and plasma glucose (G) lower than 140 mg/dl (test strips, Advantage, Roche, Indianapolis, IN, USA) were included. The test strips were used only for selection of the individuals; the oral lipid overload test was performed using standard laboratory techniques, as described later. Individuals with chronic diseases (hepatic and renal) and who use drugs known to interfere in lipid or glucose metabolism (lipid-lowering drugs, anti-hyperglycemic drugs, hormone replacement therapy, vitamin supplements, thiazides, β-blockers) were excluded. Subjects who were not in the fasting state or because they had pre-determined exclusion criteria were excluded. Because of this, most individuals from the 309 who came to the Hospital were excluded.

The selected subjects were submitted to a 75-g oral glucose tolerance test (OGTT) in accordance with the recommendations of the American Diabetes Association [33]. Those diagnosed as diabetics (fasting G > 126 mg/dl or 2 h G > 200 mg/dl, n = 6) were excluded. Subjects with 2 h G < 140 mg/dl, n = 37 were considered normal (C); those with 2 h G between 140 and 200 mg/dl, n = 17 were considered to have IGT.

One week after the individuals were selected they returned to the hospital, on 12-hour fasting. Blood was collected in the fasting state and 4 and 6 h after the oral intake of the test meal. The subjects had to spend the time during the test in the sitting position to avoid physical activity. During the time the participants spent waiting for blood collections, a questionnaire and clinical examination were performed.

The oral lipid overload (OLO) consisted of a mixed meal composed of 200 ml milk, 100 ml coffee, 16 g sugar, 50 g scrambled eggs, 15 g sausage, 10 ml soybean oil, 50 g bread, 10 g margarine, 30 g ham, 25 g cheese and 100 g avocado (1000 kcal, 27% carbohydrates, 15% proteins and 58% lipids or 64 g total fat, 20 g saturated fat, 22 g monounsaturated, 20 g polyunsaturated and 300 mg cholesterol) as proposed by Boquist et al. [6]. Each subject gave written informed consent, and the protocol was approved by the Hospital Ethics Committee.
Plasma glucose, aminotransferases (aspartate and alanine aminotransferases), bilirubins, alkaline phosphatase, creatinine, urea, total cholesterol, high-density lipoprotein cholesterol (HDL-c) and TG were determined by automated enzymatic commercial kits (Roche, Manheim, GE). Serum insulin was determined by enzyme immunoassay commercial kits (Abbot-Murex, Park, IL, USA). Low-density lipoprotein cholesterol (LDL-c) was calculated by the formula of Friedwald and very low density lipoprotein cholesterol (VLDL-c) was calculated by the TG/5 formula. Insulin resistance was assessed by the HOMA-IR (homeostasis model assessment of insulin resistance), which is the product of the fasting plasma glucose (mmol/l) by plasma insulin (µ/ml), divided by a constant (22.5) [34]. Fibrinogen (F) was evaluated on Fibrintimer II (Dade Behring Inc., Newark, DE, USA) and processed in the auto-analyser (CA-540, Sysmex) and CRP by nephelometry (nephelometer BN100, Dade Behring Inc., Newark, DE, USA).

All these measurements were determined in fasting blood samples; 4 and 6 h after the oral lipid overload samples were analyzed for plasma glucose and TG. Fibrinogen was evaluated in fasting blood samples and 6 h after the OLO.

**Carotid intima-media thickness (IMT)**

The measurements of the intima-media thickness were performed in a noninvasive manner using echo B mode ultrasonography with an ultrasound device (HP SONOS 2500) and a 7-megahertz transducer. The value used as a measure of thickness of the intima-media layer was obtained after recording all the extensions of both common carotid arteries in VHS tape (off line). The measurements of the intima-media thickness were performed by an examiner who ignored whether the specimen belonged to the control or IGT group. The site chosen for measurement was the segment with the thickest intima-media layer, independent of whether it was the right or left carotid artery. Only the arterial wall further away from the transducer (contralateral to the transducer) was used for measurement, and an average of 3 measurements were taken. The intima-media thickness considered on ultrasound is the distance between the luminal face of the endothelium and the distal interface of the muscle layer [35].

**Statistical analysis**

All data are expressed as mean ± SEM. For all analyses, the level of significance was 0.05. Differences between mean values of variables were tested by the Student t-test. Categorical variables were analyzed using Chi-square analysis. A parametric regression model (Pearson) was used to assess the relationship between variables. The variables obtained after the lipid overload (G, TG and F) were compared at each point of evaluation between groups (baseline, 4 and 6 hours after the lipid overload; Student unpaired t-test) and for each group at the different moments of the evaluation (0 vs 4 and vs 6 h after the lipid overload; repeated measure ANOVA, post-hoc Student Newman Keuls) and by comparison of the areas under the curve (AUC) of the 2 groups (Student t-test).

**Results**

**Basal characteristics of the individuals studied**

The clinical characteristics of the studied sample are shown on Table I. There were no differences between groups concerning mean age, male gender percentage and fasting lipid profile. However, fasting plasma glucose and 2-h plasma glucose after the OGTT, HOMA-IR, weight, abdominal circumference and body mass index were significantly higher in the IGT group. Higher insulin levels were observed in the same group as compared to C, although significance was borderline (P = 0.08). The number of smokers was similar between groups (13.5 vs 5.9% in C and IGT, P > 0.05).

**Oral lipid overload response**

Figure 1 shows plasma triglycerides (A), glucose (B) and fibrinogen (C) after the ingestion of the OLO. No differences were observed between groups in regard to 4 (P = 0.54) and 6-h (P = 0.74) triglyceride oral lipid overload response, as well as to 4 (P = 0.40) and 6-h (P = 0.48) plasma glucose. Fibrinogen was more elevated in IGT vs C after the OLO, although significance was borderline (284.3 ± 6 and 305.0 ± 10 mg/dl, P = 0.05).

The AUC for triglyceride response to the OLO was similar between the studied groups (1144.7 ± 75 and 1171.4 ± 109 mg/dl in C and IGT, P = 0.36). There was a significant difference between the AUC for plasma glucose in response to the OLO, which was higher for the IGT group (507.4 ± 7.3 and 540.0 ± 17.0 mg/dl in C and IGT, P = 0.04). For the fibrinogen response to the OLO there was a borderline difference between groups, higher in the IGT group (1709.3 ± 31.3 and 1818.70 ± 55.8 mg/dl in C and IGT, P = 0.07).

**Carotid intima-media thickness**

There was no difference between groups concerning IMC (0.1116 ± 0.023 vs 0.0935 ± 0.006 mm, in C and IGT, respectively, P = 0.58).

**Inflammatory markers**

High sensitive C-reactive protein was higher in individuals with IGT (2.11 ± 0.33 vs 4.19 ± 0.65 mg/l, P = 0.0026). These data are shown in Table I. Fasting fibrinogen was similar between groups (285.0 ± 6 vs 301.2 ± 10 mg/dl in C and IGT, P > 0.05).
and IGT, P = 0.13, Table I), but higher in the IGT groups after the OLO, as described above.

Correlation among the studied variables

High sensitive C-reactive protein was positively correlated with fasting plasma glucose (r = 0.47, P = 0.001), HOMA-IR (r = 0.45, P = 0.001, Figure 2 A) and abdominal circumference (r = 0.45, P = 0.0006), all surrogate markers of insulin resistance. Besides that, we showed a positive correlation between the CRP and fasting fibrinogen (r = 0.36, P = 0.01) and fibrinogen evaluated after the OLO (r = 0.42, P = 0.003, Figure 2 B). We did not find any statistically significant correlation between IMT and CRP (r = -0.02, P = 0.87), OLO 6-h triglycerides (r = -0.07, P = 0.61), plasma glucose in response to the OGTG (r = -0.07, P = 0.58), OLO 6-h plasma glucose (r = 0.03, P = 0.81) and OLO 6-h fibrinogen (r = -0.03, P = 0.83).

Discussion

In this study we evaluated CRP, postprandial hypertriglyceridemia and fasting and postprandial fibrinogen in subjects with impaired glucose tolerance. Although a subclinical inflammatory process was already present, no early atherosclerotic structural changes could be observed, as evaluated by the carotid intima-media thickness. Interestingly, the triglyceride response to an oral lipid overload was similar between groups, whilst fibrinogen, a thrombosis and inflammatory marker, was higher in subjects with impaired glucose tolerance.

Data from prospective studies have shown that CRP levels are predictive of cardiovascular events in healthy individuals, showing that CRP evaluation can improve the predictive power of the fasting lipoprotein profile [36]. We and others [29] demonstrated the elevation of this marker in impaired glucose tolerance [17,37-39]. The positive correlation between CRP and variables that reflect insulin resistance is in accordance with data from Festa et al [37] and Temelkova-Kurktschiev et al [17] in larger samples. The association between subclinical inflammation and insulin resistance, one of the cornerstones of the metabolic syndrome, reinforces its role in its development, characterizing the “common soil” theory in the causality of type 2 diabetes and cardiovascular disease [18,40].

The subclinical inflammatory process was observed before any atherosclerotic structural changes have been detected, suggesting that CRP elevation precedes the intima-media thickness abnormalities in this set of patients. The association between CRP and early intima-media thickness changes was, however, demonstrated in healthy individuals by some authors [21,22], but not by others [41]. Perhaps this marker has a greater association with clinical events, being a marker of plaque rupture and subsequent thrombosis, rather than a marker of the degree of atherosclerotic lesions. A higher intima-media thickness was demonstrated by Hidvegi et al. in impaired glucose tolerance, but these authors did not evaluate inflammatory markers, as

Table I

<table>
<thead>
<tr>
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<th>C  (n = 37)</th>
<th>IGT (n = 17)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58.3 ± 1.8</td>
<td>56.7 ± 3.2</td>
<td>0.63</td>
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<tr>
<td>Male gender (%)</td>
<td>40.5</td>
<td>41.2</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.76 ± 0.8</td>
<td>29.44 ± 1.2</td>
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<td>Abdominal Circumference (cm)</td>
<td>90.2 ± 2.3</td>
<td>101.2 ± 2.3</td>
<td>0.008</td>
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<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>137.4 ± 3.6</td>
<td>125.3 ± 3.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>84.03 ± 2.0</td>
<td>82.4 ± 2.8</td>
<td>0.63</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>85.4 ± 1.3</td>
<td>94.8 ± 2.5</td>
<td>0.0004</td>
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<tr>
<td>2-h plasma glucose (mg/dl)*</td>
<td>104.9 ± 3.5</td>
<td>160.1 ± 3.7</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Insulinemia (mU/l)</td>
<td>8.14 ± 0.8</td>
<td>10.79 ± 1.5</td>
<td>0.08</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.68 ± 0.2</td>
<td>2.93 ± 0.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>206.8 ± 6.4</td>
<td>225.1 ± 13.5</td>
<td>0.15</td>
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<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>124.4 ± 5.8</td>
<td>141.9 ± 11.1</td>
<td>0.12</td>
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<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>57.6 ± 2.1</td>
<td>57.9 ± 2.4</td>
<td>0.93</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>127.1 ± 8.2</td>
<td>133.6 ± 18.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>285.0 ± 6.0</td>
<td>301.2 ± 10.1</td>
<td>0.13</td>
</tr>
</tbody>
</table>

BMI: body mass index;*75-g oral glucose tolerance test. Mean ± SEM.
we did [42]. As might be expected, a larger sample could detect this difference between the studied groups.

A positive relationship was observed between CRP and fasting and post-oral lipid overload fibrinogen (6 h), suggesting an inflammatory process and a thrombotic trend in impaired glucose tolerance, in the fasting and postprandial state. Acute glycemic excursions followed by changes in coagulation could contribute to thrombotic events, since hyperglycemia reduces fibrinogen half-life, raises prothrombin, factor VII and platelet aggregation [43].

The triglyceride response to an oral lipid overload in impaired glucose tolerance was not different from controls, as other authors showed, but they did not evaluate inflammatory markers [31,32]. One study showed a more significant rise of triglyceride-rich lipoproteins after an oral lipid overload in this set of patients, and demonstrated that these abnormalities were associated with central obesity and high levels of fasting triglycerides [44]. Fasting hypertriglyceridemia is a well-known determinant of the postprandial response [45], and this was controlled in our study: the subjects have normal fasting triglycerides.

We could not find any association between triglycerides evaluated after an oral lipid overload and carotid intima-media thickness. Some case-control studies demonstrated a strong relationship between hypertriglyceridemia and carotid intima-media thickness if the blood samples were collected in the postprandial state and not in the fasting

Figure 1
Triglyceride (Panel A), plasma glucose (Panel B) and fibrinogen (Panel C) after the oral lipid overload ingestion (1000 kcal, 65 g lipids).
* P = 0.05 vs N.

Figure 2
Scattergrams plotting C-reactive protein (CRP) and HOMA-IR (Panel A) and CRP and fibrinogen after the oral lipid overload ingestion (Panel B). OLO: oral lipid overload.
state [6,8,46,47]. These studies, however, were performed in normal and diabetic subjects, none in subjects with impaired glucose tolerance.

The adhesion of leukocytes to endothelial cells has an important role in atherosclerosis development, occurring in response to cellular adhesion molecules overexpression on the endothelial surface [1]. Hyperlipidemia has been associated with high levels of adhesion molecules, a phenomenon that occurs mainly during the postprandial phase. A rise in nitrotyrosine, intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-1) and E-selectin was shown after an oral lipid and glucose overload, changes that were reversed by the use of sinvastatin [48]. Thus, even in the presence of normal triglyceride levels, there is a more intense inflammatory reaction in response to the oral lipid overload in subjects with impaired glucose tolerance, since they have high CRP levels in the fasting state and borderline postprandial fibrinogen rise.

A better understanding of the mechanisms involved in atherosclerotic cardiovascular disease has brought new diagnostic possibilities, including CRP and postprandial lipaemia evaluation. In this study these variables were studied in impaired glucose tolerance, and we concluded that inflammatory markers are elevated in the fasting state earlier than postprandial lipaemia changes can be observed, pointing out the former as possible early cardiovascular risk factor. However, prospective studies are necessary to evaluate both variables and their relationship with cardiovascular endpoints, in order to confirm this hypothesis.

(MTO de Ugarte, AA Dias and DM Hatem participated in this study in data collection exclusively)

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