Prevalence and atherosclerosis risk in different types of non-diabetic hyperglycemia. Is mild hyperglycemia an underestimated evil?

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Key words: Hyperglycemia, intima-media thickness, atherosclerosis, postprandial state, coronary risk factors

Summary: So far little is known about the importance of different types of non-diabetic hyperglycemia for the development of macrovascular disease. The aim of this work was to examine the intima-media thickness (IMT) of the common carotid artery (CCA), a well-accepted marker of atherosclerosis, as well as various risk factors for atherosclerosis in non-diabetic subjects with isolated fasting (IFH; n=67), isolated postchallenge (IPH; n=82) and combined hyperglycemia (CH; n=88) in comparison to normoglycemic (NG; n=265) controls. Subjects were participants of the RIAD study (Risk Factors in IGT for Atherosclerosis and Diabetes). IMT in the IPH (IMTmean: 0.89±0.02 mm; IMTmax: 1.01±0.02 mm; mean±SEM) and CH group (IMTmean: 0.91±0.02 mm; IMTmax: 1.03±0.02 mm) was significantly increased vs. the NG (IMTmean: 0.82±0.01 mm; IMTmax: 0.94±0.01 mm) and IFH group (IMTmean: 0.81±0.02 mm; IMTmax: 0.90±0.03 mm). IMT of the IFH group was similar to the normoglycemic controls. Subjects in the first and second tertile for postchallenge plasma glucose have similar carotid IMT irrespective of the level of fasting plasma glucose. The individuals of the third tertile for 2 h plasma glucose, whether in the first, second or third tertile for fasting plasma glucose, showed the same carotid IMT, which was significantly higher than all other groups, except for the one with lowest tertile for fasting and postchallenge plasma glucose. Except for total cholesterol and von Willebrand factor the levels of all other risk parameters were significantly higher in the hyperglycemic groups in comparison to the normoglycemic controls. Among the hyperglycemic subjects the CH group was at the highest risk for atherosclerosis with significantly increased levels of plasma triglycerides, fibrinogen, PAI-1, albuminuria, free fatty acids, insulin and proinsulin, and significantly reduced HDL-cholesterol in comparison to the normoglycemic controls. In summary, postchallenge hyperglycemia within the non-diabetic range is associated with atherosclerosis, as measured by the increased intima-media thickness of the common carotid artery. Furthermore, cardiovascular risk factors are significantly raised in all types of non-diabetic hyperglycemia.

Introduction

Hyperglycemia in type 2 diabetes mellitus is a well established risk factor for macrovascular disease (Kannel et al., 1979; Klein, 1995; Andersson et al. 1995; Hanefeld et al., 1996; Laakso et al., 1996; Hanefeld et al., 1997). The UK Prospective Diabetes Study (UKPDS Group, 1998) found that intensive blood glucose control substantially decreases the rate of microvascular diseases and of all diabetes related end-points. With respect to the relevance of non-diabetic hyperglycemia as a risk factor for atherosclerosis, however, there are different opinions and the studies conducted to clarify this issue have yielded conflicting results (Barrett-Connor, 1997; Stern, 1997). Thus, in several prospective trials in non-diabetic populations hyperglycemia was found to be predictive for the subsequent development of cardiovascular disease (Scheidt-Nave et al., 1991; Gerstein et al., 1996), whereas other large prospective studies failed to confirm the relationship to cardiovascular disease in moderate degrees of hyperglycemia (Stamler et al., 1979; Ohlson et al., 1986). We assume that hyperglycemia is of heterogeneous nature and its qualities depend to a great extent on the type of hyperglycemia being analysed. Thus, we would differentiate three types of non-diabetic hyperglycemia: isolated fasting (IFH), isolated postchallenge (IPH) and combined fasting and postchallenge hyperglycemia (CH). We hypothesise that these three types of non-diabetic hyperglycemia are of different importance with respect to atherosclerosis. To test this hypothesis we examined the intima-media thickness of the common carotid artery in subjects with IFH, IPH and CH in comparison to normoglycemic controls. The ultrasound examination of the artery wall is a suitable, highly reproducible, non-invasive method to assess directly the vessel status (Pignoli et al., 1986; Belcaro G et al., 1993; Bots et al., 1994; Persson et al., 1992). The intima-media thickness (IMT) of the common carotid artery (CCA) was shown to be associated to cardiovascular
risk factors and occurrence of macrovascular disease (Salonen et al., 1991). Furthermore, it was recently found to be a strong predictor for myocardial infarction and stroke in subjects without clinical cardiovascular disease (O’Leary et al., 1999). Therefore, carotid IMT has become a generally accepted good marker of atherosclerosis. To shed some light on the atherogenecity of the different types of non-diabetic dysglycemia various risk factors for atherosclerosis, such as plasma lipoproteins, blood pressure, insulin fractions, albuminuria, coagulation and fibrinolytic parameters were examined.

Material and methods

Material

Subjects were analysed from the RIAD Study (Risk factors in IGT for Atherosclerosis and Diabetes), details of which have been published elsewhere (Temelkova-Kurktschiev et al., 1998; Temelkova-Kurktschiev et al., 1999). Briefly, more than 1100 middle-aged subjects (40–70 years of age) were examined who were at risk to develop type 2 diabetes, such as positive familial history for diabetes, dys/hyperlipoproteinaemia and/or obesity. Since the IMT measurement of the CCA, due to technical reasons, was started several months after study begin, not all of the participants could be enclosed. In the present work we provide data from 502 non-diabetic individuals, defined according to the new ADA (The Expert Committee on the Diagnosis and Classification of Diabetes mellitus, 1997) and WHO criteria (Alberti et al., 1998), who had a complete examination programme. These subjects were divided into four groups: 1) normoglycemic (NG) controls (n = 265) with fasting plasma glucose (FPG) below 6.1 mmol/l and 2 h plasma glucose in oral glucose tolerance test (OGTT) below 7.8 mmol/l; 2) isolated fasting hyperglycemia (IFH) with FPG exceeding 6.1 mmol/l and 2 h plasma glucose in OGTT below 7.8 mmol/l (n = 67); 3) isolated postchallenge hyperglycemia (IPH) with FPG below 6.1 mmol/l and 2 h postprandial glucose level exceeding 7.8 mmol/l (n = 82); 4) combined fasting and postchallenge hyperglycemia (CH) with FPG above 6.1 mmol/l and 2 h plasma glucose in OGTT above 7.8 mmol/l (n = 88). Basic data of the examined subjects are shown in Table 1.

Oral glucose tolerance test (OGTT)

The participants were asked to abstain from heavy exercise or sedentary behaviour as well as from food excess or hunger for three days prior to the test. Venous blood was drawn after an overnight fast and further analysis conducted following a strict protocol. Standard OGTT was performed with 75 g glucose (Glucodex, Rougier Inc, Chambly, Quebec, Canada).

Laboratory methods

Plasma glucose was measured in fresh material by the hexokinase method. HbA1c was examined by high performance liquid chromatography (HPLC) on a Diamat analyser (BioRad Laboratories, München, FRG). HDL cholesterol was determined after precipitation with dextran sulfate on a Ciba Corning Express Plus analyser (Ciba Corning Diagnostics, Fernwald, FRG). Triglycerides and total cholesterol were measured enzymatically on a Ciba Corning Express Plus analyser (Boehringer, Mannheim, FRG). Free fatty acids were analysed by enzyme colorimetric assay with Boehringer Mannheim test kit. Proinsulin was measured by highly specific enzyme immunoassay (DGR Instruments, Marburg, FRG). Insulin was also determined by specific enzyme immunoassay (Medgenix Diagnostics Fleurus, Belgium). The total and active concentration of plasminogen activator inhibitor-1 (PAI-1) was examined using commercially available enzyme immunoassays (Immuno AG, Heidelberg, FRG), tissue plasminogen activator (tPA) by enzyme immunoassay (TintElize; Biopool, Umea, Sweden), fibrinogen by the method of Clauss (Fibrinogen; Boehringer Mannheim) and von Willebrand factor antigen by electroimmunoassay (Immuno AG). Urine was collected as fresh morning urine samples and albuminuria measured by nephelometry (Nephelometer BNII, Behring, FRG).

Ultrasound examination

B-mode ultrasound of the CCA was performed with Acuson 128XP computed sonography system using a 10 MHz linear array transducer, as previously described (Temelkova-Kurktschiev et al., 1998). In brief, the thickness of the intima-media complex was assessed in plaque-free portions of the 10 mm linear segment proximal to the carotid bulb. For each patient two measurements were performed bilaterally and the values were averaged (IMTmean). In addition, the maximal thickness (IMTmax) of the CCA was determined, visually judged by the observer, independently of the localization. Both study participants and physicians were blind to the laboratory values, as the ultrasound examination was performed on the day of blood collection for laboratory analysis.

Statistics

Statistical analysis was conducted using the SPSS/PC+ programme. IMT as well as metabolic and clinical parameters of the groups were compared by ANOVA. The level of significance was determined by p<0.05. Data are presented as mean±SEM. Since the χ²-test, used to check the sex distribution within the
groups, showed a significant difference, adjustment for gender was performed when comparing the IMT and atherosclerosis risk factors between the groups.

**Results**

In the analysed non-diabetic population we found 53% normoglycemic individuals, 13% subjects with IFH, 16% with IPH and 18% with CH. Basic characteristics of these subjects are summarized in Table 1. Study participants in the four groups were of similar age. The groups differed significantly for sex distribution, therefore all examined parameters, including the IMT were presented after adjustment for sex. All hyperglycemic groups showed significantly higher BMI and WHR in comparison to the controls. The android obesity was especially expressed in the CH group. Blood pressure, both systolic and diastolic, was significantly increased in the CH group in comparison to the normoglycemic group. HbA1c level was highest in the CH group, followed by the group with isolated fasting hyperglycemia.

As presented in Figure 1 the subjects with postchallenge non-diabetic hyperglycemia (group IPH and CH), irrespective of the level of fasting plasma glucose, showed significant thickening of the intima-media complex of the CCA in comparison to the individuals with normal glucose tolerance (NG and IFH group). The IMT of the subjects with isolated fasting hyperglycemia was similar to the normoglycemic controls. This was valid for both IMTmean and IMTmax.

The analysis of the atherosclerosis risk factors reveals that except for total cholesterol and von Willebrand factor the level of all other parameters was significantly higher in the hyperglycemic groups.

**Table 1** Basic characteristics of the examined subjects

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=265)</th>
<th>IFH (n=67)</th>
<th>IPH (n=82)</th>
<th>CH (n=88)</th>
<th>Significant difference between the groups (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (male/female)</td>
<td>115/150</td>
<td>33/34</td>
<td>29/53</td>
<td>48/40</td>
<td>P=0.039</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.3±0.5</td>
<td>56.0±1.0</td>
<td>54.1±0.9</td>
<td>56.1±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure syst. (mmHg)</td>
<td>131.5±1.2</td>
<td>135.5±2.3</td>
<td>136.3±2.0</td>
<td>138.7±1.9</td>
<td>1 to 3, 4</td>
</tr>
<tr>
<td>Blood pressure diast. (mmHg)</td>
<td>82.6±0.6</td>
<td>82.8±1.2</td>
<td>84.5±1.1</td>
<td>85.8±1.1</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6±0.2</td>
<td>27.5±0.5</td>
<td>27.6±0.4</td>
<td>28.7±0.4</td>
<td>1 to 2, 3, 4</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.87±0.00</td>
<td>0.89±0.01</td>
<td>0.89±0.01</td>
<td>0.92±0.01</td>
<td>1 to 2, 3, 4; 2 to 4; 3 to 4</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.45±0.02</td>
<td>6.41±0.04</td>
<td>5.69±0.03</td>
<td>6.46±0.03</td>
<td>1 to 2, 3, 4; 2 to 3; 3 to 4</td>
</tr>
<tr>
<td>2 h plasma glucose in OGTT (mmol/l)</td>
<td>5.77±0.1</td>
<td>6.12±0.1</td>
<td>8.85±0.1</td>
<td>9.14±0.1</td>
<td>1 to 2, 3, 4; 2 to 3, 4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.4±0.02</td>
<td>5.7±0.06</td>
<td>5.5±0.04</td>
<td>5.8±0.06</td>
<td>1 to 2, 3, 4; 2 to 4; 3 to 4</td>
</tr>
</tbody>
</table>

Data are mean±SEM. Values are shown after sex adjustment.

![Fig. 1 Carotid intima-media thickness in subjects with isolated fasting (IFH), isolated postchallenge (IPH) and combined non-diabetic hyperglycemia (CH) in comparison to normoglycemic controls (NG) after age and sex-adjustment. Data are mean±SD; *p <0.01 vs. NG; *p<0.01 vs. IFH](image)
in comparison to the normoglycemic controls (Table 2). Among the hyperglycemic subjects the CH group was at the highest risk for atherosclerosis with significantly increased levels of plasma triglycerides, fibrinogen, PAI-1, albuminuria, HDL-triglycerides, free fatty acids, real insulin and proinsulin, and significantly reduced HDL-cholesterol in comparison to the normoglycemic or some of the other hyperglycemic groups as indicated in the Table 2.

The three-dimensional presentation of IMT (Figure 2a, 2b) with respect to tertiles of fasting and 2 h plasma glucose in OGTT revealed that subjects in the first and second tertile for postchallenge plasma glucose have similar thickness of the intima-media complex irrespective of the level of fasting plasma glucose. The individuals of the third tertile for 2 h plasma glucose, whether in the first, second or third tertile of fasting plasma glucose, showed the same carotid IMT, which was significantly higher than all other groups, except for the one with lowest tertile for fasting and postchallenge plasma glucose.

**Discussion**

So far it is an open question whether non-diabetic hyperglycemia is related to macrovascular disease. The fact that some of the studies provide positive (Scheidt-Nave et al., 1991; Gerstein et al., 1996) and others negative results (Stamler et al., 1979; Ohlson et al., 1986) could be partially explained by the different way used to define the individuals as diabetic or non-diabetic, with or without applying

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Risk factors in isolated fasting (IFH), isolated postchallenge (IPH) and combined non-diabetic hyperglycemia (CH) in comparison to normoglycemic controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>N=265</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.77±0.06</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.36±0.07</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.55±0.02</td>
</tr>
<tr>
<td>HDL-triglycerides (mmol/l)</td>
<td>0.19±0.00</td>
</tr>
<tr>
<td>Free fatty acids (mmol/l)</td>
<td>0.42±0.01</td>
</tr>
<tr>
<td>Proinsulin 0’ (pmol/l)</td>
<td>1.68±0.08</td>
</tr>
<tr>
<td>Proinsulin 120’ (pmol/l)</td>
<td>9.21±0.6</td>
</tr>
<tr>
<td>Insulin 0’ (pmol/l)</td>
<td>64.1±2.9</td>
</tr>
<tr>
<td>Insulin 120’ (pmol/l)</td>
<td>278.8±20.6</td>
</tr>
<tr>
<td>v. Willebrandt factor (%)</td>
<td>122±5</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.87±0.03</td>
</tr>
<tr>
<td>PAI-1total (ng/ml)</td>
<td>61.1±4.6</td>
</tr>
<tr>
<td>PAI-1active (ng/ml)</td>
<td>35.4±2.5</td>
</tr>
<tr>
<td>TPA (ng/ml)</td>
<td>9.15±0.25</td>
</tr>
<tr>
<td>Albuminuria (mg/l)</td>
<td>11.5±2.1</td>
</tr>
</tbody>
</table>

Data are mean±SEM. Variables are adjusted for sex
OGTT or relying only on medical history (Barrett-Connor, 1997; Stern, 1997). In a well-defined non-diabetic population, diagnosed by using a standard OGTT we found some conflicting results on the issue of whether mild hyperglycemia is associated to intima-media thickening as a marker of atherosclerosis. Thus, in a previous publication (Temelkova-Kurktschiev et al., 1998) a weak association was established between fasting plasma glucose (FPG) and IMT in non-diabetic individuals, classified according to the old WHO criteria, with a cut-off limit for FPG of 7.8 mmol/l. The significant difference for IMT was found only in the top quintile of FPG (6.65 to 7.69 mmol/l) in men but not in women and was not confirmed if subjects with FPG level above 7.0 mmol/l were excluded from analysis (Hanefeld et al. (1), 1999). On the contrary, a rise of carotid IMT by quintiles of 2 h and maximal postprandial plasma glucose in OGTT was observed which was significant for the top quintile (8.24 to 11.1 mmol/l for 2 h plasma glucose; 11.6 to 15.27 mmol/l for maximal postprandial plasma glucose) (Hanefeld et al. (1), 1999). Neither of these previous analyses had taken into consideration the different patterns of hyperglycemia and in general the heterogeneity of hyperglycemia is usually being neglected. Recently isolated diabetic postchallenge hyperglycemia was reported to be highly atherogenic (Barrett-Connor et al., 1998). Therefore, in the present work we compared different types of non-diabetic hyperglycemia with respect to IMT and atherosclerosis risk factors. Our data demonstrate convincingly that postchallenge non-diabetic hyperglycemia, whether combined with fasting hyperglycemia or not, is associated with increased intima-media thickness of the CCA. Subjects with isolated postchallenge hyperglycemia have almost the same intima-media thickening as subjects with combined fasting and 2 h plasma glucose in OGTT. Taking into consideration the relatively high prevalence of IPH cases and the fact that these individuals would have remained undetected if restraining from OGTT, we would recommend that OGTT should be performed when screening for subjects at risk. These data are confirmed by the three-dimensional distribution of IMT in tertiles of fasting and postprandial plasma glucose. Actually, the third tertile for 2 h plasma glucose consisted of subjects with impaired glucose tolerance (2 h PG ≥7.8 mmol/l and <11.1 mmol/l). Thus, IGT is associated to increased IMT, no matter how high the level of fasting plasma glucose.

The isolated fasting hyperglycemia was not found to be related to carotid intima-media thickening. This is consistent with the finding of a previous publication of our group (Hanefeld M et al. (2), 1999) which in a matched-pairs designed study showed that impaired fasting glucose (IFG) is not a risk factor for atherosclerosis. The present work provides for the first time epidemiological data on the prevalence and atherosclerosis risk of the different types of non-diabetic hyperglycemia from a middle-aged European population in a cross-sectional study design and evaluation of a large spectrum of risk factors.

It should be noted that all hyperglycemic groups showed the typical signs of what is called “diabetic” dyslipidemia with increased level of plasma triglycerides and reduced HDL-cholesterol. Though there is no general agreement on the atherogenicity of plasma triglycerides, it is clear that hypertriglyceridemia (HTG) is associated with alterations of the LDL and HDL lipoprotein fractions, such as preponderance of the small dense LDL (Temelkova-Kurktschiev et al., 1997), which are particularly atherogenic (Austin, 1994). Furthermore, the HDL particles in HTG subjects are triglyceride-enriched, which was the case in the IFH and CH groups.

![Fig. 2b Maximal intima-media thickness (IMTmax) in tertiles (T) of fasting and 2 h plasma glucose (2 h PG) in OGTT in non-diabetic individuals after adjustment for age and sex. *p<0.05 vs all groups of the second tertile for 2 h PG and to second and third tertile of PG0 in the first tertile of 2 h PG](image-url)
Triglyceride-rich HDL are more susceptible to lipolysis by the hepatic lipase and are cleared more rapidly from the bloodstream which results in disturbed reverse cholesterol transport.

Clustering of standard risk factors for atherosclerosis was observed in all hyperglycemic groups. Thus, microalbuminuria, which is a well established independent predictor of macrovascular disease and mortality in diabetic and non-diabetic population (Mogensen, 1984; Damsgaard et al., 1990) was somewhat higher in the IFH and IPH groups and significantly increased in the CH individuals vs. the normoglycemic controls. Blood pressure also increased in parallel to plasma glucose with a significant difference between the CH vs. NG group. Hypertension is an accepted risk factor for cardiovascular disease and stroke as well as a determinant of carotid intima-media thickness (Gariety et al., 1993). Increased levels of insulin and proinsulin, detected by highly specific immunoassays, as well as impaired fibrinolysis, which is supposed to play a role in atherogenesis (Fujii, 1997), were observed in all hyperglycemic groups in comparison to the normoglycemic controls.

In summary, postchallenge hyperglycemia within the non-diabetic range is associated with atherosclerosis, as measured by the increased intima-media thickness of the common carotid artery. Furthermore, cardiovascular risk factors are significantly raised in all types of non-diabetic hyperglycemia.

References


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