The index of insulin resistance (FIRI) is not associated with plasma homocysteine levels in young, non-obese healthy men and women

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Summary

Study aim: To evaluate plasma homocysteine (Hcy), insulin and glucose levels in blood and the insulin resistance index (FIRI) in young, healthy non-obese men and women.

Material and methods: A total of 152 young, healthy, non-obese (BMI<30) men (n = 81) and women (n = 71) participated in the study. The following substances were assayed in blood using commercial kits: total plasma homocysteine by fluorescence polarisation immunoassay, plasma glucose – by the oxidase method, and insulin by radioimmunoassay using monoclonal antibodies. From the latter two, the index of insulin resistance (FIRI) was computed.

Results: Mean plasma homocysteine concentration in men was significantly (p<0.001) higher than in women (10.3 ± 3.0 and 8.4 ± 2.4 µmol/l, respectively) and that of FIRI was significantly (p<0.001) lower than in women (1.310 ± 0.483 and 1.437 ± 0.420, respectively). Neither in men nor in women were plasma homocysteine concentrations correlated with FIRI.

Conclusions: Although no association between circulating homocysteine and FIRI was found in young, non-obese men and women, the existence of such association in Type 2 diabetes cannot be ruled out.

Key words: Homocysteine – Insulin resistance index – Non-obese subjects

Introduction

Homocysteine (Hcy), a non-protein sulphur-containing amino acid, is formed during the metabolism of dietary methionine. Under physiological conditions, Hcy is either trans-sulphurated into cysteine in a reaction catalysed by cystathionine β-synthase (CBS), or remethylated back to methionine in two reactions: folate-independent, catalysed by methionine synthase (MS), or folate-dependent, catalysed by betaine-homocysteine S-methyltransferase (BHMT), the methylenetetrahydrofolate reductase (MTHFR) playing the key role [30].

Plasma Hcy concentrations are controlled by a variety of genetic and environmental factors. It is well documented that in humans and animals, mutations in the gene encoding enzymes of Hcy metabolism, result in hyperhomocysteinemia [4,15]. Similarly, deficiency of B-vitamins, high coffee consumption and smoking bring about elevated plasma Hcy levels [22]. In contrast, B-vitamins and folate supplementation has a potential to decrease circulating Hcy [17].

Epidemiological data and evidence from observational studies indicated that hyperhomocysteinaemia brings about several metabolic disorders, like e.g. atherosclerosis, thrombosis and endothelial dysfunction [27]. Moreover, elevated plasma Hcy levels were reported to adversely affect the pregnancy outcome, bone turnover, cognitive functions in the elderly, and recently also liver function [2,5,14,16].

There is also a wealth of studies focused on the relationship between circulating homocysteine (Hcy) and insulin resistance. However, a consensus on this association remains elusive. In Type 2 diabetic subjects, insulin resistance was identified as an independent determinant of plasma Hcy levels [8]. In addition, a population-based study on healthy, non-obese middle aged men and women, indicated that increased plasma Hcy concentrations are associated with insulin resistance [1,9]. On the other hand, no relationship between insulin resistance and circulating Hcy has been found in middle-aged men and women and in premenopausal women aged 17 – 43 years [13,26]. Moreover, the inverse
The relationship between plasma Hcy concentrations and insulin resistance was noted in men and women of mean age of 51 years [24].

It should be emphasised that all the cited studies focused on middle-aged subjects or on subjects characterised by highly differentiated age. However, no data concerning the relationship between plasma Hcy levels and insulin resistance in young individuals were found in the available literature. Thus, our study aimed at the evaluation of the association between plasma Hcy levels and insulin, as well as between circulating Hcy and the calculated insulin resistance index (FIRI) in college-age, healthy, non-obese men and women.

Material and Methods

Subjects: The participants were recruited by advertisements posted in student dormitories and by spreading oral information. A total of 83 college-aged men and 80 women volunteered to participate in the study. All subjects were healthy, non-smokers, not taking any regular medication and non-obese (BMI<30). All subjects qualified for the study submitted their written consents to participate in the study which was approved by the local Ethics Committee. Two men and 4 women were excluded due to insulin and glucose plasma levels exceeding relevant physiological limits, which suggested non-fasting condition, and 5 other women due to obesity (BMI>30).

In consequence, data analysis was performed for 81 men and 71 women. In all subjects body mass and height were measured using standard medical scales and anthropometer; body fat content was determined using the bioelectrical impedance technique (BC 418 MA equipment, Tanita Co., Japan). Inter- and intra-assay coefficients of variation for body fat measurements did not exceed 2%.

Methodology: Blood was withdrawn between 8:00 – 8:30 a.m. after overnight fasting from the antecubital vein into heparinised plastic tubes and immediately centrifuged for 15 min at 4000 rpm, 4°C. The collected plasma was stored at -70°C until assayed. Plasma glucose was determined using the oxidase method (commercial kits of Randox Laboratories, U.K.), inter and intra-assay coefficients of variation not exceeding 5%. Total plasma homocysteine was determined using fluorescence polarisation immunoassay (FPIA) (commercial kits of Abbot, USA), inter and intra-assay coefficients of variation not exceeding 5.2%. Insulin was radioimmunoassayed using monoclonal antibodies (commercial kits of BioSource, Belgium), inter and intra-assay coefficients of variation equal to 2.2 and 6.5%, respectively. All assays were run in duplicates. Insulin resistance was evaluated by homeostasis model assessment (FIRI) calculated from fasting insulin and glucose concentrations (insulin [µIU/ml] × glucose [mmol/L]/25) [7].

Data analysis: All variables proved normally distributed by the Shapiro-Wilk’s test. Student’s t-test for independent data was used to assess the between-group differences. Pearson’s correlations between plasma Hcy and other biochemical variables were computed. Statistica 7.1 (Statsoft, USA) software was used in data analysis, the level of p≤0.05 being considered significant.

Results

The results of the study are presented in Table 1. Plasma Hcy and glucose levels in men were significantly higher than in women (p<0.001 and p<0.05, respectively), in case of plasma insulin the situation was reversed (p<0.001). Mean FIRI value was significantly lower in men than in women (p<0.001). Neither in men nor in women was circulating Hcy correlated with insulin, glucose or FIRI values.

Table 1. Mean values (±SD) of anthropometric and biochemical variables in young non-obese men and women

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 81)</th>
<th>Women (n = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.8 ± 0.8</td>
<td>19.9 ± 1.1</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>180.6 ± 6.1</td>
<td>167.3 ± 5.3</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>76.6 ± 8.9</td>
<td>59.0 ± 7.1</td>
</tr>
<tr>
<td>BMI</td>
<td>23.5 ± 2.5</td>
<td>21.1 ± 2.2</td>
</tr>
<tr>
<td>Body fat content (%)</td>
<td>12.4 ± 4.5</td>
<td>22.1 ± 4.3</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.7 ± 0.5</td>
<td>4.5 ± 0.4*</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>6.9 ± 0.8</td>
<td>8.1 ± 2.4***</td>
</tr>
<tr>
<td>FIRI</td>
<td>1.310 ± 0.483</td>
<td>1.437 ± 0.420***</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>10.3 ± 3.0</td>
<td>8.4 ± 2.4***</td>
</tr>
</tbody>
</table>

Significantly different from the respective value in men: * p<0.05; *** p<0.001

Discussion

The higher Hcy levels in male than in female subjects found by us were in agreement with other data [19] and close to those reported by others for subjects of similar age [3]. The gender-related differences in plasma Hcy concentrations have not been explained; however, a higher remethylation rate of Hcy to methionine in women than in men might be, at least partially, responsible [10]. In addition, the contribution of sex hormones to the regulation of plasma Hcy concentration was discussed but, until now, the data are contradictory indicating an inverse or no correlation between plasma Hcy and female sex hormones [12,20].
No relationship between circulating Hcy and insulin resistance index (FIRI) was found in this study which was at variance with other reports [1,9] in which, however, the subjects had higher BMI values suggesting a higher body fat content than in our participants. Considering the positive relationship between plasma Hcy and body fat content, and between body fat content and insulin resistance [11,28], an indirect relationship between insulin resistance and circulating Hcy could not be ruled out. Such an assumption is supported by data which indicate that elevated plasma Hcy levels in Type 2 diabetic patients are due to insulin-induced decrease in glomerular filtration, but not to hyperinsulinemia per se [21]. In addition, the pharmacological improvement in insulin action does not necessarily mean decreased plasma Hcy levels [6]. Thus, it seems feasible that elevated plasma Hcy concentrations observed in hyperinsulinemic subjects do not reflect a direct relationship between insulin action and plasma Hcy concentration and correlations occur in case of complications of Type 2 diabetes. Moreover, it should be stressed that insulin per se has a potential to decrease plasma Hcy levels due to activation of Hcy metabolising enzymes – cystationine β-synthase (CBS), and betaine-homocysteine S-methyltransferase (BHMT) in the liver [29]. Therefore, hyperinsulinemia would directly lead to decreased circulating Hcy. On the other hand, high levels of circulating Hcy may induce insulin resistance since Hcy was found to disrupt the insulin-signalling pathway and to depress adiponectin while inducing the resistin synthesis in vitro and in vivo [18,23,25].

In conclusion, it seems that there is no association between circulating homocysteine and insulin resistance index – FIRI, at least in young, healthy non-obese men and women. However, such a relationship may develop with increasing body fat, in Type 2 diabetes and/or hyperhomocysteinaemia.

References


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