Gender modulates the relationship between body weight and plasma glucose in overweight or obese subjects

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1. Introduction

Overweight and obesity are, as long since known, related to impaired glucose metabolism and diabetes[1–3]. Furthermore in obese or in non-obese people of both sexes, even small increases in body weight after the age of 18 years, lead to a significant increase in the relative risk to develop diabetes mellitus[4–9].

It is likewise known that fasting plasma glucose (FPG) is an important predictor for the development of diabetes, even when it is in its normal range[10–12], and it is thereby possible to hypothesise that weight change during the adult life and
plasma glucose are each other related even in non-diabetic people.

Besides, in addition to being related to body weight, plasma glucose and its metabolism are influenced by gender [13–16] and in line with this assumption a question which awaits an answer is whether gender modifies the relationship between plasma glucose and body weight or its change during the adult life.

With such premises we performed this study utilizing the database of the Outpatient Clinic of the Obesity Unit of our Hospital, concerning overweight or obese patients without frank diabetes, to investigate firstly how strictly fasting plasma glucose correlates with weight, as well as with its increase after the age of 18 years, and, secondly, whether gender plays a role in these relationships.

### 2. Materials and methods

#### 2.1. Subjects

Study population was composed by all patients consecutively sent by their family physicians to obtain dietetic advice during a 2-year period at the Obesity Unit of our Hospital, as recorded by the database of the Outpatient Clinic of the Obesity Unit. Patients were considered for this study if BMI was ≥25 kg m⁻², had no history of diabetes mellitus, plasma glucose was <7 mmol/l, did not receive any antidiabetic treatment, and if they had no history of coronary heart disease, peripheral vascular disease or cancer.

We enrolled 1063 patients of whom 395 males and 668 females of whom 394 were pre- and 274 were post-menopausal. All subjects were Caucasian.

In all patients blood pressure was the mean value of two consecutive measurements while sitting and fasting plasma glucose was routinely performed by means of standard methods (Autoanalyzer) in the morning before breakfast.

#### 2.2. Methods

Both actual weight (measured in light cloths) and height and accordingly Body Mass Index (BMI), as well as weight at age of 18 years (as reminded by patients) were recorded: the weight change was determined by subtracting the weight at 18 years from actual weight (weight-diff) and only those with a weight-diff > 0 were considered. By doing so we excluded 81 individuals (34M/47F) corresponding to the 7% of the original database population.

To diagnose impaired fasting glucose (IFG) we used the 1997 ADA criteria considering FPG ranging between 6.1 and <7 mmol/l [17] for two reasons, first it has been observed that, at least in European populations, reducing the threshold from 6.1 to 5.6 mmol/l, as suggested by ADA in 2003 [18], decreases both the specificity and the sensitivity of prediction for conversion from IFG to frank type 2 diabetes [19–22], and second 6.1 mmol/l constitutes the lower cut off value of the upper FPG decile in our population.

Diabetes in first-degree relatives was considered to define family history of diabetes.

Smoking habit referred to current status, while both ex-smokers and no-smoking people were considered as non-smokers.

Hypertension was diagnosed, according to standard criteria, when systolic blood pressure was >140 mmHg and/or diastolic blood pressure was ≥90 mmHg, or in presence of antihypertensive therapy.

The study was approved by the Ethics Committee of our Hospital.

#### 2.3. Statistical analysis

Univariate analysis comprised t-test with Bonferroni adjustment, χ², and regression analysis with computation of Pearson’s correlation coefficients.

To test the independence of the relation between FPG and weight change we used a multiple regression models where FPG was the dependent variable and waist circumference, weight change, age, presence of menopause and smoking acted as covariates. This model was moreover used to estimate the percentage of FPG variance explained by the set of independent variables.

Relative risks, defined as odds ratio, were calculated by using a multiple logistic analysis model (Logistic Procedure of SAS software) where glucose tolerance was categorised as presence-absence of IFG (dependent variable), and age, waist circumference, menopausal status and smoking habit were the independent variables.

All values are expressed as means ± S.D. and the level of significance was set at p < 0.05 for all analyses.

The statistical tests were performed by using SAS software for Windows, version 8.2 (SAS Institute Inc., Cary, NC, USA).

#### 3. Results

Weight change after 18 years, waist circumference and plasma glucose as well as prevalence of current smoking and percentage of individuals with IFG were significantly dissimilar in men as compared to women as shown in Table 1. In particular both mean plasma glucose and prevalence of IFG were significantly higher among males.

By univariate analysis age, actual BMI, waist circumference and weight change appeared loosely related to FPG in males as well as in women, even if the relation between plasma glucose and these anthropometric variables was more consistent in females (Table 2).

According to the multiple regression model waist circumference and weight change were related to FPG only in females (Table 3). As indicated by the R² values, the cumulative variance explained by this set of covariates was about twofold higher in females compared to males (0.15 vs. 0.08; Table 3).

The relative risk for entering into the IFG category, calculated as OR (95% CI) for each S.D. increase in weight change (~12 kg), adjusted for age, waist circumference, menopausal status and smoking habit is represented in Fig. 1. For each S.D. unit increase in weight change the relative risk of being classified as IFG was significantly raised of ~80% only in women (p = 0.002). Quite similar results were obtained when waist circumference was substituted by BMI or
when both variables were simultaneously present in the model (data not shown).

To evaluate the possible role of body weight at ‘baseline’ we divided the whole population into those with BMI at 18 years < 30 kg m\(^{-2}\) and those who were obese at that time. Obese subjects at 18 years were equally distributed between sexes, being 15 (3.8%) among males and 22 (3.3%) among females (Table 1). The inclusion of this new categorical variable into the logistic model did not change the results. Unchanged results were also obtained as regards the relationship weight change-FPG after the inclusion of obesity at 18 years or weight at 18 years as independent variables into the multiple regression model (data not shown).

Each S.D. increment in actual BMI or waist circumference predictably increased IFG risk adjusted for age either in males [1.321(1.004–1.724); \(p = 0.003\) and 1.316(0.999–1.719); \(p = 0.04\)] or females [1.843(1.435–2.378); \(p = 0.04\), and 2.022(1.548–2.657); \(p = 0.0001\), once again with a greater effect in women.

### Table 1 – Main characteristics of subjects under study

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>(p^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>395</td>
<td>668</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.1 ± 13.7</td>
<td>46.6 ± 12.9</td>
<td>NS</td>
</tr>
<tr>
<td>Post-menopausal (%)</td>
<td>–</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>21</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg m(^{-2})) at 18 years</td>
<td>31.5 ± 4.1</td>
<td>31.7 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>107.9 ± 8.6</td>
<td>99.4 ± 9.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>41</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>106.9 ± 12.1</td>
<td>105.6 ± 13.1</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>29</td>
<td>21</td>
<td>0.003</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>5.4 ± 0.7</td>
<td>5.1 ± 0.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>IFG (%)</td>
<td>14.4</td>
<td>8.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Diabetes in first-degree relatives.
** Tested by t-test after Bonferroni adjustment.
*** Impaired fasting glucose (FPG between 6.1 and 7 mmol/l).

### Table 2 – Pearson’s correlation coefficients (\(r\)) between fasting plasma glucose and age or body weight variables in males and females

<table>
<thead>
<tr>
<th></th>
<th>Males (r) ((p))</th>
<th>Females (r) ((p))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.23 (0.0001)</td>
<td>0.26 (0.0001)</td>
</tr>
<tr>
<td>Actual BMI</td>
<td>0.15 (0.003)</td>
<td>0.25 (0.0001)</td>
</tr>
<tr>
<td>Weight change after 18 years</td>
<td>0.19 (0.0001)</td>
<td>0.33 (0.0001)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.14 (0.004)</td>
<td>0.30 (0.0001)</td>
</tr>
</tbody>
</table>

4. Discussion

In agreement with previous studies our findings show that fasting plasma glucose is on average higher and IFG more prevalent in males, once more suggesting the role of sex hormones on blood glucose metabolism [16].

Furthermore, both cross-sectional and prospective studies have since long well established that weight increase after the age of 18–20 years has a strong predictive value for incident type 2 diabetes in both sexes [4–9,23]. In this regard it has been shown that weight increment predicts incident type 2 diabetes independently of baseline ‘early’ BMI, and that this trend is equally evident in obese as well as in non-obese people [9]. This finding has, moreover, been overall reinforced by the evidence of a significant reduction in diabetes risk after weight reduction [24–27].

It has also been previously found that either fasting plasma insulin or glucose, which can together be assumed as a proxy

![Fig. 1 – Risk of fasting hyperglycaemia for each S.D. unit augment in weight increase after 18 years expressed as odds ratio (95% CI), adjusted for age, waist circumference, smoking habit, in males and also for menopausal status in women.](image-url)
for peripheral insulin resistance, increase with the progressive augment of body weight in the adult life independently of the prevailing BMI and of the length of the observation period [28].

We observed a not too elevated rate of patients with IFG as compared with the mean prevalence found in other population studies such as Hoorn and DECODE [19,29], even considering that in our case we dealt with a selected obese people, in which altered glucose metabolism should be expected to occur more frequently. This can probably be explained by the relatively younger age of the subjects.

The most relevant result of our study is that in males, even in presence of a greater prevalence of IFG, dysglycaemia was less associated with anthropometric variables such as waist circumference or weight change. In particular it was evident that gender specifically modified IFG risk, since this latter was associated with weight increase only in females, independently from the menopausal status. Our data, however, do not permit to establish whether this response was really 'gender specific' or was differently due to behavioural aspects such as, for instance, difference in physical activity whose reduction permit to establish whether this response was really 'gender specific' and was differently due to behavioural aspects such as, for instance, difference in physical activity whose reduction has been identified as an important independent risk factor for impairing glucose metabolism [28]. As regards this point a limitation of this study was absence of information about physical activity as well as about nutritional habits. This issue remains thereby open also because, to our knowledge, the great majority of previous studies did not specifically address the question whether and/or eventually how much gender modifies the risk of altered glucose metabolism associated with weight gain. Even considering the background effect exerted by sex hormones on glucose metabolism [16], an indirect confirm of our findings comes from a recent European study, which, interestingly reported that severe weight gain in subjects aged 25 and 40 years was associated with an about threefold higher diabetes risk in women (4.3 times) then in men (1.5 times) [30].

The robustness of our finding is based on three points; first in females the rise in IFG risk is independent from menopausal status, even considering the confounding variable of the exposure time. This is important since menopausal state is a possible confounding variable due to the modulation of glucose metabolism by female sex hormones [31,32]. Second, this difference remains unchanged in spite of a weight increase which was on average nearly equal in both sexes (about 23 kg) and, third, this result remains consistent even after adjusting for BMI or waist circumference.

As to the possible effect exerted by exposure time which is, in our case, equivalent to subtracting 18 years from age, it seems to be equally associated with IFG risk in males and in females, being increased in both sexes by about 3–4% for any augment in each year (data not shown). This is in agreement, at least in males, with the findings of a previous large cohort study regarding about 7000 British men, which demonstrated a significant relationship between the duration of exposure time to weight increase on one hand and the risk for development of type 2 diabetes on the other [23].

Our findings suggest that obesity at 18 years seems to be a poor predictor of IFG, reinforcing the hypothesis that the prediction of incident diabetes is not linked with the early increase of BMI [9], even if this issue is not completely univocal [33], and is thereby still incompletely clarified.

There are several limits in the present study: first, it is a cross-sectional retrospective study, dealing with selected overweight-obese individuals, and it is therefore unable to clearly identify any cause-and-effect relationship as well as to evaluate any time-to-event analysis as regards the onset of IFG status.

Second, data about alteration of post-load glucose metabolism including impaired glucose tolerance and diabetes, were not available in our patients, even if there is to underline that IFG, especially using the 1997 ADA definition, is 'per se' a very robust risk factor for evolution to clinical diabetes, since about 6–7 persons with IGF progress to diabetes each year [19–22] and about the 30% of patients with IFG is expected to be classified as diabetic after an oral glucose load test [34].

Third, BMI at 18 years was self-reported, possibly introducing some flaws in its measure. However in this respect, self-reported weight and height have been shown to be reliable for population studies, even in the more advanced age [35,36], although no previous study has raised the issue of the reliability for self-reporting 18 years’ weight about 26–27 years later.

In conclusion our findings suggest that FPG is related to BMI, waist circumference and weight increase after 18 years in non-diabetic overweight-obese people, and that, after adjusting for main confounders, anthropometric variables and in particular weight change are linearly related to FPG in women, independently predicting fasting hyperglycaemia only in these latter. Although with the above reported limitations, this result suggests that the control of body weight could have a more profound effect in reducing the risk to develop type 2 diabetes in females and that this occurs independently from the hormonal status.

**Conflicts of interest**

All authors declare of not having any conflict of interest regarding the submitted manuscript.

**REFERENCES**


