Sex-specific differences in myocardial glucose metabolic rate in non-diabetic, pre-diabetic and type 2 diabetic subjects

Elena Succurro

University Magna Graecia of Catanzaro

Patrizia Vizza

University Magna Graecia of Catanzaro

Francesco Cicone

Magna Graecia University of Catanzaro

Velia Cassano

University Magna Graecia of Catanzaro

Mattia Massimino

University Magna Graecia of Catanzaro

Federica Giofrè

University Magna Graecia of Catanzaro

Teresa Vanessa Fiorentino

University Magna Graecia of Catanzaro

María Perticone

University Magna Graecia of Catanzaro

Angela Sciacqua

University Magna Graecia of Catanzaro

Pietro Hiram Guzzi

University Magna Graecia of Catanzaro

Pierangelo Vetri

University of Calabria

Francesco Andreozzi

University Magna Graecia of Catanzaro

Giuseppe Lucio Cascini

Magna Graecia University of Catanzaro

Giorgio Sesti

University of Rome-Sapienza

Research Article

Keywords: sex-differences, myocardial glucose metabolism, cardiovascular disease, type 2 diabetes, prediabetes, cardiac 18F-FDG PET

Posted Date: November 15th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3596006/v1

License: Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Cardiovascular Diabetology on April 26th, 2024. See the published version at https://doi.org/10.1186/s12933-024-02246-7.
Abstract

Background

Evidence has shown that women with type 2 diabetes (T2DM) have a higher excess risk for cardiovascular disease (CVD) than men with T2DM. Subjects with either T2DM or prediabetes exhibit myocardial insulin resistance, but it is still unsettled whether sex-related differences in myocardial insulin resistance occur in diabetic and prediabetic subjects.

Methods

We aimed to evaluate sex-related differences in myocardial glucose metabolic rate (MRGlu), assessed using dynamic PET with $^{18}$F-FDG combined with euglycemic-hyperinsulinemic clamp, in subjects with normal glucose tolerance (NGT; n = 20), prediabetes (n = 11), and T2DM (n = 26).

Results

Women with prediabetes or T2DM exhibited greater relative differences in myocardial MRGlu than men with prediabetes or T2DM when compared with their NGT counterparts. As compared with women with NGT, those with prediabetes exhibited an age-adjusted 35% decrease in myocardial MRGlu (P = 0.04) and women with T2DM a 74% decrease (P = 0.006), respectively. Conversely, as compared with men with NGT, men with T2DM exhibited a 40% reduction in myocardial MRGlu (P = 0.004), while no significant difference was observed between men with NGT and prediabetes. The statistical test for interaction between sex and glucose tolerance on myocardial MRGlu (P < 0.0001) was significant suggesting a sex-specific association.

Conclusions

Our data suggest that deterioration of glucose homeostasis in women is associated with a greater impairment in myocardial glucose metabolism as compared with men. The sex-specific myocardial insulin resistance could be an important factor responsible for the greater effect of T2DM on the excess risk of cardiovascular disease in women than in men.

Introduction

Cardiovascular disease (CVD) represents the leading causes of death worldwide both in men and women (1). In 2021, the International Diabetes Federation (IDF) Atlas estimated that 2.30 million cardiovascular deaths and 5.4 million deaths overall were attributable to elevated fasting plasma glucose (2, 3). Indeed, data from large longitudinal studies have shown that the risk for major cardiovascular events is 2–3 times higher in individual with type 2 diabetes (T2DM) as compared to people without diabetes (2, 4–10).

Although men have a higher absolute risk of CVD, several studies have shown that women with T2DM have an excess risk of CV events, including coronary heart disease and stroke as compared with men (5–10). The factors contributing to sex-related differences in relative risk of CV events is still a subject of debate. It has been suggested that deterioration in glucose homeostasis from normal glucose tolerance to prediabetes to overt T2DM is associated with worsening in metabolic risk profile and target organ damage in women than men (5, 11–15). CV risk factors progress during menopausal transition, determining greater accumulation of fat in visceral and ectopic tissues and aggravating insulin resistance, inflammation and dyslipidemia in women with T2DM (16). Moreover, it has been hypothesized that hyperglycaemia has a stronger effect on CV risk factors in women than men (5, 11–16).

It has been reported that subjects with T2DM and individuals at increased risk of T2DM, including those with prediabetes and metabolic syndrome, exhibit myocardial insulin resistance, considered an independent predictor of CV events (17–24). Impaired insulin-stimulated myocardial glucose metabolism has been associated with reduced myocardial mechano-energetic efficiency, and increased cardiac workload (24–25), both alterations linked to the development of heart failure and CV events (26, 27). Furthermore, a reduced myocardial glucose uptake has been associated with carotid, aortic and coronary atherosclerosis (23, 24, 28).

However, it is still unsettled whether sex-related differences in myocardial insulin resistance occur in diabetic and prediabetic subjects.

In light of the significant pathophysiological role of myocardial insulin resistance, in this study we aimed to investigate sex-related differences in insulin-stimulated myocardial glucose metabolic rate (MrGlu) using dynamic myocardial positron emission tomography (PET) with $^{18}$F-Fluorodeoxyglucose ($^{18}$F-FDG) combined with euglycemic-hyperinsulinemic clamp, in individuals without history of heart disease having different degrees of glucose tolerance.

Methods

Study participants

The study cohort comprised 57 subjects participating in the CATAnzaro MEtabolic Risk factors (CATAMERI), an ongoing observational study recruiting adult individuals with one or more cardio-metabolic risk factors recruited at a referral hospital of the University “Magna Graecia” of Catanzaro (18, 22). Eligible subjects were recruited according to the following inclusion criteria: age between 30 and 70 years, and positivity for one or more cardio-metabolic risk factors including family history of diabetes, dysglycemia, hypertension, dyslipidemia, and overweight/obesity. Exclusion criteria were type 1 diabetes, end-stage renal
disease, previous CVD on the basis of medical history, resting electrocardiogram and stress test or myocardial scintigraphy for individuals with T2DM, history of atrial fibrillation or other arrhythmias, right and left bundle branch block, dysynchrony in ventricular contraction, valvular heart disease, liver cirrhosis, history of malignant or autoimmune diseases, acute or chronic infections, history of alcohol or drug abuse and treatment with drugs known to influence glucose tolerance such as steroids and estro-progestins and medicaments affecting heart function including beta blockers and antiarrhythmic drugs. All subjects underwent anthropometrical evaluation including measurements of body mass index (BMI), waist circumference and body composition by bioelectrical impedance. Readings of blood pressure (BP) were obtained in the left arm of the supine patients, after 5 min of rest, using a standard sphygmomanometer. BP values were the average of three measurements after a 10 min period of rest in the supine position. After an overnight fasting, biochemical determinations and a 75g OGTT was performed in individuals with FPG < 126 mg/dl, HbA1c < 6.5% and no history of T2DM. According to the ADA criteria (29), individuals were classified as having normal glucose tolerance (NGT) when fasting plasma glucose was < 100 mg/dl (5.5 mmol/l), 2-h postload glucose < 140 mg/dl (< 7.77 mmol/l) and HbA1c < 5.7%, prediabetes when fasting plasma glucose was 100–125 mg/dl (5.5–6.9 mmol/l), 2-h postload glucose 140–199 mg/dl (7.77–11.0 mmol/l) or HbA1c 5.7–6.4%, T2DM when fasting plasma glucose was ≥ 126 mg/dl (> 7 mmol/l), 2-h post-load glucose was ≥ 200 mg/dl (> 11.1 mmol/l), HbA1c ≥ 6.5% or in treatment with antidiabetic drugs.

On the second day, after 12-h fasting, all subjects underwent \( ^{18} \text{F-FDG PET} \) scan combined with euglycemic hyperinsulinemic clamp.

The study was approved by the Ethical Committee (Comitato Etico Azienda Ospedaliera “Mater Domini”), and informed consent was obtained from each subject in accordance with principles of the Declaration of Helsinki.

\( ^{18} \text{F-FDG PET scan combined with euglycemic hyperinsulinemic clamp} \)

Myocardial glucose metabolic rate (MrGlu) was measured by \( ^{18} \text{F-FDG-PET} \) acquired during an euglycemic hyperinsulinemic clamp as previously described (24). Subjects received a priming dose of insulin (100 U/mL) (Humulin R, Eli Lilly) during the initial 10 min to raise the serum insulin concentration acutely (80 mU/m2 × min), and then it was maintained by continuous insulin infusion fixed at 40 mU/m2 × min (30). The blood glucose level was maintained constant at 90 mg/dl for the next 120 min by infusing 20% glucose at varying rates according to blood glucose measurements performed at 5-min intervals (mean coefficient of variation of blood glucose was < 4%). Glucose metabolized by the whole body (M) was calculated as the mean rate of glucose infusion measured during the last 60 minutes of the clamp examination (steady state) and was expressed as milligrams per minute per kilogram fat-free mass (M_{FFM}).

The \( ^{18} \text{F-FDG-PET imaging} \) procedure was performed on a hybrid PET/CT scanner (GE Discovery ST8: 2D PET scanner), starting 60 minutes after the insulin infusion. A 60-min dynamic acquisition was started simultaneously with the intravenous injection of 370 MBq \( ^{18} \text{F-FDG} \), according to the following time frame sampling: 8 x 15s, 2 x 30s, 2 x 120s, 1 x 180s, 6 x 300s, 2 x 600s (31). PET images were reconstructed in a 128 x 128 matrix using a OSEM algorithm, and corrected for decay and attenuation based on co-registered CT. The insulin-glucose infusion continued during the entire PET acquisition. The estimation of myocardial MrGlu was performed by Patlak compartmental modelling (32), using the graphical tool specific for cardiac images analysis (PCARD) implemented in PMOD Software platform (Version 3.806) (31). In PCARD, the full dynamic study is used for MRGlu calculation, and the arterial input function is extracted from a volume of interest (VOI) semi-automatically placed in the left ventricular cavity (32).

\textbf{Laboratory determinations}

Plasma glucose, total and HDL cholesterol, and triglycerides were assayed using enzymatic methods (Roche Diagnostics, Mannheim, Germany). HbA1c was measured with high performance liquid chromatography using an NGSP-certified automated analyzer (Adams HA-8160 HbA1c analyzer, Menarini, Italy).

\textbf{Statistical analyses}

Variables with skewed distribution including triglycerides were natural log transformed for statistical analyses. Continuous variables are expressed as means ± SD. Categorical variables were compared by \( \chi^2 \) test. Comparisons between women and men were performed using unpaired Student’s \( t \) test. Comparisons between NGT, prediabetes and T2DM groups were performed separately in men and women using a general linear model with post hoc Fisher’s least significant difference correction for pairwise comparisons. For all analyses a P value < 0.05 was considered to be statistically significant. All analyses were performed using SPSS software Version 29 for Mac.

\textbf{Results}

\textit{3.1 Differences in anthropometric and cardiovascular features between subjects with NGT, prediabetes and T2DM according to sex}

Anthropometric and cardiovascular features of individuals with NGT, prediabetes and T2DM according to sex are shown in Table 1. No sex-related differences in age, anthropometric, and cardiometabolic features were observed across the three glucose tolerance categories, except for levels of HDL cholesterol which were significantly lower in men as compared with women in all three glucose tolerance categories (Table 1).
Table 1
Differences in clinical characteristics of men and women with NGT, prediabetes, and T2DM

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Prediabetes vs. NGT</th>
<th>T2DM vs. NGT</th>
<th>Men</th>
<th>Prediabetes vs. NGT</th>
<th>T2DM vs. NGT</th>
<th>Women vs. Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT (n = 12)</td>
<td>Prediabetes (n = 7)</td>
<td>T2DM (n = 8)</td>
<td>P value</td>
<td>NGT (n = 8)</td>
<td>T2DM (n = 16)</td>
<td>P values</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>42 ± 8</td>
<td>49 ± 13</td>
<td>57 ± 2</td>
<td>0.1</td>
<td>46 ± 11</td>
<td>55 ± 5</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 ± 5.9</td>
<td>30.5 ± 7</td>
<td>31.2 ± 5.4</td>
<td>0.5</td>
<td>29.5 ± 3.8</td>
<td>25 ± 0.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>96.5 ± 13</td>
<td>99.5 ± 17</td>
<td>104.7 ± 11</td>
<td>0.6</td>
<td>104 ± 9</td>
<td>95 ± 6</td>
<td>0.08</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>112 ± 16</td>
<td>129 ± 10</td>
<td>125 ± 11</td>
<td>0.01</td>
<td>121 ± 19</td>
<td>127 ± 18</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 ± 10</td>
<td>76 ± 9</td>
<td>73 ± 10</td>
<td>0.3</td>
<td>76 ± 12</td>
<td>74 ± 11</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>66 ± 4</td>
<td>72 ± 11</td>
<td>75 ± 9</td>
<td>0.1</td>
<td>69 ± 10</td>
<td>68 ± 14</td>
<td>0.8</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>194 ± 47</td>
<td>200 ± 38</td>
<td>161 ± 22</td>
<td>0.7</td>
<td>193 ± 29</td>
<td>206 ± 27</td>
<td>0.5</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>57 ± 11</td>
<td>51 ± 6</td>
<td>48 ± 7</td>
<td>0.1</td>
<td>45 ± 12</td>
<td>41 ± 8</td>
<td>0.5</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>125 ± 39</td>
<td>136 ± 41</td>
<td>108 ± 24</td>
<td>0.5</td>
<td>125 ± 36</td>
<td>141 ± 22</td>
<td>0.3</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>117 ± 83</td>
<td>118 ± 34</td>
<td>156 ± 59</td>
<td>0.9</td>
<td>133 ± 75</td>
<td>130 ± 53</td>
<td>0.9</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>88 ± 6</td>
<td>94 ± 19</td>
<td>150 ± 37</td>
<td>0.5</td>
<td>&lt; 0.0001§</td>
<td>85 ± 6</td>
<td>0.5</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.5 ± 0.4</td>
<td>5.7 ± 0.3</td>
<td>7.8 ± 0.9</td>
<td>0.5</td>
<td>&lt; 0.0001§</td>
<td>5.4 ± 0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Anthypertensive therapy (%)</td>
<td>8.3</td>
<td>14.3</td>
<td>62.5</td>
<td>0.7</td>
<td>37.5 ± 25</td>
<td>66.7 ± 6</td>
<td>0.6</td>
</tr>
<tr>
<td>Lipid-lowering therapy (%)</td>
<td>8.3</td>
<td>14.3</td>
<td>75</td>
<td>0.9</td>
<td>12.5 ± 25</td>
<td>44.4 ± 6</td>
<td>0.6</td>
</tr>
<tr>
<td>Glucose-lowering therapy (%)</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>0.9</td>
<td>&lt; 0.0001§</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mefortin (%)</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>0.9</td>
<td>&lt; 0.0001§</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Whole body insulin-stimulated glucose disposal (mg/min x Kg FFMI</td>
<td>9.58 ± 8.3</td>
<td>3.74 ± 1.6</td>
<td>2.54 ± 2.7</td>
<td>0.2§</td>
<td>6.9 ± 6.1</td>
<td>5.6 ± 5.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Myocardial MRGlucose (µmol/min/100g)</td>
<td>25.7 ± 6.9</td>
<td>16.7 ± 7.2</td>
<td>6.6 ± 7.01</td>
<td>0.04§</td>
<td>28.3 ± 5.4</td>
<td>18.6 ± 6.4</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise indicated. Categorical variables were compared by χ² test. Comparisons between the three groups of glucose tolerance using a general linear model with post hoc Fisher’s least significant difference correction for pairwise comparisons. Comparisons between women and men using unpaired Student’s t test. §P values refer to results after analyses with adjustment for age. Triglycerides levels were log transformed for statistical analysis, b1 represent a back transformation to the original scale.

3.2 Differences in myocardial glucose metabolic rate and insulin sensitivity between subjects with NGT, prediabetes and T2DM according to sex

No sex-related differences in whole-body insulin-stimulated glucose disposal were observed between the three glucose tolerance categories (Table 1). No sex-related differences in myocardial glucose metabolic rate were observed in NGT and prediabetes groups (Table 1). Conversely, among T2DM patients, women exhibited a significant decrease in myocardial glucose metabolic rate than men (Table 1).
3.3 Age-adjusted differences in cardiovascular risk factors between women with NGT, prediabetes and T2DM

As compared with women with NGT, those with T2DM were older, and showed an increase in age-adjusted fasting plasma glucose and HbA1c (Table 1). In addition, as compared with women with NGT, both those with prediabetes and T2DM exhibited a progressive increase in age-adjusted values of systolic blood pressure. Moreover, women with T2DM were significantly more likely to be treated with lipid-lowering therapy as compared with those with NGT (Table 1).

3.4 Age-adjusted differences in cardiovascular risk factors between men with NGT, prediabetes and T2DM

As compared with men with NGT, those with T2DM were older, and showed an increase in age-adjusted fasting plasma glucose and HbA1c (Table 1). No significant age-adjusted differences were observed in cardiovascular risk factors among men with different glucose tolerance status.

3.5 Age-adjusted differences in myocardial glucose metabolic rate and insulin sensitivity between women with NGT, prediabetes and T2DM

Age-adjusted myocardial glucose metabolic rate was significantly lower in women with prediabetes (P = 0.04), and T2DM (P = 0.006) as compared with those with NGT (Table 1). Conversely, as compared with women with NGT, only women with T2DM exhibited a significant (P = 0.02) reduction in age-adjusted whole-body insulin-stimulated glucose disposal (Table 1).

3.5 Age-adjusted differences in myocardial glucose metabolic rate and insulin sensitivity between men with NGT, prediabetes and T2DM

As compared with men with NGT, age-adjusted myocardial glucose metabolic rate and whole-body insulin-stimulated glucose disposal were significantly lower in men with T2DM, but not in those with prediabetes (Table 1).

The estimated marginal means of myocardial glucose metabolic rate and whole-body insulin-stimulated glucose according to sex and glucose tolerance status are reported in Fig. 1. Prediabetic and T2DM women exhibited greater relative differences in myocardial glucose metabolism and whole-body insulin-stimulated glucose disposal, than prediabetic and diabetic men when compared with their NGT counterparts. Formal tests for glucose tolerance status × sex interaction were statistically significant for myocardial glucose metabolic rate (P < 0.0001), and whole-body insulin-stimulated glucose disposal (P = 0.01) (Fig. 1).

Discussion

To the best of our knowledge, the present study was the first to examine sex-related differences in myocardial glucose metabolism in individuals having different degrees of glucose tolerance. We found that deterioration in glucose homeostasis from normal glucose tolerance to prediabetes to T2DM was associated with a greater impairment in myocardial glucose metabolic rate, assessed using dynamic PET with \(^{18}\)F-FDG combined with euglycemic-hyperinsulinemic clamp technique, which allows the valuation of myocardial insulin resistance. Additionally, we found that prediabetic and T2DM women exhibited greater relative differences in whole-body insulin-stimulated glucose disposal, than prediabetic and diabetic men when compared with their NGT counterparts. These findings confirm and extend the notion that deterioration of glucose homeostasis in women is associated with a worsening in insulin sensitivity as compared with men (11, 14, 33). In keeping with the present data, a previous study reported a greater impairment in insulin sensitivity assessed by euglycemic hyperinsulinemic clamp in women with prediabetes than men when compared with their NGT counterparts (14). Accordingly, other studies have examined sex-related differences in insulin sensitivity using indices derived from oral glucose tolerance test (OGTT) in individuals having different degree of glucose tolerance showing that sex advantage in glucose metabolism seen in women with NGT vanished in T2DM (11, 33).

Growing evidence has shown that women with T2DM have a considerably higher diabetes-related relative risk for the incident of major CV events and mortality, including a 44% higher relative risk for coronary heart disease event, as compared with men (5–10). We found a significant reduction in myocardial glucose metabolic rate in women with T2DM than male counterparts. An impairment in insulin-stimulated myocardial glucose metabolism in women with T2DM may indicate an early stage of myocardial energy disarrangement and reduced cardiac mechano-energetic performance (22, 23). Indeed, lower myocardial glucose metabolic rate has been associated with a worse CV risk profile (23), and carotid and coronary atherosclerosis (23, 24, 28). Furthermore, we have previously shown that as compared with men with T2DM, women with T2DM exhibited a higher reduction in cardiac mechano-energetic efficiency, and an increase in left ventricular mass, both being predictors of CV events (12, 26–27, 34). Overall, the higher degree of myocardial insulin resistance observed in women with the altered glucose homeostasis as compared with men may be an early metabolic trigger leading to subsequent maladaptive changes involving cardiac geometry, myocardial mechanical energy efficiency, and coronary atherosclerosis, thus eventually ensuing in excess CV risk in women compared to men when diagnostic threshold of T2DM is reached. Clearly, further studies are warranted to confirm the role of myocardial insulin resistance in the sex-related differences in the development of CVD in T2DM.

The current results should be interpreted within the context of its strengths and limitations. A main strength is the use of gold standard methods to assess myocardial glucose metabolism by cardiac \(^{18}\)F-FDG PET scan combined with euglycemic hyperinsulinemic clamp technique, which allows the valuation of insulin-stimulated myocardial glucose uptake under uniform experimental conditions of euglycemia and physiological hyperinsulinemia (17, 39). Moreover,
glucose tolerance was accurately assessed using FPG, 2h post-load glucose levels during an OGTT, and HbA1c according to ADA criteria thus excluding any potential misclassification of participants (29). Additionally, all tests including $^{18}$F-FDG PET scan combined with euglycemic hyperinsulinemic clamp were collected by skilled examiners after a standardized training, who were blinded to the clinical data of the study participants.

Nonetheless, the present study also has some limitations. The results are only based on White individuals aging between 30 and 70 years thus limiting the generalizability of the present data to other ethnicities or to older individuals. Additionally, the cross-sectional design of the study precludes causal inferences, and, therefore, no conclusions regarding cause-effect relationships can be made.

**Conclusions**

In conclusion, the present study suggests that deterioration of glucose homeostasis in women is associated with a greater impairment in myocardial glucose metabolism in women as compared with men. These findings may help to clarify the pathophysiological mechanisms by which hyperglycemia exceeding the diagnostic threshold of T2DM almost completely abolish the female protection from CVD.

**Abbreviations**

- CVD: cardiovascular disease
- IDF: International Diabetes Federation
- T2DM: type 2 diabetes mellitus
- MrGlu: myocardial glucose metabolic rate
- PET: positron emission tomography
- $^{18}$F-FDG: $^{18}$F-Fluorodeoxyglucose
- BMI: body mass index
- BP: blood pressure
- OGTT: oral glucose tolerance test
- FPG: fasting plasma glucose
- ADA: American Diabetes Association
- NGT: normal glucose tolerance
- $M_{FFM}$: Insulin-stimulated glucose disposal corrected for fat-free mass
- FFM: fat-free mass
- PCARD: tool specific for cardiac images analysis
- VOI: volume of interest

**Declarations**

*Ethics approval and consent to participate*

The study was approved by the Ethical Committee (Comitato Etico Azienda Ospedaliera "Mater Domini"), and informed consent was obtained from each subject in accordance with principles of the Declaration of Helsinki.

*Consent for publication*

Not applicable.

*Availability of data and materials*

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.
**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This research received no external funding.

**Authors’ contributions**

E.S. researched and analyzed data and wrote and edited the manuscript. P.Vi. and P.H.G. analyzed the data from the cardiac PET scans, F.C. performed cardiac PET scans. V.C., M.M., F.G., T.V.F., M.P., A.S. researched data and reviewed the manuscript. P.Ve., F.A. and G.L.C. contributed to the discussion and reviewed the manuscript. G.S. designed the study, analyzed the data, and wrote and reviewed the manuscript. All authors have read and approved the final manuscript. G.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Acknowledgements**

Not applicable.

**References**


34. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991;114:345–52.

Figures
Figure 1

The estimated marginal means of cardiovascular variables according to sex and glucose tolerance status. A) Myocardial glucose metabolic rate; B) Whole-body insulin-stimulated glucose disposal.