Relative contribution of muscle and liver insulin resistance to dysglycemia in postmenopausal overweight and obese women: A MONET group study

Belinda Elisha, Emmanuel Disse, Katherine Chabot, Nadine Taleb, Denis Prud’homme, Sophie Bernard, Rémi Rabasa-Lhoret, Jean-Philippe Bastard

Abstract

Objectives. – The relative contribution of muscle and liver insulin resistance (IR) in the development of dysglycemia and metabolic abnormalities is difficult to establish. The present study aimed to investigate the relative contribution of muscle IR vs. liver IR to dysglycemia in non-diabetic overweight or obese postmenopausal women and to determine differences in body composition and cardiometabolic indicators associated with hepatic or muscle IR. Material and methods. – Secondary analysis of 156 non-diabetic overweight or obese postmenopausal women. Glucose tolerance was measured using an oral glucose tolerance test. Whole-body insulin sensitivity (IS) was determined as glucose disposal rate during a euglycemic-hyperinsulinemic clamp. Muscle and liver IR have been calculated using Abdul-Ghani et al. OGTT-derived formulas. Participant’s body compositions as well as cardiometabolic risk indicators were also determined. Results. – Overall, 57 (36.5%) of patients had dysglycemia, among them 25 (16.0%); 21 (13.5%); 11 (7.1%) had impaired fasting glycaemia, impaired glucose tolerance and combined glucose intolerance respectively. Fifty-three (34.0%) participants were classified as combined IS while on the opposite 51 participants (32.7%) were classified as combined IR and 26 (16.7%) participants had either muscle IR or liver IR. For similar body mass index and total fat mass, participants with liver IR were more likely to have lower whole-body IS, dysglycemia and higher visceral fat, liver fat index, triglycerides and alanine aminotransferase than participants with muscle IR. Conclusion. – In the present study, the presence of liver IR is associated with a higher prevalence of dysglycemia, ectopic fat accumulation and metabolic abnormalities than muscle IR.

Keywords: Obesity; Muscle insulin resistance; Liver insulin resistance; Glucose homeostasis

Résumé

But de l’objectif. – La contribution relative de la résistance à l’insuline (IR) musculaire (M) et hépatique (H) dans le développement des troubles de la régulation glycémique est difficile à établir. L’objectif de ce travail était d’étudier l’impact de l’IR M vs l’IR H sur les anomalies glycémiques dans

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une cohorte de patientes non diabétiques ménopausées obèses ou en surpoids et de déterminer les éventuelles différences de composition corporelle et de biomarqueurs cardiometaboliques associés à l’IR M ou H. Matériels et méthodes. — Cent cinquante-six femmes non diabétiques ménopausées obèses ou en surpoids ont été étudiées dans une analyse secondaire. La tolérance au glucose a été mesurée au cours d’une hyperglycémie provoquée par voie orale (HGPO). La sensibilité à l’insuline (SI) a été mesurée par une épreuve de clamp hyperinsulinémique euglycémiqne. L’IR M et l’IR H ont été calculées en utilisant les formules dérivées de l’HGPO décrites par Abdul-Ghani et al. La composition corporelle et des biomarqueurs de risque cardiometabolique ont également été déterminés. Résultats. — Globalement, 36,5 % (57) des participantes avaient une dysglycémie dont 25 (16,0 %) avaient une hyperglycémie modérée à jeun non diabétique, 21 (13,5 %) une intolérance au glucose et 11 (7,1 %) une anomalie combinée. Cinquante-trois (34,0 %) participantes étaient classées comme IS M et H tandis que 51 (32,7 %) avaient une IR combinée M et H, 26 (16,7 %) une IR M et 26 (16,7 %) une IR H. Enfin, pour un même indice de masse corporelle et une masse grasse totale comparables, les participantes avec une IR H étaient plus susceptibles d’avoir une IS globale réduite, une dysglycémie, un taux de graisse viscérale plus élevé, des triglycérides et des enzymes hépatiques plus élevés que celles avec IR M. Conclusion. — Cette étude démontre que l’IR H est associée à une plus forte prévalence de dysglycémie, d’accumulation de graisse ectopique et d’anomalies métaboliques que l’IR M.

Mots clés : Obésité ; Insulinorésistance musculaire ; Insulinorésistance hépatique ; Homéostasie du glucose

1. Introduction

Insulin resistance (IR) is defined by impaired response of a target tissue such as adipose tissue, liver and muscle to insulin [1]. Obesity predisposes to IR, which represents a core pathophysiological defect associated with an increase cardiometabolic risk including the development of type 2 diabetes [2]. However, due to the variety of tissues targeted by insulin action, the relative contribution of each insulin-responsive organ in the development of whole-body IR is difficult to establish [3]. In addition, the nature of the tissue (muscle or liver) more affected by IR might be determinant in the expression of the dysglycemia with predominantly fasting or postprandial hyperglycemia. According to previous report, muscle IR was related to postprandial hyperglycaemia while liver IR was rather associated to impaired suppression of hepatic glucose production by insulin resulting into fasting hyperglycaemia [4]. However, Abdul-Ghani et al. found in a sample of non-diabetic Mexican-American participants that those having muscle IR demonstrated both elevated fasting and postprandial glucose levels [5]. Knowing which organ is predominantly affected by IR could allow to investigate if some therapeutic interventions are more efficient in some patients e.g. Metformin in patients with predominant liver IR.

In the present study, we aimed to investigate the relative contribution of muscle IR vs. liver IR to dysglycemia in non-diabetic overweight and obese postmenopausal women. We will also determine if participants with muscle IR present differences in body composition and cardiometabolic risk factors when compared to those with liver IR.

2. Methods

2.1. Participants

For the present secondary cross-sectional analysis, the cohort examined was pooled baseline data from two lifestyle intervention studies in comparable populations. Participants to the two studies: the Montreal-Ottawa New Emerging Team (MONET) Study (N = 137) [6] and the Complications Associated with Obesity (CAO) Study (N = 59) [7] were non-diabetic overweight or obese postmenopausal women. The studies were approved by the University of Montreal ethics committee. Recruitment procedure and inclusion criteria have been previously described [6,7]. Briefly, women were included in the studies if they were postmenopausal (cessation of menstruation for more than 1 year and a follicle-stimulating hormone level ≥ 30 U/L and no hormone replacement therapy), with a body mass index of 27 kg/m² or more (30–40 kg/m² for the CAO study) and apparently healthy with no disease requiring immediate medical intervention. Moreover, no participants were taking medication, which could affect glucose homeostasis. Among the 196 subjects recruited in the two studies, 156 subjects had a complete set of baseline data for both the oral glucose tolerance test (OGTT) and the euglycemic hyperinsulinemic clamp. They were thus included in the present secondary analysis.

2.2. Body composition and body fat distribution

As previously described [8], body weight, lean body mass (LBM) and fat mass (FM) were measured using dual-energy X-ray absorptiometry (General Electric Lunar Corporation version 6.10.019, Madison, WI). Body mass index (BMI) was calculated as follow: BMI (kg/m²) = [weight/height²]. Waist circumference (WC) was measured with a non-extendable linear tape measure at the mid-distance between the lowest rib and the iliac crest [9]. A GE High Speed Advantage CT-scanner (General Electric Medical Systems, Milwaukee, WI, USA) was used to measure visceral fat (VAT) area.

2.3. Biochemical measurements

After an overnight fast (12 hours), venous blood samples were collected. Fasting total cholesterol, high-density lipoproteins cholesterol (HDL-C), triglycerides (TG), apolipoprotein-B (ApoB), liver enzymes and high-sensitivity c-reactive protein (hs-CRP) were measured as previously described [10–12].

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2.6. Hyperinsulinemic-euglycemic clamp

Whole-body insulin sensitivity (IS) was measured using the hyperinsulinemic-euglycemic clamp technique following the procedure described by De Fronzo et al. (1979) [13]. The test began after a 12-hours overnight fasting. Details on the technique and measurement have been previously described [6,14]. Three basal blood samples were taken over 40 min, after which insulin was infused at a prime constant rate of 75 mU.m⁻².min⁻¹ for 180 min. Plasma glucose was measured every 5–10 min with a glucose analyzer and maintained at the fasting level with variable infusion rates of 20% dextrose. Insulin sensitivity was determined as glucose infusion rate (GIR) during the last 30 min of the clamp at the steady state and expressed as milligrams per minute per kilogram of LBM (mg/min·kg of LBM).

2.5. Oral glucose tolerance test

A 2-hour 75-g OGTT was performed after 12-hours of fasting according to the guidelines of the American Diabetes Association [15]. Blood samples were collected through a venous catheter from an antecubital vein in vacutainer tubes containing EDTA (SST Gel et ClotActivator) at 0, 30, 60, and 120 min. Plasma glucose was rapidly measured on the COBAS INTEGRA 400+ (Roche Diagnostic, Montreal, Canada). Radioimmunoassay kits were used to quantify, in duplicate, insulin plasma levels.

Participants were classified according to their plasma glucose values at 2 h of the OGTT, as having normal glucose tolerance (NGT; <7.8 mmol/L), impaired glucose tolerance (IGT; ≥7.8 mmol/L, and ≤11.0 mmol/L). Impaired fasting glucose (IFG) was defined at plasma glucose (IFG; ≥6.1, and ≤6.9 mmol/L) using basal fasting sample before the OGTT. Those with both IFG and IGT were classified in the group of combined glucose intolerance (CGI). Classifications were done according to the Canadian Diabetes Association guidelines [16].

Using OGTT data, muscle IR index was estimated using Abdul-Ghani et al. formula [17]: Muscle IR = (dG/dt)/mean plasma insulin levels, where dG/dt is the rate of decline in plasma glucose levels and is calculated as the slope of the least square fit to the decline in plasma glucose levels from peak to nadir. Liver IR was estimated according to the formula of Abdul-Ghani et al. formula [17]: Liver IR = glucose (0–30) [AUC] × insulin (0–30) [AUC], where AUC is the area under the curve during the OGTT.

2.6. Insulin secretion assessment

The first phase insulin secretion was determined with Stumvoll’s early insulin secretion index [18]: 1.283 + 1.829 × Ins₃₀ (pmol/L) − 138.7 × Glyc₃₀ (mmol/L) + 3.772 × Ins₀ (pmol/L). Using this index and the GIR we determined the disposition index which reflects the capacity of β-cells to compensate for IR.

2.7. Insulin resistance groups

Participants were divided according to the present study population median values of Abdul-Ghani et al. [17] muscle and liver IR indices respectively. Participants in the upper median for muscle IR index but in the lower median for liver IR index were considered to be muscle IR and hepatic insulin sensitive (muscle IR group). Conversely, participants in lower median for muscle IR index but in the upper median for liver IR index were considered to have liver IR and muscle IS (liver IR group). Group of combined IR were in the upper median, while participants with combined IS were in the lower median for both muscle and liver IR index.

2.8. Adiposity indices

Visceral adiposity index (VAI), was calculated using the formula suggested by Amato et al. [19] The fatty liver index (FLI) was calculated as proposed by Bedogni et al. [20] The lipid accumulation product (LAP) was calculated as: LAP = (WC (cm) − 81) × (TG concentration (mmol/L)) [21].

2.9. Statistical analyses

The data are expressed as mean ± SD. A one-way ANOVA test was used for means comparison of OGTT glucose and insulin as well as cardiometabolic risk indicators values across groups. For significant different a Scheffé post-hoc test has been used. Chi-square test was used to determine difference between groups according to glucose tolerance status (NGT, IFG, IGT and CGI). Statistical analysis was performed using SPSS Version 17.0 for Windows (Chicago, IL, USA). Statistical significance was set at P < 0.05.

3. Results

In our sample of 156 postmenopausal women, 53 (34.0%) participants were classified as combined IS while on the opposite 51 participants (32.7%) were classified as combined IR. Finally 26 (16.7%) participants had either muscle IR or liver IR. All these four groups presented similar weight, BMI, WC and total FM (Table 1). However, muscle IR group had similar VAT values than combined IS group but significantly lower than liver IR group or combined IR group. Similar trend was found for LBM.

A total of 57 (36.5%) of patients had dysglycemia, among them 25 (16.0%); 21 (13.5%); 11 (7.1%) had IFG, IGT and CGI respectively. We examined the relative contribution of muscle and liver IR to dysglycemia by comparing subjects with either combined IS, muscle IR, liver IR or combined IR. As shown in Fig. 1, participants with liver or combined IR were more likely to display dysglycemia when compared to those with muscle IR or combined IS (41.2% and 69.2% vs. 19.2 and 23.1%). Close to 50% of individuals with liver IR and dysglycemia displayed IFG. Moreover, 80% of those with muscle IR and dysglycemia had IGT. The higher prevalence of CGI (15.4%) was found among individuals with combined IR. In this group, 30.8 and 23.1% of individuals had IFG and IGT respectively. Fig. 2 shows plasma glucose excursion during the OGTT for each group of IS/IR. For fasting values and for each time point, individuals with muscle IR showed similar glucose levels when compared to participants with combined IS. On the other hand, fasting glucose values as
Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Muscle IS and liver IS (N = 53)</th>
<th>Muscle IR and liver IS (N = 26)</th>
<th>Liver IR and muscle IS (N = 26)</th>
<th>Liver IR and muscle IR (N = 51)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>82.1 ± 13.0</td>
<td>83.6 ± 13.9</td>
<td>87.6 ± 11.1</td>
<td>87.2 ± 14.8</td>
<td>0.174</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.9 ± 4.1</td>
<td>32.6 ± 5.2</td>
<td>33.5 ± 3.4</td>
<td>33.4 ± 3.4</td>
<td>0.218</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>101.7 ± 11.4</td>
<td>101.8 ± 11.1</td>
<td>104.8 ± 9.3</td>
<td>106.5 ± 10.2</td>
<td>0.089</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>41.8 ± 5.4a</td>
<td>40.7 ± 4.9b</td>
<td>44.6 ± 5.3b</td>
<td>43.9 ± 6.7b</td>
<td>0.026</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>37.9 ± 9</td>
<td>40.6 ± 10.8</td>
<td>40.7 ± 7.0</td>
<td>41.0 ± 9.3</td>
<td>0.325</td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>168.2 ± 44.9a</td>
<td>176.9 ± 51.8a</td>
<td>190.5 ± 56.3b</td>
<td>209.3 ± 51.6b</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.2 ± 0.4a</td>
<td>5.2 ± 0.6a</td>
<td>5.4 ± 0.5ab</td>
<td>5.5 ± 0.6b</td>
<td>0.017</td>
</tr>
<tr>
<td>2 h OGTT glucose (mmol/L)</td>
<td>5.8 ± 1.4a</td>
<td>6.2 ± 1.5b</td>
<td>7.3 ± 1.7b</td>
<td>6.7 ± 1.9b</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting insulin (µUI/mL)</td>
<td>12.0 ± 1.4a</td>
<td>14.1 ± 4.7b</td>
<td>16.3 ± 4.2b</td>
<td>20.7 ± 1.9b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 h OGTT insulin (µUI/mL)</td>
<td>50.9 ± 25.8a</td>
<td>75.9 ± 26.2ab</td>
<td>88.6 ± 42.3b</td>
<td>132.7 ± 92.5b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.4 ± 0.5a</td>
<td>1.5 ± 0.5ab</td>
<td>1.6 ± 0.8ab</td>
<td>1.9 ± 0.8b</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.5 ± 0.3</td>
<td>1.6 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>0.130</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.3 ± 0.9</td>
<td>5.9 ± 0.9</td>
<td>5.3 ± 0.8</td>
<td>5.4 ± 0.9</td>
<td>0.709</td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>0.384</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121 ± 15</td>
<td>122 ± 13</td>
<td>120 ± 12</td>
<td>125 ± 15</td>
<td>0.461</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 ± 8</td>
<td>76 ± 6</td>
<td>77 ± 7</td>
<td>78 ± 9</td>
<td>0.714</td>
</tr>
<tr>
<td>hsCRP (g/L)</td>
<td>2.3 ± 1.8a</td>
<td>3.2 ± 2.4ab</td>
<td>3.4 ± 2.7ab</td>
<td>4.2 ± 2.2b</td>
<td>0.001</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>19.0 ± 5.6a</td>
<td>20.4 ± 5.3b</td>
<td>20.2 ± 5.7b</td>
<td>23.7 ± 8.6b</td>
<td>0.003</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>19.9 ± 9.9b</td>
<td>28.0 ± 12.6b</td>
<td>34.3 ± 7.7b</td>
<td>31.7 ± 18.4c</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GGT (IU/L)</td>
<td>22.3 ± 23.8</td>
<td>26.5 ± 14.6</td>
<td>25.8 ± 12.4</td>
<td>36.5 ± 36.8</td>
<td>0.047</td>
</tr>
<tr>
<td>VAI</td>
<td>1.9 ± 0.9a</td>
<td>2.0 ± 0.9b</td>
<td>2.4 ± 1.5ab</td>
<td>2.8 ± 1.6b</td>
<td>0.001</td>
</tr>
<tr>
<td>LAP</td>
<td>58.0 ± 22.5a</td>
<td>66.7 ± 27.6b</td>
<td>77.8 ± 44.1b</td>
<td>89.0 ± 41.0b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FLI</td>
<td>61.4 ± 19.4a</td>
<td>69.3 ± 18.7b</td>
<td>74.8 ± 17.8b</td>
<td>79.0 ± 17.6b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.7 ± 0.7a</td>
<td>3.0 ± 0.9a</td>
<td>3.8 ± 1.2b</td>
<td>4.5 ± 2.0b</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose disposal rate (mg/min/kg of LBM)</td>
<td>13.5 ± 3.1a</td>
<td>12.6 ± 2.2b</td>
<td>10.6 ± 2.8b</td>
<td>10.2 ± 2.8b</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IS: insulin sensitive. IR: insulin resistant. BMI: body mass index. LBM: lean body mass. VAT: visceral fat. OGTT: oral glucose tolerance test. HDL-C: high-density lipoprotein cholesterol. ApoB: apolipoprotein B. hsCRP: high sensitive C-reactive protein. AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: gamma-glutamyl transpeptidase. VAI: visceral adiposity index. LAP: lipid accumulation product. FLI: fatty liver index. LBM: lean body mass. Significant difference between the groups for the variables having the same letters on the same row of the table. Significant difference from P < 0.05 to P < 0.001.

well as postprandial values were alike between participants with liver IR and combined IR. Muscle IR group presented lower plasma glucose values during OGTT than liver IR group, however these differences were not statistically significant. Insulin secretion during each of the OGTT time point was significantly higher in the combined IR group than the other groups of IR/IS (Fig. 3). No significant difference for plasma insulin values was found between muscle IR and liver IR group at baseline and during OGTT.

In Fig. 4, we present the distribution of IS/IR groups according to tertiles of insulin sensitivity values as measured by the clamp. According to the results, 59.6% of participants with combined IS were in the higher tertile of IS compared to 42.3, 11.5 and 13.7% of participants with muscle IR, liver IR and combined
IR respectively. In addition, 50% of participants with liver IR were in the lower tertile of IS compared to 11.5% in the muscle IR group.

Fig. 5 presents the disposition index: early insulin secretion during the OGTT adjusted for insulin sensitivity as determined by the clamp among each group of IR/IS. Results showed an increased insulin secretion and reduced IS in the presence of IR.

The cardiometabolic risk indicators for each group of IS/IR are shown in Table 1. When considering lipid profile biomarkers, no significant difference was found between groups for total cholesterol, HDL-C, and ApoB. However, TG values were significantly higher in liver IR or combined IR groups than muscle IR or combined IS groups. As an inflammatory status marker, hsCRP values were significantly higher in the combined IR group than the combined IS group but not significantly different than muscle IR and liver IR groups. Similar trends were found for FLI and LAP indices. Liver enzymes were increased in presence of liver IR. For example, ALT values were significantly higher in liver IR than muscle IR and combined IS groups.

4. Discussion

4.1. Insulin resistance and dysglycemia

In the present study, as expected, we found that IFG was the glucose abnormality phenotype most related to liver IR while muscle IR was often associated with IGT phenotype. Furthermore, CGI prevalence was higher among subjects with combined IR. These results are in line with previous investigations [4,22]. However, not all participants with IR have glucose abnormalities. Individuals with muscle IR had significantly less dysglycemia and more efficient IR compensation by insulin secretion than those with liver IR. Abdul-Ghani et al. [5] have previously found that subjects with muscle IR had a greater fasting and 2-h plasma glucose concentration during the OGTT than those with liver IR but they did not determine IR compensation by insulin secretion in the two groups. It should be also emphasized that we performed the hyperinsulinemic-euglycemic clamp technique using relatively
high dose of insulin (i.e. 75 mU.m\(^{-2}\).min\(^{-1}\)). Thus, our measurement of whole-body insulin probably reflected more skeletal muscle utilization (but not exclusively) than liver’s and the discordance between the assessment of liver and muscle IS/IR was expected (Fig. 4). However, 42.3% of the subject of the highest IS tertile as determined with the clamp technique were classified as liver IS and muscle IR. We could speculate that this subgroup of post-menopausal overweight and obese women, even though classified as muscle IR by the Abdul-Ghani muscle IR index, might have greater skeletal muscle ability for glucose uptake. Therefore, the remained muscle IS is efficient enough to help display high whole-body IS in presence of liver IS.

Previous studies using animals models with isolate muscle IR or liver IR had suggested difference in muscle vs. liver IR for dysglycemia and diabetes development [23,24]. Indeed, the tissue-specific muscle insulin receptor knockout (MIRKO) mouse does not develop hyperinsulinemia or diabetes despite muscle IR [23] while the Liver-specific insulin receptor knockout (LIRKO) mouse displays dysglycemia and progressive liver function impairment [24]. The MIRKO mouse demonstrated a development of adaptive mechanisms in white adipose tissue to compensate for muscle IR to maintain glucose homeostasis while LIRKO mouse was unable to respond to hyperinsulinemia. Even though our findings seem to be in line with the results reported on these investigations with MIRKO and LIRKO.
mouse, it should be noted that we did not have direct measurement of muscle and hepatic IR. Moreover, adipose tissue function has not been investigated. However, we used validated surrogate indices.

4.2. Insulin resistance and body composition

We determined the relationship between liver vs. muscle IR and body composition. For similar total FM and BMI, liver IR subjects had more VAT than muscle IR subjects. Accumulation of VAT often indicated fat accumulation in other ectopic sites such as liver and muscle. Accordingly, the FLI, a liver fat accumulation index, was higher in liver IR than muscle IR. Increased ectopic fat, which is considered as a consequence of adipose tissue dysfunction, has been associated with IR independently of overall obesity [25]. More specifically, evidences suggest an association between liver lipid synthesis alteration, insulin signalling and liver IR [26]. Thus in the present study participants with high VAT probably had liver fat infiltration and related liver IR. It should be noted that fat infiltration in muscle has not been measured in the present investigation, however, Grunnet et al. [27] have reported that muscle TG content is also associated with hepatic but not peripheral IR in elderly twins.

4.3. Insulin resistance and cardiometabolic risk factors

Our results showed that liver IR was more related to cardiometabolic abnormalities such as altered lipid profile and higher inflammation state than muscle IR. Due to the coexistence of hyperinsulinemia with ectopic fat accumulation, it is difficult to isolate the role of liver IR in these metabolic impairments. Another investigation using the LIRKO mouse has shown that liver IR alone is sufficient to produce dyslipidemia and increased risk of atherosclerosis [28]. Nevertheless, in the present study the impaired metabolic state in the participants with liver IR could be a resultant of the combined effect of liver IR and/or related to ectopic fat accumulation.

Our data did not allow explaining why some individuals would have muscle IR rather than liver IR or both IR. More studies are needed to better understand those observations. It is also important to determine what kind of lifestyle intervention is more appropriate to improve IS in each phenotype. Even though pancreas β-cell mass and function is important in the development of dysglycemia and type 2 diabetes [29], clinical studies have demonstrated the significant effect of lifestyle intervention in IS improvement and the risk to develop type 2 diabetes [30]. Therefore screening for the presence of IR and specifically liver IR should remain a key tool in the prevention of type 2 diabetes as well as associated cardiovascular events among high risk non-diabetics individuals such as those with obesity.

Our study results are supported by the use of gold standard methods to evaluate whole-body IR, glucose tolerance and visceral fat. However, we did not measure direct hepatic glucose production as well as IR and fat infiltration in the skeletal muscle has not been measured.

In conclusion, we demonstrated among a sample of non-diabetic postmenopausal overweight and obese women that liver IR was related to higher prevalence of dysglycemia than muscle IR. Moreover, liver IR was also associated with ectopic fat accumulation, lipid profile alteration and sub-chronic inflammation state.

Disclosure of interest

The authors declare that they have no competing interest.

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References


