The patients diagnosed with gestational diabetes mellitus (GDM) constitute a population at risk of developing DM2 or glucose intolerance, with an incidence published by Albareda et al., in Spain, of 13.8 and 42% (respectively) in a follow-up of 11 years.1 The condition of insulin resistance (IR) is known during pregnancy2,3 and how this can be an early manifestation of a metabolic syndrome4 associated to a sub-clinical inflammatory condition.5,6 These women constitute a target population, with risk of endothelial damage and later cardiovascular disease7 even in the previous stage known at present as “pre-diabetes”.8 The genes responsible for the IR and the MS are scarcely known, and the investigation results are controversial sometimes. Several works address the attention towards the positive association between polymorphisms of genes that inhibit the receptor tyrosine kinase activity. The reduction of such activity in the muscle has been proved and in other insulin-sensitive tissues in non-diabetic and non-obese patients,9,10 and in obese patients.11 Other candidate genes to be identified would be the K121Q polymorphism of the plasma cell membrane glycoprotein (PC-1)
and the insulin receptor substrate 1 (IRS-1), though only the first one has been associated to the IR, in Caucasian populations and in Asiatic Indians. Likewise, there are studies that state the combined effect of the PPARγ and PC-1 (K121Q), increasing significantly the BMI and the insulinemia, and reducing the sensitivity and insulin secretion. The identification of a soluble form of PC-1 in plasma has allowed, in a simple manner, the performance of population studies at a higher scale in order to understand the role of the PC-1 in conditions known of IR as GDM, and its association to other cardiovascular risk factors related to it. The finding of an association between a determined polymorphism and a pathologic condition might allow stating prevention and treatment strategies.

The objective of this study has been to assess the presence of carbohydrate metabolism impairment in women with medical history of GMD and variables related to cardiovascular risk after delivery, and if there is an association with the K121Q polymorphism of the gene that synthesizes the PC-1.

Materials and methods

Ninety-seven (97) women have been studied with previous GMD diagnosis, of a mean age (±SD) of 35.6 ± 5.6 years of age, seen in the consultation of Diabetes-Gestation of the Endocrinology and Nutrition Service of our hospital during 2006-2008. Once breastfeeding concluded, or after 3 months of delivery, an oral glucose overload (OGO) has been done with 75 g for the classification of the carbohydrate metabolism (HCM). According to the criteria of the American Diabetes Association, three study groups were determined: women with pre-diabetes for showing an altered baseline glycemia and/or altered tolerance to the glucose after 2 hours of oral overload; women who met diagnosis criteria of DM and women who showed a normal glucose tolerance (NGT). An anthropometric assessment was performed, with measurement of weight, height, BMI and the waist circumference. The body composition was measured, with measurement of the fat mass, the free fat mass and the total body water using the bioimpedancemeter Hologic. The systolic and diastolic blood pressure was obtained in two consecutive measurements in the right arm and in resting conditions, considering the mean of both measurements. A biochemical study included the measurement of the glycemia and the insulinemia, in fasting period and after 120 minutes after an oral overload; women who showed a normal glucose tolerance (NGT). An informed consent has been requested previous to the performance of the study, observing the rules of the Declaration of Helsinki, and the Ethics Committee of the Hospital Universitario San Cecilio approved the study.

Results

From a total of 97 women re-classified immediately after delivery, 59 (61%) showed a normal glucose tolerance, 28 (29%) met the pre-diabetes criteria and 10 women (10%) showed diagnosis DM criteria. From a total of 97 women re-classified immediately after delivery, 59 (61%) showed a normal glucose tolerance, 28 (29%) met the pre-diabetes criteria and 10 women (10%) showed diagnosis DM criteria.

Table 1 describes the clinical characteristics of the three groups of patients; a relevant increase can be observed in weight, the BMI, the fat mass and the blood pressure (BP) in women with pre-diabetes, compared to the women who showed a NGT. Likewise, there have been relevant differences among those with NGT and the diabetic women, showing these last ones a higher weight, BMI and systolic BP. No relevant differences were observed among the diabetic women and those with pre-diabetes concerning clinical characteristics.

Table 2 depicts the relevant differences among the groups in the insulinemia levels, both basal and after 2 hours of the OGO, and in the HOMA-IR index, showing the patients with pre-diabetes the highest levels. There has been a relevant reduction in the levels of HDL cholesterol, as well as an increase of triglycerides, when comparing the pre-diabetes and diabetes groups, versus the group with NGT. We have not found relevant differences when comparing the pre-diabetes group with the group of patients that showed diabetes, except in the HbA1c levels (4.8 ± 0.4 versus 5.8 ± 1.0; p <0.001).

Statistical method

We carried out an estimation of the sample size focused on the K121Q polymorphism of the PC-1 gene, taking into account that the presence of the Q allele, in a Caucasian population as the sample, would be in the region of 12-15% with a error level of 5% and to detect a relative risk of allele presentation when a carbohydrate pathology is diagnosed (compared when it is not suffered) of 2 and with a strength of 80%. An analysis of contingency tables using the exact Fisher test has been used in the statistical study; and for the quantitative variables, the t Student test for the comparison of means among independent groups. A p <0.05 has been considered as minimum level of significance. All the results have been processed and analyzed by means of SPSS 14.0.

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Genetics study

The allele frequency and the different genotypes of the codon 121 of the gene that codifies the PC-1 protein have been studied, both in homo and in heterozygosis, in women with NGT and in those who showed pre-diabetes and diabetes. The prevalence of each of the genotypes is detailed in table 3; no relevant differences were found between the groups for the presence of such alleles.

Table 4 details the results of the anthropometric and analytical characteristics of the women with GDM that have been compared regardint to bear or not the 121Q allele of the gene that codifies the PC-1 protein. There have not been relevant differences between both groups for any of the studied metabolic variables.

Discussion

Though most of the women with GDM history revert to a normal glucose tolerance after delivery, previous studies have demonstrated a prevalence of 25% of DM and 33% of glucose intolerance in a population of women with GDM followed-up in a hospital environment a year after the delivery.\(^1^9\) This prevalence is higher than the values found in a population from primary care environment, though we could also detect a high prevalence of DM and pre-diabetes both in homo and in heterozygosis, in women with NGT and in those who showed pre-diabetes and diabetes. The prevalence of the glucose metabolism immediately after delivery.

In previous studies of the group we also found that the age, the weight and the pregestational BMI constituted themselves in risk factors to develop a GDM, when compared to a control population of pregnant women without pathology. Likewise, it points out the fact that the pregnant women with GDM had a relevant higher percentage of personal and family history of cardiovascular risk factors.\(^2^0\)

In this new study of women with GDM, studied after delivery, we provided new results that are still deepening in the metabolic importance of these patients and in their future cardiovascular risk. The patients with pre-diabetes showed already a high percentage (29%) and besides they differ significantly from those who show a NGT in the cluster of metabolic anomalies, as they are women with higher weight and a higher percentage of fat mass in their body composition. Anyway they show, compared to those who have a NGT, an increase in the BP, higher levels of insulinemia and insulin resistance and a reduction of the HDL cholesterol. Recently it is being paid special attention to the epidemiological and clinical importance and to the pre-diabetes prevention and treatment strategies and it is calculated that approximately 314 million people worldwide are affected, with a projection for 2025 of 418 millions.\(^2^1\) Likewise, it is known that at short term, the absolute risk of showing T2D increases 3 to 10 times, with an accumulated incidence after 6 years of 65%, compared to 5% for those persons who show a normal glucose metabolism.\(^2^2\) The epidemiological evidence already indicates us that the complications of the diabetes start in this continuum between the normal glucose tolerance and the overt diabetes. Several studies have demonstrated that the early identification and the treatment of the persons with pre-diabetes has the potential to reduce or delay the progression to diabetes,\(^2^3\) as well as the cardiovascular\(^2^4^,2^5\) and micro vascular disease.\(^2^6\)

Moreover, this study tries to know if the K121Q polymorphism of the gene that codifies the PC-1 protein is associated to some type of metabolic glucose alteration in these women or with variables regarding to the cardiovascular risk profile. The results show that the 121Q allele is not relevantly present in women with GDM history and after delivery they show some anomaly of the glucose, including both the pre-diabetes and diabetes condition. The consistency of the effect prediction of this

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics</th>
<th>NGT (n= 59)</th>
<th>Pre-diabetes (n= 28)</th>
<th>Diabetes mellitus (n= 10)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.6 ± 4</td>
<td>37.5 ± 4</td>
<td>36.7 ± 9</td>
<td>0.16</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.8 ± 13</td>
<td>74.9 ± 12</td>
<td>73.6 ± 23(^a)</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.9 ± 5</td>
<td>31.3 ± 9</td>
<td>29.1 ± 5(^a)</td>
<td>0.04</td>
</tr>
<tr>
<td>CC (cm)</td>
<td>90 ± 10</td>
<td>92 ± 10</td>
<td>92 ± 18</td>
<td>0.08</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>33.9 ± 7</td>
<td>36.7 ± 6</td>
<td>35.2 ± 9</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 14</td>
<td>130 ± 17</td>
<td>130 ± 9(^a)</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77.4 ± 10</td>
<td>83.4 ± 11</td>
<td>82.7 ± 8</td>
<td>0.04</td>
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</tbody>
</table>

p*: Student t test, p <0.05, pre-diabetes versus NGT, \(p<0.03\), diabetes versus NGT.

<table>
<thead>
<tr>
<th>Table 2. Analytical characteristics</th>
<th>NGT</th>
<th>Pre-diabetes</th>
<th>Diabetes mellitus</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal glycemia (mg/dL)</td>
<td>85.7 ± 6</td>
<td>99.3 ± 9</td>
<td>139.6 ± 36</td>
<td>0.000</td>
</tr>
<tr>
<td>Glycemia after 120 min (mg/dL)</td>
<td>85.7 ± 6</td>
<td>99.3 ± 9</td>
<td>196.7 ± 38</td>
<td>0.000</td>
</tr>
<tr>
<td>Basal IRI (µIU/mL)</td>
<td>9.5 ± 7</td>
<td>16.8 ± 21</td>
<td>10.7 ± 5</td>
<td>0.04</td>
</tr>
<tr>
<td>IRI 120 min (µIU/mL)</td>
<td>47.9 ± 31</td>
<td>90.9 ± 40</td>
<td>65 ± 44</td>
<td>0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.0 ± 1.5</td>
<td>4.1 ± 5</td>
<td>3.8 ± 2(^a)</td>
<td>0.01</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.4 ± 0.8</td>
<td>0.38 ± 0.4</td>
<td>0.4 ± 0.5</td>
<td>0.21</td>
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<tr>
<td>Uric acid (mg/dL)</td>
<td>4.7 ± 1</td>
<td>4.6 ± 1.0</td>
<td>4.4 ± 1.6</td>
<td>0.45</td>
</tr>
<tr>
<td>c-HDL (mg/dL)</td>
<td>62 ± 15</td>
<td>56.1 ± 12</td>
<td>52.3 ± 13(^a)</td>
<td>0.04</td>
</tr>
<tr>
<td>c-LDL (mg/dL)</td>
<td>113.9 ± 26</td>
<td>114.7 ± 34</td>
<td>119.3 ± 22</td>
<td>0.34</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>91.9 ± 47</td>
<td>118.9 ± 68</td>
<td>109.6 ± 56</td>
<td>0.01</td>
</tr>
</tbody>
</table>

p*: Student t test, significance p <0.05, pre-diabetes versus NGT, \(p=0.003\); \(p=0.03\); diabetes versus NGT. C- reactive protein; HOMA-IR: homeostasis model assessment insulin resistance; ICR: immune-reactive insulin; NGT: normal glucose tolerance.
polymorphism on the presence of T2D has been observed in three different cohorts, along with the role that the IR plays, about which Maddux and Goldfine add that it might be associated to the inhibition of the insulin receptor, interacting directly with a specific region of the alpha sub-unit, besides reducing the tyrosine-kinase activity. Though Abate et al. have also observed that such polymorphism is associated to the T2D in the Caucasian population and from the South of Asia, the results do not support a relation with the insulin resistance.

Though the insulin sensitivity is not measured adequately in this study, we do not find differences among those women with the 121Q genotype and those with normal genotype in the indirect measurement of the IR. We neither observe differences regarding to the BMI or the fat mass, or from the rest of the assessed metabolic variables. Other authors, as González-Sánchez et al., who have studied this polymorphism in Spanish population on an epidemiological basis, do not find such association; the reasons for these apparent discrepancies are not clear. The authors conclude that it might have an impact on the insulin-leptin signalling complex favoring the onset of hyperleptinemia as an early manifestation of the MS. It is obvious that the magnitude of the IR induced by this sole polymorphism might be modulated by its interaction with other genetics and environmental factors.

**Conclusions**

We conclude that the patients with GDM have a high prevalence of carbohydrate alteration after delivery, stressing on a high frequency of the pre-diabetes stage with a risk profile associated to the obesity, IR and other metabolic markers. The 121Q allele of the gene that codifies the PC-1 protein is not associated, in this study, to the alteration of the glycidic metabolism nor with the cardiovascular risk profile. Therefore, more studies are needed, with a bigger sample and in other populations in order to verify if it is considered as a genetic marker of diabetes and/or MS.

We insist that the patients with GDM constitute a risk population; therefore we recommend carrying out a screening after delivery, with special attention on the prevention of stages previous to DM and the cardiovascular disease. The acting strategies that are proposed are mainly concerning to the modification of the lifestyle, to avoid the obesity by means of healthy diet habits and physical exercise. Likewise, new drugs have to be investigated to support their efficiency in order to prevent or delay the diabetes.

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**Declaration of potential conflict of interests**

The authors state that there are no conflicts of interest as regards to the content of this article.

**References**


