GLUCOSE INTOLERANCE IS PREDICTED BY THE HIGH FASTING INSULIN-TO-GLUCOSE RATIO

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SUMMARY - Objective: To determine whether impaired glucose tolerance (IGT) is predicted by high Fasting Insulin-to-Glucose (FIG) ratio and to establish its correlation with insulin resistance and fasting insulin.

Material and Methods: A population-based three-year follow-up study was performed. The target population consisted of healthy volunteers, men and non-pregnant women aged 30 years or over. Participants were required to have normal referenced ranges of OGTT and blood pressure. Previous diagnosis of chronic diseases was an exclusion criterion. At baseline and at the 3-yr of follow-up, an OGTT was performed. The ratio of serum Fasting Insulin (µUI/ml)/Fasting Glucose (mg/dl) was used to calculate the FIG ratio. Insulin action and secretion were estimated by HOMA and Insulinogenic index, respectively.

Results: The FIG ratio was directly correlated with the HOMA index (r = 0.83, p < 0.01) and fasting insulin (r = 0.95, p < 0.001). Multivariate logistic regression analysis showed that IGT was more likely to develop in subjects with high FIG ratio (RR 5.01; CI95% 1.9-12.2, p = 0.02), high HOMA index (RR 6.1; CI95% 2.1-11.1, p = 0.01), and fasting hyperinsulinemia (RR 4.7 CI95% 2.7-13.2, p < 0.05). The cutoff point of FIG ratio for determining the risk of developing IGT was 0.25 ± 0.05.

Conclusions: The FIG ratio could be a reliable alternative for the screening of apparently healthy subjects in high risk groups.

Key-words: impaired glucose tolerance, risk factors, serum glucose, serum insulin, HOMA index, insulinogenic index, insulin-to-glucose ratio.

RE´ SUME´ - L’intolérance au glucose est prédite par un rapport insulínémie/glycémie à jeun élevé.

Objetif: Déterminer si l’intolérance au glucose (IGT) est prédite par un rapport Insulínémie/glycémie à jeun (FIG) élevé et établir sa corrélation avec l’insulinorésistance et l’insulínémie à jeun.

Matériel et méthodes: Une étude de suivi sur 3 ans d’un échantillon de population a été conduite. La population cible consistait en volontaires sains, hommes et femmes non enceintes âgés de 30 ans ou plus. Le critère d’inclusion était des valeurs normales sur l’HGPO et de pression artérielle. Un diagnostic antérieur de maladie chronique était un critère d’exclusion. Une HGPO a été pratiquée au départ et après 3 ans. Le rapport Insulínémie à jeun (µUI/ml)/Glycémie à jeun (mg/dl) a servi à calculer le ratio FIG. L’action et la sécrétion de l’insuline ont été respectivement estimées par HOMA et par l’index insulinogénique.

Résultats: Le ratio FIG était directement corrélé avec l’index HOMA (r = 0.83, p < 0.01) et l’insulínémie à jeun (r = 0.95, p < 0.001). La régression logistique multivariée a montré que l’IGT était plus prévisible chez les sujets ayant un index FIG élevé (RR 5,01 ; CI95 % 1,9-12,2, p = 0,02), un index HOMA élevé (RR 6,1 ; CI95 % 2,1-11,1, p = 0,01), et une insulínémie à jeun élevée (RR 4,7 CI95 % 2,7-13,2, p < 0,05). Le seuil du ratio FIG déterminant le risque de développer une IGT était de 0,25 ± 0,05.

Conclusions: Le ratio FIG pourrait être une alternative fiable pour le dépistage chez des individus apparemment sains dans des groupes à haut risque.

Mots-clés: intolérance au glucose, facteurs de risque, glycémie, insulínémie, index HOMA, index insulinogénique, ratio Insulínémie/Glycémie.

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Insulin action and secretion are physiologically interconnected [1], so an initial defect in either leads to a deficit in the metabolism of glucose. Current evidence supports the view that increased insulin resistance and impaired insulin secretion precede and predict the onset of Impaired Glucose Tolerance (IGT) [1, 2], which is an early feature of type 2 diabetes.

Because the type 2 diabetes onset can be traced back through earlier stages of IGT and subclinical defects in the beta-cell response to glucose may be widespread in the population [1], strategies for an early detection of the risk factors for developing IGT constitute a relevant topic of public health. However, few prospective data are available on the predictive value of early metabolic changes for the development of IGT [2].

Insulin secretion and sensitivity are the main features determining the glucose tolerance. Fasting insulin has been found to be closely correlated to insulin sensitivity [2, 3]. The vast majority of subjects with IGT shows fasting hyperinsulinemia and decreased early insulin secretion [3].

Fasting Insulin-to-Glucose (FIG) ratio shows the degree of pancreatic insulin secretion in relation to serum glucose concentration, and thus could be an appropriate indicator for insulin sensitivity. The FIG ratio has been successfully used for estimating insulin resistance in relatives of hypertensive subjects [4] and as an index to differentiate normo from hyperinsulinemic women with polycystic ovary syndrome [5].

The relationship between FIG ratio and the development of IGT has not been documented in prospective studies so, the aim of this study was to determine whether impaired glucose tolerance (IGT) is predicted by high Fasting Insulin-to-Glucose (FIG) ratio and to establish its correlation with insulin resistance and fasting insulin.

**MATERIAL AND METHODS**

**Design and Setting** – With the approval of protocol by the Mexican Social Security Institute Research Committee and after obtaining the subject informed consent, a 3-year follow-up study was performed.

The study sample included men and non-pregnant women aged 30 yr or over, randomly selected from the city of Durango, urban community from the North of Mexico. Medical examination and laboratory tests were performed before subjects were included in the study. Participants were required to have normal referenced ranges of blood pressure and Oral Glucose Tolerance test. Previous diagnosis of chronic diseases was an exclusion criteria.

Subjects were distributed according to the quartile distribution of the FIG ratio value.

**Measurements** – Applying a standardized questionnaire sociodemographic data were obtained. Family history of type 2 diabetes was carefully corroborated achieving a medical history that included laboratory tests of the parents of surveyed subjects, and/or carefully revising its certificates of death.

Blood pressure measurement and diagnosis criteria for high blood pressure were based on the VI Joint National Committee recommendations [6].

Body Mass Index (BMI), as a measure of obesity was calculated as weight (in kilograms) divided by height (in meters) squared.

At baseline and at the 3-yr of follow-up, after overnight fasting a venous blood sample was drawn by venipuncture. Then, subjects received 75-g glucose oral load, and both 30 minutes and two hours later a second venous blood sample was obtained.

Serum glucose was determined by glucose-oxidase method, its intraassay and interassay coefficients of variation were of 2.1% and 1.5%, respectively. Total cholesterol, LDL-cholesterol and HDL-cholesterol and triglycerides were determined by enzymatic methods. Measurements of glucose and lipid profile were performed using an Express 500 clinical chemistry autoanalyzer (Ciba Corning, Diagnostic Corp., Over- ling, Ohio).

Insulin levels were measured by radioimmunnoassay (Diagnostic Products Corporation, Los Angeles, CA, USA) with intra- and inter-assay coefficients of variation of 3.5 and 5.1, respectively.

The ratio of serum Fasting Insulin (µUI/ml)/ Fasting Glucose (mg/dl) was used to calculate the Fasting Insulin-to-Glucose ratio.

Insulin secretion was estimated by the insulinogenic index, calculated by the ratio of increment of insulin to that of blood glucose 30 min after glucose load [7, 8]. Insulinogenic index scored the early insulin response. The homeostasis model insulin analysis resistance index (HOMA = Fasting insulin µmol/l × Fasting insulin µUI/ml/22.5) was used for estimating the insulin action. High HOMA index denote low insulin sensitivity and thus insulin resistance [7, 9].

**Diagnoses criteria** – Results of oral glucose tolerance test (OGTT) were categorized according to American Diabetes Association criteria [10]. IGT was diagnosed if glucose concentration 2-h post-load was ≥ 140 mg/dl and < 200 mg/dl.

**Statistical analysis** – Differences between the groups studied were assessed using unpaired Student t test or Mann-Whitney U test. Multivariate logistic regression was used to compute the Relative Risk (RR) for developing IGT. Correlation between FIG ratio and HOMA index was estimated by Pearson’s coefficient.

Data were analyzed by using the SPSS 8.0 Statistics package (SPSS Inc., Chicago II, 1998).
Three-year follow-up was completed by 188 of 193 participants (97.4%). Five subjects dropped out of the study because they moved out of the city. The family history of diabetes was documented in 110 (58.5%) individuals, of whom 32 (29.1%) had high FIG ratio values.

Table I summarizes the clinical and laboratory characteristics of the population sample at baseline, according to the FIG ratio quartile distribution. There was no difference by age nor blood pressure between the subjects on the different FIG ratio quartile. At baseline, subjects with high FIG ratio showed hyperinsulinemia and the highest early insulin response and HOMA index, but they preserved serum glucose levels within normal referenced range, Table I.

Among the 3-yr followed subjects, 28 (14.9%) developed IGT (4 men and 24 women). Of them 19 (67.2%) were in the group with high FIG ratio and 9 (32.1%) within the 2nd and 3rd quartile, 23 (82.1%) had family history of diabetes, 15 (53.6%) were obese and 12 (42.8%) overweight. Table I shows the baseline data of the subjects who developed IGT. They have the highest HOMA and insulinogenic index denoting the highest insulin resistance and the highest early insulin secretion, with the lowest FIG ratio.

<table>
<thead>
<tr>
<th>Fasting Insulin-to-Glucose ratio quartile</th>
<th>IGT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st n = 47</td>
<td>2nd and 3rd n = 94</td>
</tr>
<tr>
<td>Age, Years</td>
<td>39.6 ± 7.6</td>
</tr>
<tr>
<td>Body Mass Index, Kg/m²</td>
<td>25.9 ± 4.2</td>
</tr>
<tr>
<td>Systolic Pressure, mmHg</td>
<td>109.4 ± 16.7</td>
</tr>
<tr>
<td>Diastolic Pressure, mmHg</td>
<td>73.4 ± 11.3</td>
</tr>
<tr>
<td>Fasting Glucose, mg/dl</td>
<td>82.0 ± 13.7</td>
</tr>
<tr>
<td>30’ post-load glucose, mg/dl</td>
<td>136.2 ± 40.3</td>
</tr>
<tr>
<td>2-h post-load glucose, mg/dl</td>
<td>103.2 ± 11.0</td>
</tr>
<tr>
<td>Fasting insulin, µUI/ml</td>
<td>9.5 ± 2.1</td>
</tr>
<tr>
<td>30’ post-load insulin, µUI/ml</td>
<td>47.9 ± 24.7</td>
</tr>
<tr>
<td>2-h post-load insulin, µUI/ml</td>
<td>27.8 ± 16.7</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dl</td>
<td>203.9 ± 36.9</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>46.4 ± 13.6</td>
</tr>
<tr>
<td>LDL-Cholesterol, mg/dl</td>
<td>129.1 ± 35.1</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>142.0 ± 106.1</td>
</tr>
<tr>
<td>Insulinogenic Index</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>HOMA index</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>Fasting Insulin-to-Glucose ratio</td>
<td>0.10 ± 0.02</td>
</tr>
</tbody>
</table>

Values given are mean ± Standard Deviation.

*Baseline characteristics for the subjects who developed Impaired Glucose Tolerance at 3-yr follow-up.

a p value < 0.01 between the subjects in the 2nd-3rd and 1st quartile.
b p value < 0.01 between the subjects in the 2nd-3rd and 4th quartile.
c p value < 0.01 between the subjects in the 4th and 1st quartile.

**RESULTS**

Three-year follow-up was completed by 188 of 193 participants (97.4%). Five subjects dropped out of the study because they moved out of the city. The family history of diabetes was documented in 110 (58.5%) individuals, of whom 32 (29.1%) had high FIG ratio values.

Table I summarizes the clinical and laboratory characteristics of the population sample at baseline, according to the FIG ratio quartile distribution. There was no difference by age nor blood pressure between the subjects on the different FIG ratio quartile. At baseline, subjects with high FIG ratio showed hyperinsulinemia and the highest early insulin response and HOMA index, but they preserved serum glucose levels within normal referenced range, Table I.

Subjects in the 4th quartile had higher serum triglycerides levels and low HDL-cholesterol than those in the comparative quartiles.

Among the 3-yr followed subjects, 28 (14.9%) developed IGT (4 men and 24 women). Of them 19 (67.2%) were in the group with high FIG ratio and 9 (32.1%) within the 2nd and 3rd quartile, 23 (82.1%) had family history of diabetes, 15 (53.6%) were obese and 12 (42.8%) overweight. Table I shows the baseline data of the subjects who developed IGT. They have the highest HOMA and insulinogenic index denoting the highest insulin resistance and the highest early insulin secretion, with the lowest FIG ratio.
The FIG ratio was directly correlated with the HOMA index ($r = 0.83$, $p < 0.01$) and fasting insulin ($r = 0.95$, $p < 0.001$). Multivariate logistic regression analysis showed that IGT was more likely to develop in subjects with FIG ratio within the 4th quartile (RR 5.01; CI 95% 1.9-12.2, $p = 0.02$), high HOMA index (RR 6.1; CI 95% 2.1-11.1, $p = 0.01$), and fasting hyperinsulinemia (RR 4.7 CI 95% 2.7-13.2, $p < 0.05$).

The cutoff point of the FIG ratio for determining the risk of developing IGT was $0.25 \pm 0.05$.

**DISCUSSION**

This study demonstrated that high FIG ratio values predict the development of IGT, and that FIG ratio has a high correlation value with HOMA index. Estimation of FIG ratio could be an alternative to identify those subjects at risk for developing IGT.

Insulin secretion and insulin sensitivity are the main features that determine the future deterioration in glucose metabolism [3, 11]. Increased insulin secretion and impairment of insulin action on the peripheral receptor characterize insulin resistance [12, 13], the best single predictor of developing IGT and type 2 diabetes [14, 15]. In absence of defects in the insulin secretory capacity, insulin levels correlates with insulin sensitivity [2, 3]. However, for estimating insulin sensitivity in epidemiologic studies FIG ratio has the advantage over fasting serum insulin that it considers the relation of insulin-to-glucose concentration providing data about the incremental pancreatic response necessary to maintain fasting glucose within normal referenced ranges. In the early stages of the impairment glucose metabolism the high pancreatic insulin compensatory response will determine high FIG ratio values so, a high FIG ratio denotes high insulin resistance. A progressive failure of beta-cell function with a defective insulin secretion rate characterizes the transition from IGT to type 2 diabetes [1, 16], determining a progressive decrease in FIG ratio values [17] that indicates reduced insulin secretion in relation to fasting glucose concentration.

Our results shows a high regression coefficient between FIG ratio and HOMA index ($r = 0.83$), and FIG ratio with fasting insulin (0.95), so in euglycemic subjects the high FIG ratio reflects the occurrence of both hyperinsulinemia and decreased insulin sensitivity.

The variable degrees of impairment of different phases of the insulin secretion rate will determine the progression of glucose intolerance [18, 19]. The insulin secretory deficit that is progressively worse with more severe hyperglycemia [1] could be adequately scrutinized by decreasing in the FIG ratio over time, providing a potential target for prevention of deterioration in glucose metabolism.

At baseline, subjects who developed IGT were obese, had dyslipidemia and a strong familial aggregation of type 2 diabetes in the first-degree relatives, similar findings to the recent report by Shaw et al. [20], denoting that FIG ratio could be an indicator for the early metabolic changes that characterizes the metabolic syndrome.

In conclusion the FIG ratio has an elevated correlation coefficient with both fasting insulin and insulin resistance, and predicts the development of glucose intolerance. Because FIG ratio shows the degree of insulin secretion in relation to serum glucose concentration and reflects the occurrence of hyperinsulinemia and decreased insulin action, it could be appropriate for the screening of high risk subjects.

**REFERENCES**


