Early decrease of the percent of HOMA $\delta$-cell function is independently related to family history of diabetes in healthy young non-obese individuals

HOMA-$\delta$% and family history of diabetes

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**Summary**

**Objective:** To determine the relationship between family history of diabetes (FHD) and decrease in percent of HOMA $\beta$-cell function (HOMA-$\beta$%) index in healthy non-obese Mexican subjects.

**Materials and methods:** Forty-eight individuals (30 women and 18 men) with FHD were compared vs 48 control subjects (30 women and 18 men) in a cross-sectional study matched by age, sex, and Waist-to-Hip ratio. Pregnancy, obesity, being overweight, alcohol consumption, high blood pressure, and heavy physical activity were exclusion criteria. All the participants were required to have a Body Mass Index < 25 kg/m$^2$ and serum fasting and 2-hours postload glucose levels lower than 6.1 mmol/l and 7.8 mmol/l, respectively. The reciprocal of serum fasting insulin concentrations ($1/\text{Ins}_0$) ($\mu$U/ml) and HOMA-$\beta$% index were used as indicators of insulin sensitivity and $\beta$-cell function.

**Results:** Average age was of 19.4 ± 3.6 vs 19.8 ± 2.6, $P = 0.66$ for the subjects with and without FHD. HOMA-$\beta$% index was significantly lower in the subjects with FHD (186.1 ± 74.1 vs 252.7 ± 149.5, $P = 0.01$). For similar levels of insulin sensitivity, subjects with FHD showed lower HOMA-$\beta$% index than control subjects ($P = 0.001$). Multivariate regression analysis showed a strong and independent relationship between FHD and decrease of HOMA-$\beta$% index (OR 2.6, CI95% 1.2-4.3, $P = 0.01$).

**Conclusions:** This study shows that normal-weight offspring of type 2 diabetes subjects exhibited a significant decrease of HOMA-$\beta$% index suggesting that FHD exerts an independent early negative effect on $\beta$-cell function.

**Key-words:** Insulin sensitivity · Insulin secretion · HOMA-$\beta$% cell index · Family history of diabetes · Non-insulin dependent diabetes mellitus · Non-obese.

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**Résumé**

**Objectifs:** Déterminer les liens éventuels entre l’existence d’antécédents familiaux de diabète et la diminution des capacités d’insulino-sécrétion évaluées par la méthode du HOMA-IS (HOMA-$\beta$%) chez des mexicains non obèses en bonne santé.

**Matériels et méthodes:** Quarante-huit sujets (30 femmes, 18 hommes) avec des antécédents familiaux de diabète ont été comparés à 48 témoins (30 femmes, 18 hommes) dans une étude transversale, avec appariement selon l’âge, le sexe, et le rapport taille/hanches. Étaient exclus la grossesse, l’obésité, l’excès pondéral, la prise d’alcool, l’hypertension artérielle, et un travail de force. Les participants devaient présenter un indice de masse corporelle < 25 kg/m$^2$, et des glycémies à jeun et 2 heures après charge orale en glucose respectivement inférieures à 6,1 mmol/l, et à 7,8 mmol/l. Le rapport inverse de l’insulinémie à jeun ($1/\text{Ins}_0$) ($\mu$U/ml) et l’indice HOMA-$\beta$% ont été utilisés comme indicateurs de l’insulinosensibilité et de la fonction $\beta$-cellulaire.

**Résultats:** L’âge était en moyenne de 19,4 ± 3.6 vs 19.8 ± 2.6 ans, $P = 0.66$ chez les sujets avec et sans antécédents familiaux de diabète. La valeur de l’indice HOMA-$\beta$% était significativement plus faible chez les sujets avec antécédent familial de diabète (186.1 ± 74.1 vs 252.7 ± 149.5, $P = 0.01$). Pour un même niveau d’insulinosensibilité, les sujets avec antécédent familial de diabète avaient des valeurs de l’indice HOMA-$\beta$% plus faibles que les sujets témoins ($P < 0.001$). Une analyse de régression multivariée mettait en évidence une relation étroite et indépendante entre l’existence d’antécédents familiaux de diabète et une diminution de la valeur de l’indice HOMA-$\beta$% (OR 2.6, IC 95% 1.2-4.3; $P = 0.01$).

**Conclusions:** Cette étude montre que des sujets de poids normal descendants de diabétiques de type 2 présentent une diminution significative de la valeur de l’indice HOMA-$\beta$%, ce qui suggère que des antécédents familiaux de diabète exercent un effet négatif sur la fonction des cellules $\beta$ pancréatiques, effet précoce et indépendant.

**Mots-clés:** Insulinosensibilité · Insulinosécrétion · Indice HOMA-$\beta$ · Antécédents familiaux de diabète · Diabète de type 2 · Sujets de poids normal.

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Introduction

Even though a decrease in insulin sensitivity has been described as the primary anomaly in the pathogenesis of type 2 diabetes and the fall of insulin secretion a late occurrence [1], disturbances in beta-cell function have been observed in the early stages of the natural history of diabetes [2], suggesting that decrease in insulin secretion also can exert an early contribution in the development of diabetes.

Although obesity is among the main risk factors that trigger pancreatic insulin secretion, non-obese healthy offspring of type 2 diabetic patients can exhibit elevated fasting serum insulin levels [3-5]; this finding supports a significant role that family history of diabetes (FHD) may play in pancreatic b-cell function [6, 7]. It has been reported that children of patients with type 2 diabetes have a less favorable physical and metabolic profile [8, 9, 10] and thus an increased risk for impaired glucose tolerance and type 2 diabetes compared to control subjects [11-13]. The pathophysiological mechanisms involved in the development of insulin resistance in the offspring of type 2 diabetic patients are unknown, but it has been suggested that they possibly involve the combination of genetic [14, 15] and developmental intrauterine effects associated with low birth weight [16-20] that may place this group at risk for developing impaired glucose tolerance or diabetes later on in life.

Early evidence confirms that adult normal glucose-tolerant offspring of type 2 diabetes parents show substantially decreased acute insulin response [21] and an altered homeostatic adaptation of first- and second-phase insulin secretion [22], yet such studies carried out using hyperglycemic clamp or adapted minimal model to assess beta-cell function [22] are unpractical in the clinical setting.

In this study, we evaluate the relationship between FHD and decrease in percent of HOMA b-cell function (HOMA-b% index) in healthy non-obese young Mexican subjects.

Material and methods

Design and settings

With the approval of the Mexican Social Security Institute Scientific Research Committee, a cross-sectional study was performed. All the subjects gave their informed consent, and the protocol was conducted in accordance with the principles of the Declaration of Helsinki.

Non-obese young Mexican men and non-pregnant women, 18 to 24 years age, were allocated into two groups according to the presence of FHD.

In order to control the most important risks factors, both groups were matched by age, gender, and Waist-to-Hip ratio (WHR). In addition, all participants were required to be in good health, which was corroborated by medical history, physical examination, and laboratory tests. Pregnancy, obesity, being overweight, alcohol consumption, high blood pressure, and aging were exclusion criteria. Participants were required to have body mass index (BMI) < 25 kg/m² and serum fasting and 2-hours postload glucose levels lower than 6.1 mmol/l and 7.8 mmol/l, respectively. Finally, as exercise exerts a beneficial role on insulin sensitivity, subjects who performed heavy physical activity were not enrolled.

Diagnostic Criteria

Based on BMI, only normal-weight subjects (BMI < 25 kg/m²) were eligible to participate. Subjects were considered as alcohol drinkers if they had alcohol consumption equal or greater than 30 g per day, based on the type, amount, and frequency of alcohol drink consumed during each event. Physical activity was determined based on the criteria proposed in the Honolulu Heart Program [23]. Blood pressure measurements and diagnosis were based in the VIth Joint National Committee recommendation [24]. The reciprocal of serum fasting insulin (1/Ins0) concentrations (mU/ml) [25] was used as indicator of insulin sensitivity. Based on quartile distribution of 1/Ins0 in our population, values lower than 0.05 mU/l⁻¹ define the presence of insulin resistance. The HOMA-b% index was calculated as 20 x fasting insulin (mU/ml) / (fasting glucose [mmol/l] - 3.5) [25]. Since 1/Ins0 and HOMA-b% index are based in almost reciprocal formulas, the line comparing both becomes asymptotic showing the increase of secretory b-cell function to compensate the decrease of insulin sensitivity [26, 27].

Measurements

BMI was calculated as weight (in kilograms) divided by height (in meters) squared, and the WHR as waist circumference divided by hip circumference.

The FHD was ascertained applying a standardized self-report questionnaire. Subsequently, the health status of the participants’ parents was confirmed by direct detailed medical examination, and by verification of clinical records or death certificates.

Assays

Subjects underwent a standard 75-g oral glucose load after a 10-h overnight fast. Venous whole blood samples were as collected for insulin and glucose measures before and at 2-h post load (2-h PG). Serum glucose levels were assessed by the glucose-oxidase method and lipid profile by enzymatic methods. Measurements were performed in an Express 550 clinical chemistry autoanalyzer (Ciba Corning, Diagnostic Corp., Overling, Ohio). Insulin levels were determined by a microparticle enzyme system (Abbott Axsym System, USA) with intra- and inter-assay coefficients of variation of 4.5 and 6.9, respectively.
Statistical analysis

Differences were assessed using unpaired Student t test (or Mann Whitney U, according to sample distribution) for numeric variables, and Chi-square test for differences between proportions. Multivariate logistic regression analysis, adjusted by WHR, was used to compute the relationship between the FHD (independent variable) and pancreatic b-cell dysfunction (dependent variable). All significant variables at the 10% level were included in the regression analysis model as covariates and stepwise forward selection was used. A 95% confidence interval was used. Data were analyzed using the statistical package SPSS 10.0. (SPSS Inc., Chicago Il).

Results

Forty-eight individuals (30 women and 18 men) with FHD were compared to 48 control subjects (30 women and 18 men). Twenty-five (52.1%) subjects had FHD in the maternal branch, 9 (18.7%) in the paternal branch, and 14 (29.2%) in both the maternal and paternal branch.

Table I summarizes the characteristics of the target population. Subjects with FHD exhibited dyslipidemia and showed higher serum fasting insulin and glucose concentrations than control individuals. On the other hand, subjects in both groups had similar values of 1/Ins0 index, but HOMA-b% index was significantly lower in those with FHD.

Among the subjects with FHD, fasting insulin and 2-h post-load glucose were significantly higher in the subjects who had FHD in both paternal and maternal branches. Other variables did not show significant differences.

The relationship between insulin sensitivity and insulin secretion in both groups was distributed as a hyperbolic curve, (Fig. 1). For similar levels of insulin sensitivity, subjects with FHD showed lower basal insulin secretion than control subjects. Since basal insulin secretion was lower in the subjects with FHD, its curve was displaced downwards as the curve of control subjects.

Multivariate regression analysis showed a strong and independent relationship between FHD and HOMA-b% index (OR 2.6, CI 95% 1.2-4.3, P = 0.01).

Discussion

This study provides data on the presence of an independent relationship between FHD and early decrease in HOMA-b% cell index in young non-obese Mexican subjects. This finding could be of particular interest for determining the optimal screening target populations for type 2 diabetes, which should include to offspring of type 2 diabetic subjects, independently of obesity.

Type 2 diabetes is characterized by defects in both insulin secretion and insulin action, but the exact timing and relative importance with which these two factors appear and play a role in the natural history of the disease are a matter of debate (28). In this study, because obesity and aging are among the main risk factors for development of insulin resistance, only young non-obese subjects were enrolled. In addition, controlling other potential confounders for hyperinsulinemia, our results showed a significant decrease in the HOMA-b% index of healthy young non-obese subjects with FHD, suggesting that FHD exerts an early effect on b-cell function decreasing its ability to compensate the degree of insulin resistance. So, it is probable that propensity to b-cell dysfunction could be genetically determined and that it could be detected early in the natural history of glucose metabolic disturbances. Our finding is in accordance with those showing an early appearance of defects in insulin secretion and a progressive decline of b-cell function (2, 29, 30), but inconsistent with some that emphasize the presence of early insulin resistance as the primary phenomenon in the natural history of type 2 diabetes [31, 32].

This study shows that indices of insulin sensitivity and insulin secretion derived from fasting insulin and glucose measures may be well indicators for early evaluation of the risk for developing metabolic disturbances of glucose, facilitating the early detection of subjects at risk in a clinical set-
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However, some potential limitations of this study deserve to be mentioned. First, we assessed pancreatic β-cell function and insulin sensitivity by indirect methods that are not the gold-standard ones. But, since $1/\text{Ins}_0$ mirrors the minimal model-derived measurements in discriminating subjects with different degrees of glucose tolerance [30, 33], and HOMA-β% index discriminates insulin secretion status from normal glucose tolerance to diabetes in a similar way than that derived from the intravenous glucose tolerance test [26], this potential limitation did not affect our conclusion. Second, although FHD was carefully ascertained, since type 2 diabetes is a late-onset disease, it is likely that some parents of the subjects without FHD will develop diabetes in the future; thus, this confounding variable may exert a potential source of bias. Because it is not possible to control this limitation in a transversal study design, follow-up research will be required.

In conclusion, this study shows that, independently of obesity and age, healthy offspring of type 2 diabetic subjects exhibit a significant decrease in the HOMA-β% index.

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