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Heterogeneous glycaemic and insulinaemic responses to oral glucose in non-diabetic men: interactions between duration of obesity, body fat distribution and family history of diabetes mellitus

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Summary. The interaction between environmental and genetic factors in the alterations of glucose-insulin homeostasis was studied in 104 non-diabetic men. Family history of diabetes mellitus was used as an index of genetic predisposition to diabetes. Body composition was measured by underwater weighing whereas subcutaneous and visceral adipose tissue areas were measured at the abdominal and femoral levels by computed tomography. The sample was first divided into two groups. The first group included subjects with "normal" glycaemic and insulinaemic responses during a 75 g oral glucose tolerance test. The second group was composed of subjects either with a high glucose response or high insulin response or both. Men included in the second group were different from the "normal" subjects for almost all body fatness variables. They also presented a prevalence of a positive family history of diabetes which was significantly higher than "normal" subjects. The second group was then divided into three distinct subgroups based on insulin and glucose responses of the subjects during the oral glucose tolerance test. Subjects with high insulin but "normal" glucose responses were characterized by significantly higher levels of total body fat and deep abdominal adipose tissue when compared to the "normal" group ($p < 0.05$). Men with both high insulinaemic and glycaemic responses displayed higher body fatness values and higher deep and subcutaneous abdominal adipose tissue areas ($p < 0.05$) in comparison with "normal" subjects. They also had a higher body mass index at age 20 years than control subjects and subjects with high insulin but "normal" glucose responses. In contrast, subjects with "normal" insulin but with high glucose responses were not different from the "normal" group with regard to body fat and adipose tissue areas. These results show the heterogeneous origin of altered glucose-insulin homeostasis in non-diabetic men. Finally, subjects in the altered glucose-insulin homeostasis group with no family history of diabetes displayed a higher body mass index at age 20 years ($p < 0.05$) in comparison with subjects who had a positive family history of the disease. They also presented a greater abdominal-to-thigh fat ratio measured by computed tomography. These results suggest that in men with alterations of glucose-insulin homeostasis, the relationship of body fat distribution to glucose tolerance and plasma insulin levels is different in those with no family history of diabetes than in subjects with a positive family history of diabetes.

Key words: Genetic susceptibility, obesity, Type 2 (non-insulin-dependent) diabetes mellitus, glucose tolerance, body fat distribution.

It is well established that environmental and genetic risk factors interact in the aetiology of Type 2 (non-insulin-dependent) diabetes mellitus [1–4]. The importance of environmental factors in the pathogenesis of Type 2 diabetes is evident from the increased prevalence of the disease observed during this century [4–6]. In this regard, the WHO Expert Committee on Diabetes has concluded that increased adiposity appears to be the most powerful risk factor for Type 2 diabetes [7]. Recently, emphasis has been placed on the importance of regional body fat distribution [8–11]. In fact, several studies have provided evidence that a preferential accumulation of fat in the trunk, especially abdominal fat deposition, was more closely associated with the development of metabolic alterations such as hyperinsulinaemia, insulin resistance, impaired glucose tolerance and Type 2 diabetes than obesity itself [12–16]. There are also data suggesting that the duration and the age of onset of obesity may be important in determining the risk of developing Type 2 diabetes [17, 18].

Genetic factors also play an important role in the development of metabolic alterations leading to Type 2 diabetes. Results from Köbberling and co-workers [19] indicate that 43 % of first-degree relatives of Type 2 diabetic patients will eventually develop the disease. In addition, the concordance for Type 2 diabetes between monozygotic twins varies between 60 to almost 100 % [1, 20, 21].

Furthermore, Fujimoto and collaborators [22] have demonstrated that the relationships between diabetes and general adiposity as well as body fat distribution were more apparent in men without a family history of diabetes than in those with a family history.

Insulin resistance (evidenced by hyperinsulinaemia with or without hyperglycaemia) or defective insulin secretion (which may be suspected with hyperglycaemia) are two possible factors that have been suggested in the pathogenesis of Type 2 diabetes [23]. However, the study of the interactions between family history of diabetes, adipose tissue distribution, obesity and its duration, and glucose tolerance and insulin levels has never, to the best of our knowledge, been performed in non-diabetic men characterized by low or high insulin responses.

The aim of the present study was therefore to search for the potential determinants of either hyperglycaemia or hyperinsulinaemia or both in a group of non-diabetic men in an attempt to obtain clues to the pathogenesis of Type 2 diabetes. Moreover, we wanted to further investigate the potential interactions between family history of diabetes, body fat distribution, duration of obesity and glucose-insulin homeostasis in a sample of non-diabetic men.

Subjects and methods

Subjects

One hundred and four men of French ancestry, aged 20 to 42 years, were recruited through the media to participate in this study, which was approved by the Medical Ethics Committee of Laval University. Before entering the study, participants were subjected to a complete medical examination and were asked to sign an informed consent document. All these men were apparently healthy, i.e. free from overt diseases requiring treatment (diabetes, hypercholesterolaemia, coronary heart disease). However, 12 men were diagnosed as having impaired glucose tolerance according to the classification of the National Diabetes Data Group [24].

Body composition and anthropometry

Body density was measured by the hydrostatic weighing technique [25] and the mean of six measurements was used in the calculation of body density. Pulmonary residual volume was measured before immersion in the hydrostatic tank, using the helium dilution method of Meneely and Kaltreider [26]. Percent body fat was derived from body density using the equation of Siri [27]. Waist and hip circumferences were measured following the procedures recommended by the Airlie Conference [28], and the waist-to-hip ratio was calculated.

Computed tomography

Computed tomography (CT) was performed on a Siemens Somatom DRH scanner (Erlanger, FRG) by using the procedure of Sjöström et al. [29] as previously described [30]. Briefly, subjects were examined in the supine position with both arms stretched above their heads. CT scans were performed at the abdominal (between L4 and L5 vertebraes) and at the femoral (mid-distance between the knee joint and the iliac crest) levels, using a radiograph of the skeleton as a reference to establish the position of the scan to the nearest millimeter. Total fat areas were calculated by delineating these areas with a graph pen and then computing the adipose tissue surfaces using an attenuation range of −30 to −190 Hounsfield units (HU) [29, 31]. The intra-abdominal fat area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal subcutaneous fat area was calculated by subtracting the amount of intra-abdominal fat from the total fat area.

Oral glucose tolerance test

A 75 g oral glucose tolerance test (OGTT) was performed the morning after an overnight fast. Blood samples were collected in EDTA and Trasylol-containing tubes (Miles Pharmaceuticals, Rexdale, Ontario, Canada) through a venous catheter placed in an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min for the determination of plasma glucose and insulin concentrations. Plasma glucose was measured enzymatically [32], whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation [33]. The total glucose and insulin areas under the curve during the OGTT were determined with the trapezoid method. Glucose and insulin responses were calculated by subtracting the fasting area (fasting level over 180 min) from the total area under the curve.

Classification of subjects into "normal" and altered glucose-insulin homeostasis subgroups

Subjects were first divided into two groups based upon their insulin and their glucose responses during the OGTT. The first group was arbitrarily composed of men with insulin and glucose responses less than or equal to the 75th percentile of the total sample for both variables. The remaining subjects (altered glucose-insulin homeostasis) were subdivided into three distinct subgroups. The first subgroup was composed of subjects with insulin responses above the 75th percentile (high insulin) but with glucose responses below the 75th percentile ("normal" glucose). The second subgroup included subjects with both insulin and glucose responses greater than the 75th percentile (high insulin, high glucose). Finally, the third subgroup was characterized by subjects with insulin responses below the 75th percentile ("normal" insulin) but with glucose responses greater than the 75th percentile (high glucose).

Family history of diabetes

Family history of diabetes was used as an index of genetic predisposition to diabetes [22]. Family history was considered positive when subjects reported that at least one full sibling or parent had diabetes. Family history was considered negative when the subject reported that none of his siblings and neither parent had diabetes.

Body weight history

Each subject was questionned about his weight at age 20. The change in weight since age 20 was thus obtained by subtracting the weight at 20 years from the current weight. The weight at age 20 and the change in weight provided us with a simple indicator of the body weight history for each subject.

Statistical analysis

The Student's *t*-test was used to compare "normal" subjects to those with alterations in glucose-insulin homeostasis. The same statistical test was used to compare subjects with and without a positive family history of diabetes. One-way analysis of variance was used to compare the group with "normal" glucose-insulin homeostasis with sub-

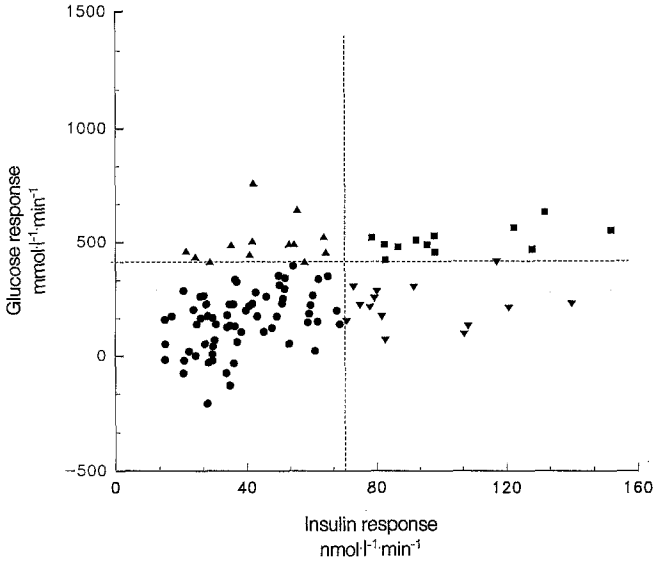

Fig. 1. Relationship between plasma glucose and insulin responses during a 75 g oral glucose tolerance test in a sample of 104 non-diabetic men. Dotted lines represent the 75th percentile for both glucose and insulin responses. A negative value indicates that plasma glucose levels following the oral glucose administration eventually fell below basal values during the 180-min test, thereby generating a negative glucose response. ●, normal glucose-insulin homeostasis; ▼, high insulin, normal glucose responses; ■, high insulin, high glucose responses; ▲, normal insulin, high glucose responses

groups of men showing disturbances in glucose-insulin homeostasis. When this procedure revealed the presence of a significant difference, the Duncan multiple range test was used for posteriori comparisons. Chi-square test was used to compare the prevalence of positive family history of diabetes among the group with "normal" glucose-insulin homeostasis and subjects with disturbed glucose-insulin homeostasis. All statistical analyses were performed with the SAS (Statistical Analysis System) statistical package (SAS Institute, Cary, NC, USA).

Results

The relationship between plasma glucose and insulin responses to a 75 g OGTT in the overall sample of 104 non-diabetic men is shown in Figure 1. Most of the subjects (62.5%) had glucose and insulin responses which were considered to be "normal". Since we studied a sample of non-diabetic subjects, "normality" was arbitrarily considered as a value less than or equal to the 75th percentile of the total sample distribution for both variables. All 12 subjects who were diagnosed as having impaired glucose tolerance were found in the group with altered glucose-insulin homeostasis.

Morphological and metabolic characteristics of subjects with "normal" insulin and glucose responses, in comparison with the sample of men with either high insulin or high glucose responses or both, are presented in Table 1. Except for the abdominal visceral to subcutaneous adipose tissue ratio, all body fatness variables were significantly different between the two groups. Subjects with alterations in glucose-insulin homeostasis displayed significantly higher plasma glucose and insulin levels in the fasting state, as well as a higher ratio of plasma insulin to glucose areas during the OGTT.

Subjects with altered glucose-insulin homeostasis were then further subdivided into three subgroups based on their plasma insulin and glucose responses measured during the OGTT. Table 2 presents comparisons among the four subgroups obtained for morphological and metabolic variables. Men with a high glucose response but with "normal" insulin levels during the OGTT were not significantly different from "normal" subjects with respect to their morphological variables. Subjects with high insulin responses but with "normal" glucose responses during the OGTT had higher percentage of body fat, body mass index (BMI), waist-to-hip ratio and visceral fat levels ($p < 0.05$) compared to "normal" subjects. Finally, the subgroup of men with both elevated glucose and insulin responses had higher BMI, percentage of body fat, waist-to-hip ratio, as well as greater abdominal adipose tissue area and abdominal to femoral ratio values than "normal" men ($p < 0.05$). Furthermore, men with both high insulin and glucose responses had significantly higher mean BMI at age 20 years ($p < 0.05$) than control subjects. They also had higher BMI at age 20 years than men characterized by "normal" glucose and elevated insulin responses during the OGTT ($p < 0.05$).

A significantly greater proportion of subjects characterized by elevated plasma glucose or insulin responses or

Table 1. Morphological and metabolic variables in normal men and in men with altered glucose-insulin homeostasis

	Normal insulin-glucose homeostasis ($n = 65$)	Altered insulin-glucose homeostasis ($n = 39$)
Age (years)	33.54 ± 6.14	35.49 ± 4.85
BMI at 20 years (kg/m²)	23.22 ± 2.68	24.39 ± 2.90
Change in weight since age 20 (kg)	9.60 ± 8.83	13.92 ± 7.44[a]
BMI (kg/m²)	25.72 ± 4.00	28.34 ± 3.41[b]
Body fat (%)	22.08 ± 8.54	27.08 ± 7.86[b]
WHR	0.90 ± 0.07	0.96 ± 0.06[d]
Computed tomography		
Abdominal fat areas		
Subcutaneous (cm²)	223.93 ± 102.67	293.58 ± 80.93[b]
Visceral (cm²)	103.18 ± 35.31	148.33 ± 50.93[d]
Visceral: subcutaneous	0.51 ± 0.18	0.52 ± 0.16
Midthigh fat area (cm²)	193.80 ± 77.07	226.10 ± 56.93[a]
Abdominal: midthigh (total)	1.72 ± 0.41	1.97 ± 0.36[b]
Fasting		
Glucose (mmol/l)	5.0 ± 0.4	5.3 ± 0.6[a]
Insulin (pmol/l)	65 ± 20	91 ± 36[c]
OGTT		
Glucose resp. (mmol·l⁻¹·min⁻¹)x10⁻³	0.15 ± 0.13	0.40 ± 0.16[d]
Insulin resp. (pmol·l⁻¹·min⁻¹)x10⁻³	38.55 ± 14.29	80.34 ± 32.46[d]
Insulin area: glucose area	47.4 ± 13.1	72.7 ± 29.5[d]

Number of subjects for computed tomography variables is 54 for the normal glucose-insulin homeostasis group.
[a] Significantly different from normal subjects, $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$; [d] $p < 0.0001$
Data are means ± SD. BMI, Body mass index; WHR, waist-to-hip ratio; OGTT, oral glucose tolerance test

Table 2. Morphological and metabolic variables in men with high insulin and normal glucose responses; high insulin and high glucose responses, and normal insulin and high glucose responses in comparison with control men

	Control men ($n = 65$)	High insulin normal glucose responses ($n = 13$)	High insulin high glucose responses ($n = 13$)	Normal insulin high glucose responses ($n = 13$)
Age (years)	33.54 ± 6.14	37.07 ± 2.87	36.75 ± 3.22	32.65 ± 6.54[b]
BMI at 20 years (kg/m^2)	23.22 ± 2.68	23.18 ± 2.55	25.86 ± 3.50[a, b]	24.69 ± 2.03
Change in weight since age 20 (kg)	9.60 ± 8.83	15.72 ± 7.07	14.30 ± 6.50	10.64 ± 8.65
BMI (kg/m^2)	25.72 ± 4.00	28.47 ± 2.68[a]	30.47 ± 1.53[a]	25.89 ± 4.09[c]
Body fat (%)	22.08 ± 8.54	28.57 ± 3.84[a]	30.50 ± 4.61[a]	21.75 ± 11.00[b, c]
WHR	0.90 ± 0.07	0.96 ± 0.05[a]	0.99 ± 0.03[a]	0.93 ± 0.07[c]
Computed tomography				
Abdominal fat areas				
Subcutaneous (cm^2)	223.93 ± 102.67	265.82 ± 72.30	327.87 ± 67.10[a]	284.16 ± 99.91
Visceral (cm^2)	103.18 ± 35.31	146.09 ± 42.56[a]	174.62 ± 50.18[a]	113.59 ± 45.16[b, c]
Midthigh fat area (cm^2)	193.80 ± 77.07	209.41 ± 39.68	249.20 ± 56.11	216.84 ± 72.62
Abdominal: midthigh (total)	1.72 ± 0.41	1.97 ± 0.26	2.06 ± 0.41[a]	1.85 ± 0.41
Fasting				
Glucose (mmol/l)	5.0 ± 0.4	5.4 ± 0.4[a]	5.4 ± 0.6[a]	5.0 ± 0.7[b, c]
Insulin (pmol/l)	65 ± 20	101 ± 30[a]	108 ± 40[a]	63 ± 19[b, c]
OGTT				
Glucose resp. (mmol·l^{-1}·min^{-1})x10^{-3}	0.15 ± 0.13	0.20 ± 0.07	0.50 ± 0.06[a, b]	0.50 ± 0.10[a, b]
Insulin resp. (pmol·l^{-1}·min^{-1})x10^{-3}	38.55 ± 14.29	91.28 ± 21.25[a]	104.95 ± 22.84[a, b]	44.81 ± 14.52[b, c]
Insulin area: glucose area	47.4 ± 13.1	93.7 ± 24.4[a]	84.0 ± 15.4[a]	40.4 ± 13.4[b, c]

Number of subjects for computed tomography variables is 54 for the normal glucose-insulin homeostasis group.
[a] Significantly different from control men, $p < 0.05$; [b] significantly different from high insulin and normal glucose responses subgroup, $p < 0.05$; [c] significantly different from high insulin and high glucose responses subgroup, $p < 0.05$
Data are means ± SD. BMI, body mass index; WHR, waist-to-hip ratio; OGTT, oral glucose tolerance test

both, had a positive family history of diabetes than men with "normal" values for both glucose and insulin responses during the OGTT (28% vs 11%, $\chi^2 = 4.68$, $p < 0.05$).

Finally, Table 3 compares subjects with and without a family history of diabetes within the group with either altered glucose or insulin responses or both. These results revealed that men with no family history of diabetes showed higher BMI values at age 20 years, and higher abdominal to femoral adipose tissue ratio ($p < 0.05$) than subjects with a family history of the disease. Men with a positive family history displayed higher plasma glucose levels in the fasting state ($p < 0.05$) than subjects with a negative family history.

Discussion

The aetiology of Type 2 diabetes has been the topic of several investigations and the reasons for its heterogeneity are only partly understood. Obesity, particularly abdominal obesity, has been proposed as being a major risk factor for the development of Type 2 diabetes [12–16]. The duration of obesity is also an important factor in the pathophysiology of Type 2 diabetes [17, 18]. Nevertheless, obesity alone cannot totally explain the prevalence of diabetes, and genetic predisposition is also an important element in the development of the disease. In this regard, studies in identical twins have shown concordance for Type 2 diabetes even when obesity was not present [34]. In addition, a possible autosomal dominant inheritance pattern in Nauruans [35] and Pima Indians [36] has been proposed, clearly indicating that obesity is not the only risk factor in the development of Type 2 diabetes. However, few studies have demonstrated the interactions between genetic susceptibility, body fat distribution, obesity and its duration in the aetiology of metabolic disturbances which may lead to Type 2 diabetes.

In the present study, we reported that subjects with altered glycaemic or insulinaemic responses had higher values for almost all body fatness variables when compared to "normal" subjects. We have also examined the role of family history of diabetes in our sample. The prevalence of diabetes in relatives of subjects with abnormal glucose-insulin homeostasis was significantly higher than in "normal" subjects. This observation was not surprising as many studies have demonstrated that obesity and genetic susceptibility are two major risk factors leading to metabolic alterations associated with the development of Type 2 diabetes [1–6, 19–21]. Furthermore, all 12 subjects who were diagnosed as having impaired glucose tolerance were found in the group with altered glucose-insulin homeostasis, characterized by high adiposity values and a high prevalence of family history of diabetes. These results further suggested that this group of men was at increased risk of developing Type 2 diabetes.

Men with altered plasma glucose or insulin responses were also further divided into three subgroups based on their glycaemic and insulinaemic responses observed during the OGTT. Both subgroups with high insulin respons-

Table 3. Morphological and metabolic variables among non-diabetic men with alterations in glucose-insulin homeostasis as a function of presence or absence of family history of diabetes

	Presence of a family history ($n = 11$)	Absence of a family history ($n = 28$)
Age (years)	35.45 ± 4.95	35.50 ± 4.90
BMI at 20 years (kg/m^2)	22.64 ± 2.71	25.26 ± 2.64[a]
Change in weight since age 20 (kg)	15.65 ± 7.34	13.02 ± 7.52
BMI (kg/m^2)	27.36 ± 2.88	28.74 ± 3.57
Body fat (%)	26.81 ± 6.67	27.19 ± 8.41
WHR	0.96 ± 0.04	0.96 ± 0.06
Computed tomography		
Abdominal fat areas		
Subcutaneous (cm^2)	264.90 ± 87.91	305.05 ± 76.82
Visceral (cm^2)	138.32 ± 45.90	152.33 ± 53.15
Visceral: subcutaneous	0.56 ± 0.21	0.50 ± 0.14
Midthigh fat area (cm^2)	230.34 ± 64.40	224.40 ± 55.01
Abdominal: midthigh (total)	1.77 ± 0.25	2.05 ± 0.37[a]
Fasting		
Glucose (mmol/l)	5.6 ± 0.6	5.2 ± 0.5[a]
Insulin (pmol/l)	76 ± 21	96 ± 39
OGTT		
Glucose response (mmol · l^{-1} · min^{-1})x10^{-3}	0.35 ± 0.19	0.42 ± 0.15
Insulin response (pmol · l^{-1} · min^{-1})x10^{-3}	77.53 ± 26.50	81.45 ± 34.91
Insulin area: glucose area	69.5 ± 26.4	74.0 ± 31.0

[a] Significantly different from the mean in subjects with a family history of diabetes, $p < 0.05$

Data are mean ± SD. BMI, body mass index; WHR, waist-to-hip ratio; OGTT, oral glucose tolerance test

es showed greater total adiposity and abdominal adiposity than the "normal" group. These results are concordant with the notion that deep abdominal adipose tissue area is an important correlate of metabolic alterations, such as insulin resistance and hyperinsulinaemia, potentially leading to Type 2 diabetes in some patients [37–40]. However, subjects with high abdominal adiposity were heterogeneous in regard to their insulinaemic and glycaemic responses. A subgroup of men was able to compensate insulin resistance by increased insulinaemia (high insulin-"normal" glucose responses) whereas the other subgroup could not fully compensate as they displayed high glycaemic responses (high insulin-high glucose responses). Although no difference in current body fatness and body fat distribution were noted among these two groups, hyperinsulinaemic men with high glucose responses had higher BMI values at age 20 years than hyperinsulinaemic men with "normal" glycaemic responses. Although our cross-sectional observations have obvious limitations and should be carefully discussed, results of the present study are concordant with the notion that the evolution of obesity to diabetes develops through successive phases [41–44]. The difference in the duration of obesity that we found is consistent with the sequence of events that have been proposed for the evolution of obesity to Type 2 diabetes [45]. In addition, the subgroup represented by subjects with "normal" insulin but with high glucose responses was not significantly different from the "normal" group with regard to body fatness variables. These results indicate that the major factor responsable for the higher glycaemic response in this subgroup may not be obesity or visceral fat deposition and that a major role for genetic susceptibility should be considered as a likely possibility in this subgroup. Unfortunately, because of the restricted number of subjects in each subgroup, we were not able to demonstrate statistically significant differences among the three subgroups with altered glucose-insulin homeostasis regarding the prevalence of genetic predisposition to diabetes.

Therefore, the three subgroups of men with various disturbances in their glucose-insulin homeostasis did not show similar differences when compared to the "normal" group, indicating the heterogeneous origin of altered glycaemic and insulinaemic responses noted in these non-diabetic men. To our knowledge, it is the first time that such comparisons have been performed within a sample of non-diabetic subjects with different alterations in glucose and insulin responses. We are, however, fully aware that "normality" regarding glucose and insulin responses, as defined by the 75th percentile, was arbitrarily evaluated. However, since we have studied a sample of non-diabetic subjects, these results suggest that there are significant interactions among risk factors for Type 2 diabetes in the determination of heterogeneous glycaemic and insulinaemic responses in non- or pre-diabetic men.

The sample of men with altered glucose-insulin homeostasis was further examined regarding family history of diabetes. Subjects with a positive family history of the disease were compared to those with no family history. Subjects without family history of diabetes displayed significantly higher BMI values at age 20 years and abdominal to femoral adipose tissue ratio measured by CT in comparison with subjects with a positive family history of diabetes. These results suggest that disturbances in body fat distribution, obesity and its duration were more strongly associated with the development of alterations in glucose-insulin homeostasis in subjects with no family history of diabetes. These results are concordant with the observations of Fujimoto et al. [22] who have studied the role of family history in the relation of body weight and body fat distribution to diabetes. They reported that the relationship of adiposity to diabetes was stronger when the family history of diabetes was negative, suggesting that environmental factors that lead to increased adiposity are important in the genesis of Type 2 diabetes when no family history of diabetes is found. However, among individuals with a positive family history of diabetes, our results indicate that the development of Type 2 diabetes may not require obesity or high levels of visceral adipose tissue. At this point, we are not able to determine which of our subjects are at increased risk of developing Type 2 diabetes among our group of 39 men with altered glucose-insulin homeostasis. Among these subjects with altered glucose-insulin homeostasis, although men with a positive family history did not show substantial alterations in body fat distribution when compared to men with no family history, we cannot conclude that men with positive family history were at lower risk of developing Type 2 diabetes considering the important role played by genetic susceptibility in the development of metabolic alterations potentially

leading to Type 2 diabetes. This statement is supported by our data showing prevalence of a positive family history to be significantly greater in the group with altered glucose-insulin homeostasis, as compared to the "control" group. In addition, men with a family history of diabetes displayed higher plasma glucose levels in the fasting state, suggesting that metabolic alterations predictive of an increased risk of Type 2 diabetes are present. In these men, genetic susceptibility seems to reduce the threshold of body fatness and abdominal fat deposition above which alterations in glucose-insulin homeostasis potentially leading to Type 2 diabetes are observed.

In summary, we have shown that non-diabetic subjects with altered glucose-insulin homeostasis were different from "normal" subjects with regard to many morphological and metabolic variables. Men with alterations in glucose-insulin homeostasis also presented a significantly greater prevalence of positive family history of diabetes than "normal" subjects. These men with alterations in glucose-insulin metabolism were, however, heterogeneous with regard to glycaemic and insulinaemic responses. This heterogeneity was partly attributed to differences in morphological variables and in the duration of obesity. Furthermore, we have also found that genetic susceptibility, assessed in the present study by the family history of diabetes, was an important factor in determining the heterogeneity of altered glucose-insulin responses, even in a sample of non-diabetic men. In fact, we found significant differences for body fat distribution and duration of obesity when subjects with a positive family history of diabetes were compared to those without a family history of the disease. These results suggest that genetic susceptibility, duration of obesity and regional body fat distribution may interact in the aetiology of altered insulinaemic and glycaemic responses, which could eventually lead to Type 2 diabetes.

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