Metabolic Defects in Persistent Impaired Glucose Tolerance Are Related to the Family History of Non–Insulin-Dependent Diabetes Mellitus

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Recent studies have suggested that the family history of non–insulin-dependent diabetes mellitus (NIDDM) influences glucose metabolism in subjects with normal glucose tolerance (NGT). However, it is not known whether the family history of NIDDM influences glucose metabolism in impaired glucose tolerance (IGT). We studied in a well-characterized group the impact of family history of NIDDM (diabetes mellitus [DM]-positive) in subjects with IGT on glucose disposal rate (GDR) measured by the euglycemic hyperinsulinemic clamp technique combined with indirect calorimetry. We recruited subjects from our previous population-based studies, and verified their glucose tolerance status twice during the follow-up period of 1 year. Subjects with NGT (n = 10) and IGT (n = 18) were comparable with respect to age, sex distribution, body mass index, smoking habits, and hypertension. As a group, IGT subjects showed lower GDR than the NGT group (28.6 ± 12.1 *v* 38.9 ± 13.6 μmol/kg/min, $P < .05$). IGT DM-positive subjects showed a 40% lower GDR than the NGT group ($P < .05$) and a 29% lower GDR than IGT DM-negative subjects (P = NS). IGT DM-positive subjects had lower glucose oxidation (P = NS, $P < .01$), glucose nonoxidation (P = NS, $P = .01$), and suppression of lipid oxidation (P = NS, $P < .05$) during the hyperinsulinemic euglycemic clamp as compared with IGT DM-negative and NGT groups, respectively. In conclusion, in subjects with persistent IGT, the family history of NIDDM is associated with the reduced total whole-body, oxidative, and nonoxidative GDR.

TYPICAL CHARACTERISTICS of non–insulin-dependent diabetes mellitus (NIDDM) are defects in insulin secretion and insulin action. Studies on the metabolic basis of insulin resistance in NIDDM have shown that increased insulin resistance is due to defects in both glucose oxidation and glucose nonoxidation (mainly glycogen synthesis).[1] Even normoglycemic relatives of patients with NIDDM have abnormalities in insulin action, and several studies have demonstrated that this is mainly due to defects in glucose nonoxidation.[2-3] Metabolic studies on subjects with impaired glucose tolerance (IGT), a category between diabetes and normal glucose tolerance (NGT), are missing.

The category of IGT is heterogenous.[4-5] Many of these subjects progress to diabetes at a rate of approximately 1.5% to 6% per year,[5-9] but about one third of them return to NGT status and one third remain glucose-intolerant after a 5- to 10-year follow-up period. As a group, subjects with IGT have elevated insulin concentrations both in the fasting state and after a glucose load, and they show resistance to insulin action in target tissues.[10-11] Also, defects in β-cell function have been observed.[12-13] IGT is currently defined by an elevated 2-hour glucose level after a 75-g glucose load,[14] and the range by definition is only 3.3 mmol/L (blood glucose, 6.7 to 10.0 mmol/L). Because the coefficient of variation of 2-hour blood glucose concentration is between 20% and 35%,[4] the reliability of a single test result is poor. Thus, to investigate subjects with definite IGT, repeated oral glucose tolerance tests have to be performed to find subjects with persistent IGT. This requires follow-up studies of large population-based cohorts.

There is compelling evidence for the role of genetic factors in the susceptibility to NIDDM. For example, the incidence of NIDDM among first-degree relatives is high,[15] as well as the concordance in identical twins.[16] Furthermore, a high prevalence of NIDDM has been observed in certain ethnic populations.[17] First-degree relatives of subjects with NIDDM have metabolic abnormalities even when they have NGT.[2-3,18-20] However, it is not known whether the family history of NIDDM influences glucose metabolism in IGT. If the family history of IGT identifies a subgroup of individuals who are in transition from IGT to NIDDM, studies on glucose metabolism in this subgroup provide us with important information on metabolic prestages of NIDDM. Therefore, we determined the metabolic profile of subjects with persistent IGT by an oral glucose tolerance test and the euglycemic hyperinsulinemic clamp and investigated whether the presence of the family history of NIDDM has an impact on glucose metabolism in IGT.

SUBJECTS AND METHODS

Study Population

Participants were recruited from previous population-based studies.[21-22] The screening took place during the years 1987 to 1988. Subjects for this study were a random sample from the original large cohort, and the participation rate for the baseline examination was 84%. The subjects were invited for reinvestigation after 1 year (years 1988 to 1989, participation rate 91%). However, after the repeated oral glucose tolerance test, four subjects were excluded from this study due to a change in glucose tolerance status (see next paragraph).

Three groups were studied, which included subjects with IGT at two examinations performed 1 year apart. The whole IGT group was divided into subjects with a positive family history of NIDDM in first-degree relatives (IGT DM-positive, n = 8), subjects without a family history of NIDDM (IGT DM-negative, n = 10), and a control group (n = 10) with repeatedly demonstrated NGT and without a family history of NIDDM. From the original selected cohort, two IGT DM-negative subjects and one IGT DM-positive subject showed NGT and one IGT DM-positive subject had NIDDM at the second examination and were thus excluded.

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Study Protocol

Both at baseline and at follow-up examination, the study protocol was the same for the participants, except that indirect calorimetry was not performed at baseline. The data shown are measurements obtained at the second examination. However, baseline glucose disposal rate (GDR) values are also shown in the text (as well as baseline glucose levels for IGT subgroups).

Subjects were admitted to the metabolic ward for 2 days. They were instructed to abstain from heavy physical activity at least 24 hours before admission. During their stay, a weight-maintaining diet (30 kcal/kg/d) was given; it contained 50% carbohydrate, 30% fat, and 20% protein. Twenty-four-hour urinary excretion was collected during the hospital stay. A 2-hour oral glucose tolerance test (day 1) and the euglycemic hyperinsulinemic clamp studies (day 2) were performed after a 12-hour fast. The study protocol was approved by the Ethics Committee of the University of Kuopio. Informed consent was obtained from each subject.

Procedures

Blood pressure was measured from the right arm with a mercury sphygmomanometer in the sitting position after a 5-minute rest. Systolic and diastolic blood pressures were read to the nearest 2 mm Hg. Disappearance of Korotkoff sounds (phase V) was used for determination of diastolic blood pressure. Body mass index was calculated as body weight in kilograms divided by height in meters squared.

Oral Glucose Tolerance Test

After an overnight fast, the oral glucose tolerance test was performed with 75 g glucose. Blood was drawn at 0, 60, and 120 minutes for measurement of blood glucose and plasma insulin and C-peptide concentrations.

Studies of Insulin Action

Insulin action was assessed with the euglycemic clamp technique.[23] At 7:30 AM after a 12-hour overnight fast, an intravenous catheter was placed in an antecubital vein for infusion of insulin and 20% glucose. Another cannula was inserted into a wrist vein surrounded by a heated box (70°C) for blood sampling. After baseline blood collection and measurement of gas exchange, tritiated glucose was infused as a primed (40 μCi), constant (0.40 μCi/min) infusion for 120 minutes before the start of insulin infusion. A priming dose of insulin (Velosulin Human; Nordisk Insulin, Gentofte, Denmark) was given during the initial 10 minutes in a logarithmically decreasing manner to increase serum insulin acutely to the desired level, where it was maintained by a continuous insulin infusion at a rate of 40 mU/m^2 body surface area/min. Blood glucose level was clamped at 5.5 mmol/L for the next 180 minutes by infusing 20% glucose at varying rates according to blood glucose measurements performed at 5-minute intervals (mean coefficient of variation of blood glucose, $<4\%$ in both groups). During euglycemic hyperinsulinemic clamp studies, rates of glucose appearance and disappearance were quantified from serum (3-^{3}H)glucose specific activities and calculated from Steele's equations in their modified derivate form because the tracer exhibits non–steady-state kinetics under these conditions.[24] The isotope dilution technique has been criticized for underestimating the rates of glucose appearance and disappearance. Although the reasons for this are not completely clear, it is generally recognized that this underestimation is greatest in non–steady-state conditions and at high glucose turnover rates.[25] Since all subjects were studied in steady-state conditions and the mean GDR was less than 40 μmol/kg/min, the underestimation of glucose rate of appearance is small in such conditions. The data were calculated for each 20-minute interval. The mean value for the period 60 to 120 minutes was used to calculate GDR.

Indirect Calorimetry

Indirect calorimetry was performed at the second examination with a computerized flow-through canopy gas-analyzer system (Deltatrac; Datex, Helsinki, Finland)[26] as previously described.[27] This device has a precision of 2.5% for O_2 consumption and 1.0% for CO_2 production. On the day of experiment, gas exchange (O_2 consumption and CO_2 production) was measured for 30 minutes after a 12-hour fast before the clamp and during the last 30 minutes of the clamp. Values obtained during the first 10 minutes of each data set were discarded, and the mean value of the remaining 20-minute data set was used for calculation. Protein, glucose, and lipid oxidation were calculated according to the method reported by Ferrannini.[28] Protein oxidation was calculated from urinary excretion of urea nitrogen before and during the insulin clamp (data not shown). Nonoxidative glucose metabolism was calculated as the difference between total-body metabolism of glucose and glucose oxidation, as determined by indirect calorimetry.

Analytic Methods

Blood glucose level was measured in the fasting state and during glucose clamp studies by the glucose oxidase method (Glucose Auto & Stat HGA-1120 analyzer; Daiichi, Kyoto, Japan). Plasma insulin level was determined by radioimmunoassay (Phasedeph Insulin RIA 100; Pharmacia Diagnostics, Uppsala, Sweden). Serum lipids and lipoproteins were determined from fresh serum samples drawn after a 12-hour overnight fast. Lipoprotein fractionation was performed using ultracentrifugation and selective precipitation as previously described.[29] Cholesterol and triglyceride from whole serum and from lipoprotein fractions and plasma lactate were assayed by automated enzymatic methods (Boehringer, Mannheim, Germany). Serum free fatty acids were determined by an enzymatic method (Wako Chemicals, Neuss, Germany). The 24-hour urine volume was measured, and urine aliquots were stored at −70°C until analysis. Nonprotein urinary N_2 level was measured by an automated Kjeldahl method.[30]

The study was approved by the Ethics Committee of the University of Kuopio, and informed consent was obtained from study participants.

Data Analysis

All calculations were performed using SPSS-PC programs (SPSS, Chicago, IL). Data are shown as the mean ± SD. To test differences between the three study groups, the Kruskal-Wallis one-way analysis of covariance was used. The Mann-Whitney U test or Student's t test (when variables showed normal distribution according to Kolmogorov-Smirnov's test) was used in the comparison of the two group means. In the case of dichotomous variables, the χ^2 test was used.

RESULTS

Clinical and chemical characteristics of NGT and IGT groups are listed in Table 1. There were no statistically significant differences between the groups with respect to age, sex distribution, body mass index, waist to hip ratio, reported alcohol consumption, smoking, physical activity, frequency of hypertension, measured blood pressure level, or use of diuretics or β-blocking agents. There were no statistical differences in serum lipid and lipoprotein levels between the groups, except for total cholesterol ($P = .05$),

Table 1. Clinical Characteristics of the Study Groups

Characteristic	NGT (n = 10)	IGT (n = 18)	IGT DM-Negative (n = 10)	IGT DM-Positive (n = 8)
No. of men/women	7/3	10/8	6/4	4/4
Age (yr)	59.8 ± 3.4	57.0 ± 7.0	57.4 ± 8.0	56.4 ± 6.0
Body mass index (kg/m²)	29.0 ± 2.6	28.1 ± 3.5	27.3 ± 3.9	29.1 ± 2.8
Waist to hip ratio	0.97 ± 0.09	0.99 ± 0.07	0.98 ± 0.09	1.00 ± 0.05
Use of alcohol (g/wk)	6.6 ± 8.3	2.1 ± 4.3	0.7 ± 2.2	3.9 ± 5.6
Current smokers				
No.	2	0	—	—
%	20			
Physically active				
No.	5	6	4	2
%	50	33	40	25
Hypertension‡				
No.	2	6	2	4
%	20	33	20	50
Systolic BP (mm Hg)	142 ± 14	143 ± 12	143 ± 15	144 ± 8
Diastolic BP (mm Hg)	88 ± 10	86 ± 9	88 ± 10	83 ± 5
Diuretics				
No.	1	2	2	0
%	10	11	20	
β-Blocking agents				
No.	2	7	2	5
%	20	39	20	63
Cholesterol (mmol/L)	6.79 ± 1.23	5.93 ± 0.99	5.77 ± 1.19	6.12 ± 0.70
HDL	1.16 ± 0.21	1.18 ± 0.21	1.32 ± 0.19	1.01 ± 0.06*
LDL	4.54 ± 1.32	3.94 ± 0.91	3.67 ± 1.01	4.29 ± 0.69
VLDL	0.96 ± 0.37	0.80 ± 0.30	0.79 ± 0.32	0.82 ± 0.30
Triglycerides (mmol/L)	1.98 ± 0.87	1.53 ± 0.66	1.37 ± 0.51	1.74 ± 0.80
VLDL	1.40 ± 0.80	1.00 ± 0.53	0.85 ± 0.35	1.19 ± 0.68
LDL	0.18 ± 0.06	0.43 ± 0.16	0.37 ± 0.19	0.37 ± 0.11
HDL	0.43 ± 0.16	0.20 ± 0.18	0.23 ± 0.22	0.17 ± 0.09
Apoprotein B (g/L)	1.30 ± 0.28	1.06 ± 0.24	0.96 ± 0.24	1.17 ± 0.18
Apoprotein A1 (g/L)	1.44 ± 0.12	1.40 ± 0.15	1.49 ± 0.13	1.28 ± 0.06†

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

*$P < .05$: NGT *v* IGT.

†$P < .01$: IGT DM-negative *v* IGT DM-positive.

‡Drug treatment and/or BP > 160/95 mm Hg.

which was higher, and apoprotein B ($P < .05$), which was lower, in the IGT group than in the NGT group.

IGT groups with or without a family history of NIDDM were also comparable with respect to age, sex distribution, body mass index, waist to hip ratio, physical activity, use of alcohol, frequency of hypertension, measured blood pressure levels, and use of diuretics and β-blocking agents. In those with a positive family history, high-density lipoprotein cholesterol ($P < .001$) and apoprotein A1 ($P < .01$) were lower and apoprotein B tended to be higher (P = NS) than in those without a family history of NIDDM.

At baseline, IGT subgroups did not differ in fasting and 2-hour glucose levels (fasting, 5.1 ± 0.7 *v* 5.3 ± 0.8 mmol/L, and 2-hour, 7.8 ± 1.3 *v* 7.9 ± 1.0, for IGT DM-negative and IGT DM-positive, respectively).

Table 2 lists fasting free fatty acid, plasma glucose, insulin, and C-peptide, and postload plasma glucose, insulin, and C-peptide levels during the oral glucose tolerance test in subjects with NGT and IGT and in the IGT group divided with respect to the presence of a family history of NIDDM. Fasting free fatty acid concentrations tended to be higher in the IGT as compared with NGT group (P = NS). Fasting and postload glucose levels were higher in IGT groups as compared with controls, but no statistically significant difference in this respect was observed between IGT DM-positive and IGT DM-negative groups. As a group, subjects with IGT had higher fasting and 2-hour insulin and C-peptide levels than the NGT group, but this was statistically significant only for 2-hour levels ($P < .05$). When IGT groups were then compared with respect to the presence of a family history of NIDDM, no significant differences in fasting and postload glucose levels were found. However, the IGT DM-positive group had higher fasting plasma insulin ($P < .05$) and postglucose insulin and C-peptide levels ($P < .01$ for 1-hour insulin, $P < .05$ for 1-hour C-peptide, $P < .05$ for 2-hour insulin, and P = NS for 2-hour C-peptide) than the IGT DM-negative group.

The mean steady-state insulin concentration during the euglycemic insulin clamp did not differ significantly among the groups (NGT, 102.3 ± 19.5 mU/L; IGT, 98.5 ± 26.1; IGT DM-negative, 99.6 ± 14.8; and IGT DM-positive, 97.1 ± 37.0).

Rates of hepatic glucose production in the basal state were similar between groups (Table 3). Insulin administration completely inhibited hepatic glucose production in both NGT and IGT groups.

Basal glucose oxidation rates did not differ between NGT, all IGT or IGT DM-negative, and IGT DM-positive groups (Table 3). Similarly, basal lipid oxidation did not differ between NGT and IGT groups.

At both examinations, mean GDR was lower in the IGT than in the NGT group. At baseline, GDR was 33.9 ± 13.7 μmol/kg/min for the NGT group and 21.9 ± 11.2 for the IGT group ($P < .05$). Differences between groups could be accounted for by the presence of a family history of NIDDM, since GDR was 27.0 ± 12.8 μmol/kg/min for IGT DM-negative and 15.5 ± 2.07 for IGT DM-positive groups, respectively ($P < .001$ between NGT and IGT DM-positive, $P < .05$ between the two IGT groups, and P = NS between NGT and IGT DM-negative).

At the second examination, IGT subjects also showed lower GDR than the NGT group (28.6 ± 12.1 *v* 38.9 ± 13.6 μmol/kg/min, $P < .05$). IGT DM-positive subjects (23.3 ± 1.83 μmol/kg/min) had a 40% lower GDR than the NGT group ($P < .05$) and a 29% lower GDR than IGT DM-negative subjects (32.8 ± 14.6, P = NS) (Fig 1). This impairment in GDR was accounted for by both impaired oxidative and nonoxidative glucose metabolism (Fig 1). Glucose oxidation during the euglycemic clamp tended to be higher in the NGT group (16.6 ± 3.50 μmol/kg/min) as

Table 2. Fasting Free Fatty Acids, Glucose, Insulin, and C-peptide, and 1-Hour and 2-Hour Postload Insulin Levels in Subjects in Relation to Glucose Tolerance Status and According to Family History of NIDDM in Subjects With IGT

Parameter	NGT (n = 10)	IGT (n = 18)	IGT DM-Negative (n = 10)	IGT DM-Positive (n = 8)
Fasting				
Free fatty acids (mmol/L)	0.64 ± 0.36	0.81 ± 0.26	0.84 ± 0.30	0.77 ± 0.22
Plasma glucose (mmol/L)	4.5 ± 0.3	5.2 ± 0.7†	5.1 ± 0.7	5.4 ± 0.7
Plasma insulin (mU/L)	15.2 ± 5.5	17.8 ± 6.9	14.4 ± 6.0	22.0 ± 5.6*
Plasma C-peptide (nmol/L)	1.00 ± 0.36	1.16 ± 0.39	1.03 ± 0.44	1.31 ± 0.28
1-hour postload				
Plasma glucose (mmol/L)	6.8 ± 1.5	9.4 ± 1.9†	8.7 ± 2.0	10.2 ± 1.6
Plasma insulin (mU/L)	124.8 ± 151	99.2 ± 67.9	63.9 ± 30.6	143.3 ± 77.8†
Plasma C-peptide (nmol/L)	3.82 ± 1.96	3.62 ± 1.38	2.99 ± 0.92	4.39 ± 1.5*
2-hour postload				
Plasma glucose (mmol/L)	5.2 ± 1.0	7.9 ± 1.2‡	7.8 ± 1.3	7.9 ± 1.1
Plasma insulin (mU/L)	54.8 ± 30.3	95.5 ± 47.7*	73.1 ± 32.3	123.6 ± 50.6*
Plasma C-peptide (nmol/L)	2.94 ± 1.18	4.22 ± 1.31*	3.72 ± 1.19	4.84 ± 1.26

*$P < .05$, †$P < .01$, ‡$P < .001$: NGT *v* IGT or IGT DM-negative *v* IGT DM-positive.

compared with the IGT group (14.2 ± 4.77, P = NS). Also in this respect, there were differences within the IGT group: IGT DM-negative subjects had higher glucose oxidation (16.4 ± 5.11 μmol/kg/min) than IGT DM-positive subjects (11.4 ± 2.55, P = NS). Glucose oxidation in the IGT DM-positive group was markedly impaired as compared with the NGT group ($P < .01$).

Glucose nonoxidation was also markedly impaired in the IGT group (14.7 ± 8.94 μmol/kg/min) as compared with the NGT group (22.8 ± 10.0, $P < .05$; Fig 1). In subjects with IGT, the DM-positive group had lower glucose nonoxidation (12.2 ± 5.77 μmol/kg/min) than the IGT DM-negative group (16.5 ± 10.8), although the difference was not statistically significant. However, the difference in this respect between NGT and IGT DM-positive groups was statistically significant ($P < .05$).

Lipid oxidation during the clamp tended to be more suppressed by insulin in the NGT group than in the IGT group (P = NS). It was suppressed more in the IGT DM-negative group than in the IGT DM-positive group (P = NS). The IGT DM-positive group showed statistically significantly ($P < .05$) lower suppression than the NGT group (Table 3).

There were no significant differences in mean serum lactate levels or serum free fatty acid levels during the euglycemic insulin clamp (Table 3).

DISCUSSION

In this study, our novel finding was that subjects with persistent IGT have differences in glucose metabolism depending on the presence of a family history of NIDDM in first-degree relatives. This observation extends previous findings based on subjects with NGT.[2-3] The biologic variability of oral glucose tolerance testing and narrow glucose ranges required for classification of subjects as IGT have remained problematic even in population studies.[4-5] However, in this population-based study, subjects were tested twice 1 year apart, and so subjects with transient glucose intolerance were excluded. There is wide consensus[3-9] that IGT is a risk factor for NIDDM, but not all subjects with IGT develop clinical diabetes, and thus IGT per se does not necessarily represent a phenotypic expression of NIDDM. In a cross-sectional study of monozygotic twins who were discordant for type II diabetes, borderline glucose tolerance or IGT was found in the majority.[18] Two Swedish studies in healthy subjects have demonstrated that the response of blood glucose to a glucose challenge is significantly influenced by the family history of diabetes[31-32]

Table 3. Basal Hepatic Glucose Production, Basal Glucose Oxidation, and Basal and Insulin-Stimulated Lipid Oxidation Rates, and Mean Serum Lactate and Free Fatty Acid Levels During Euglycemic Hyperinsulinemic Clamp in Relation to Glucose Tolerance Status and According to Family History of NIDDM in Subjects With IGT

Parameter	NGT (n = 10)	IGT (n = 18)	IGT DM-Negative (n = 10)	IGT DM-Positive (n = 8)
Basal hepatic glucose production (μmol/kg/min)	12.1 ± 1.33	12.3 ± 1.55	12.8 ± 1.78	11.7 ± 1.00
Basal glucose oxidation (μmol/kg/min)	7.61 ± 2.33	6.94 ± 2.50	7.49 ± 3.00	6.27 ± 1.72
Basal lipid oxidation (μmol/kg/min)	3.16 ± 1.78	3.72 ± 1.33	3.66 ± 1.61	3.77 ± 0.94
Lipid oxidation during the clamp (μmol/kg/min)	0.55 ± 1.39	1.50 ± 1.50	0.94 ± 1.67	2.17 ± 1.00*
Serum lactate levels during the clamp (mmol/L)	0.75 ± 0.29	0.90 ± 0.14	0.93 ± 0.16	0.86 ± 0.10
Serum free fatty acid levels during the clamp (mmol/L)	0.07 ± 0.05	0.08 ± 0.06	0.06 ± 0.05	0.03 ± 0.06

*$P < .05$ *v* NGT.

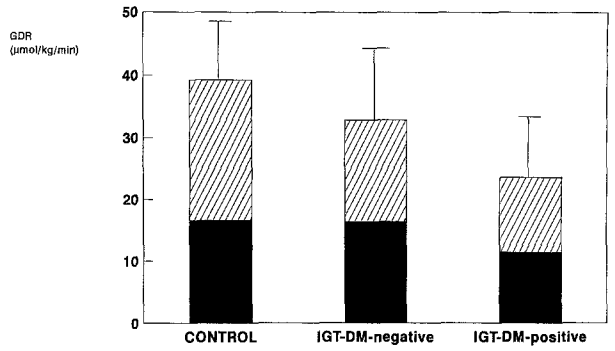

Fig 1. GDR in subjects with NGT or IGT according to family history of NIDDM (DM-negative *v* -positive). GDR: NGT *v* IGT DM-positive, $P < .05$; IGT DM-positive *v* IGT DM-negative, P = NS. Glucose oxidation: NGT *v* IGT DM-positive, $P < .01$; IGT DM-positive *v* IGT DM-negative, P = NS. Glucose nonoxidation: NGT *v* IGT DM-positive, $P = .01$; IGT DM-positive *v* IGT DM-negative, P = NS. (■) Glucose oxidation; (▨) glucose nonoxidation.

and that the genetic heritability was larger than cultural heritability. Thus, glucose tolerance is to a large extent determined by genetic factors, and IGT occurs at high frequency in first-degree relatives of patients with NIDDM. However, our study cannot separate the possible effects of shared environmental factors (eg, diet and exercise), which may affect the phenotypic expression of IGT and NIDDM.

In Pima Indians, the presence of insulin resistance in subjects with abnormal glucose tolerance predicted the development of NIDDM,[11] and it has been demonstrated that first-degree relatives of subjects with IGT and those with seemingly normal glucose tolerance have both impaired insulin action and abnormal first-phase insulin secretion.[2-3] Recently in normoglycemic offspring of NIDDM patients, impairment in both insulin-dependent and insulin-independent glucose uptake predicted the development of NIDDM.[33] Our study extends these observations and implies that the family history of NIDDM is also operative in subjects with IGT. This finding is in accordance with the finding reported by Haffner et al,[34] who demonstrated that the stronger the family history of NIDDM, the higher the fasting insulin levels in nondiabetic offspring of diabetic parents even after adjustment for body fat distribution and blood pressure levels.

In our study, the impairment in insulin action in IGT subjects with a positive family history of diabetes was accounted for by both decreased oxidative and nonoxidative glucose metabolism, but nonoxidative metabolism was quantitatively more decreased. In subjects at high risk of NIDDM, the most prominent feature has been the impairment in nonoxidative metabolism (mostly glycogen formation), but also a defect in glucose oxidation,[2-3] largely consistent with our observation. We did not find increased basal glucose production as in the study reported by Osei[20] on nondiabetic relatives of patients with NIDDM. However, our hyperinsulinemic clamp is not an ideal method to assess hepatic insulin sensitivity.

Insulin secretion was assessed only in connection with an oral glucose tolerance test in the present study. The results of insulin secretion in subjects with IGT have been variable, reflecting the heterogenic nature of IGT. However, the loss of first-phase insulin secretion[1-2] and the pulsatile nature of insulin secretion has been observed in subjects with IGT,[12] but whether there are differences in these respects with regard to the presence of a family history of NIDDM in subjects with IGT remains unknown. However, in our study, the IGT DM-positive group showed higher insulin responses after a glucose load than other groups, supporting the notion of insulin resistance as a major defect in subjects at high risk for NIDDM.

To summarize, a family history of NIDDM is associated with the metabolic profile of subjects with IGT. Although we did not study the progression to diabetes, it is possible that subjects with a positive family history of NIDDM and IGT define a group with a high risk of subsequent diabetes.

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