Peripheral Tissue Glucose Uptake Is Not Reduced After an Oral Glucose Load in Southern Italian Subjects at Risk of Developing Non–Insulin-Dependent Diabetes Mellitus

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Studies searching for the inherited defects that cause non–insulin-dependent diabetes mellitus (NIDDM) have been performed mostly in Northern European subjects using the hyperinsulinemic clamp technique. The conclusion drawn from most of these studies is that peripheral insulin resistance is likely a primary inherited defect. Our aim was to examine early defects in glucose metabolism using a more physiological technique in a different ethnic group. For this, a double-label oral glucose tolerance test (OGTT) was performed in young diabetes-prone Southern Italian subjects who had both parents with NIDDM (relatives) and in subjects with no family history of NIDDM (matched for age, weight, and ethnicity). Fasting plasma glucose and insulin in the relatives were normal; however, they had impaired glucose tolerance during the OGTT. This was due to reduced hepatic glucose uptake (17.9 ± 2.8 *v* 28.1 ± 2.3 g, $P < .02$). No defects were found in the metabolic clearance rate (MCR) of glucose or endogenous glucose production. During an intravenous glucose tolerance test (IVGTT), insulin sensitivity was again found to be normal (3.04 ± 0.65 in relatives *v* 2.33 ± 0.38 min^{-1} per $\mu mol \cdot L^{-1} \cdot min$ in controls), with a marked reduction in first-phase insulin secretion in the relatives (110 ± 12 *v* 211 ± 18 $pmol \cdot L^{-1} \cdot min$ per $mmol \cdot L^{-1}$, $P < .001$). A strong correlation was found between hepatic glucose uptake and insulin secretion ($r = .81$, $P < .001$), which may suggest that the same abnormality operates in both the liver and pancreas. Therefore, the metabolic defect that causes hyperglycemia in diabetes-prone subjects is not always a reduced peripheral insulin sensitivity. The genetic basis of NIDDM may differ between different ethnic groups.

ESTABLISHED NON–INSULIN-DEPENDENT diabetes mellitus (NIDDM) is characterized by high blood glucose levels that result from both insulin deficiency and ineffective insulin action. A strong genetic component is clearly evident in the etiology of NIDDM, but the search for the gene or genes responsible has been largely unsuccessful.

Attempts to identify early metabolic defects in the course of the disease are hampered by the fact that hyperglycemia itself can cause defects in both insulin secretion[1] and action.[2] To circumvent this problem and identify where the molecular abnormalities may occur, defects in glucose metabolism have been measured in young subjects at high risk of developing NIDDM while they still have normal fasting blood glucose. The most consistent defect found in these subjects is reduced glucose uptake into skeletal muscle.[3-7] This is associated with reduced nonoxidative glucose metabolism in muscle[3-5] and defective glycogen synthase activity.[6,7] These studies have been performed using euglycemic-hyperinsulinemic clamps—the gold standard for measuring peripheral tissue insulin sensitivity. However, this test has drawbacks because it is unphysiological. Bypassing the gut and portal route during a clamp blunts the autonomic reflex that normally occurs after a meal. This can result in different findings in clamp studies compared against oral glucose tolerance tests (OGTTs). For example, marked peripheral insulin resistance has been demonstrated in the obese *fa/fa* rat using the clamp technique,[8] yet during an OGTT, impaired glucose tolerance in these animals is due to hepatic rather than peripheral insulin resistance.[9] The peripheral defect is overcome by an increase in insulin. Both the clamp and OGTT studies illustrate that peripheral tissues are insensitive to insulin in the *fa/fa* rat; however, the conclusions as to the cause of hyperglycemia in these animals are different.

For this reason, we performed the present study to examine whether peripheral insulin resistance is present during an OGTT in young diabetes-prone Southern Italian subjects and whether this is responsible for the impaired glucose tolerance found in these subjects. Insulin sensitivity was also assessed using an intravenous glucose tolerance test (IVGTT).

SUBJECTS AND METHODS

Subjects

Six subjects who had both parents with NIDDM (relatives) and seven subjects with no family history of NIDDM (controls) participated in the studies. There were four female and two male relatives and three female and four male controls. All were of Southern Italian origin whose parents migrated to Australia from Italy (mainly from Campania, Calabria, and Sicily). The prevalence of NIDDM in Italians living in Italy is similar to that of other European populations;[10] however, the prevalence of NIDDM in Italian immigrants living in Australia is two to three times the rate in Australian-born people.[11] Clinical characteristics of the subjects are shown in Table 1.

Relatives and controls were well matched for body mass index and ethnicity. Because of the potential confounding effect of variations in dietary intake on glucose kinetics, subjects were asked to complete a 4-day estimated-record food diary.[12] Five relatives and five controls completed the diaries. Analysis of these records with Diet/1 Nutrient Calculation software (Xyris Software, Brisbane, Queensland, Australia) showed no significant difference in carbohydrate, fat, or protein intake between relatives and controls.

Written informed consent was obtained from each subject, and the experimental protocol was approved by the Royal Melbourne Hospital Board of Medical Research and Human Research Ethics Committee. The study was conducted according to the principles expressed in the Declaration of Helsinki.

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Table 1. Clinical Characteristics of Southern Italian Subjects Who Had Both Parents With NIDDM (relatives) or No Family History of NIDDM (controls)

Characteristic	Relatives	Controls
Age (yr)	33 ± 1	25 ± 1*
Weight (kg)	65 ± 7	70 ± 3
Height (cm)	162 ± 4	164 ± 3
Body mass index (kg/m²)	24 ± 1	26 ± 1
Waist to hip ratio		
Females	0.82 ± 0.02 (4)	0.77 ± 0.06 (3)
Males	0.90 ± 1.00 (2)	0.95 ± 0.03 (4)
Fasting plasma glucose (mmol/L)	5.0 ± 0.2	4.5 ± 0.1
Fasting plasma insulin (pmol/L)	65 ± 7	50 ± 7
Fasting plasma FFA (mmol/L)	0.21 ± 0.04 (5)	0.22 ± 0.05
Fasting plasma glucagon (ng/L)	38 ± 8 (5)	37 ± 7 (5)
Fasting plasma C-peptide (nmol/L)	0.74 ± 0.13 (5)	0.61 ± 0.03 (5)

NOTE. Data are the mean ± SEM for 6 relatives and 7 controls except where subject numbers are given in parentheses.

*$P < .05$, relatives *v* controls.

Double-Label OGTT

After an overnight fast, subjects reported to the Department of Medicine at Royal Melbourne Hospital where the studies were performed. Details of the double-label OGTT procedure and the analytical methods used have been previously published.[13] Briefly, a primed continuous intravenous infusion of 6,6 dideuterated glucose (Tracer Technologies, Sommerville, MA) was administered for 6 hours. After an initial 90-minute equilibration period to achieve tracer steady state, four basal blood samples were taken at 10-minute intervals to measure glucose and percent enrichment of 6,6 dideuterated glucose. At 120 minutes, the subjects drank 75 g glucose to which was added 100 μCi 6-^{3}H glucose (NEN-Dupont Research Products, Boston, MA). Blood samples were taken at 10-minute intervals for the next 2 hours and then at 15-minute intervals for another 2 hours for measurement of glucose, percent enrichment of 6,6 dideuterated glucose, and specific activity of 6-^{3}H glucose. Plasma insulin, free fatty acids (FFAs), and glucagon were determined every 30 minutes throughout the study.

Calculations

Glucose kinetics were estimated basally and during the OGTT with a modified one-pool non–steady-state model proposed by Steele et al,[14] using 0.65 as the rapidly mixing portion of the glucose pool and estimating the extracellular glucose space as 25% of body weight. This model has been shown to adequately predict the rate of glucose appearance under simulated OGTT conditions.[15] The two-pool model was not used because the exchange coefficients of the model are insulin-dependent[16] and therefore vary during an OGTT.

Total glucose appearance and disappearance were determined from the change in percent enrichment of 6,6 D_2 glucose. The metabolic clearance rate (MCR) of glucose into peripheral tissues was calculated by dividing the rate of glucose disappearance by the plasma glucose concentration. The rate of appearance of ingested glucose (Ra gut) was determined by transposition of the Steele equation[14] and the known specific activity of the drink.

Endogenous glucose production was calculated as the total rate of appearance of glucose minus the rate of appearance of gut-derived glucose. Hepatic glucose uptake was equal to the glucose load (75 g) minus the amount of glucose appearing in the systemic circulation (calculated as the area under the Ra gut curve × 4 hours). Four hours after the oral load was given, Ra gut had not returned to baseline in two of the relatives and three of the controls. This means that hepatic glucose uptake was overestimated in these subjects. However, the overestimation is likely insignificant, since no correlation was found between Ra gut at 4 hours and hepatic glucose uptake ($r = .16$), and our values for hepatic glucose uptake are similar to those reported in the literature when Ra gut has returned to zero.[17-20]

IVGTT

On another occasion 1 week before or after the OGTT, an IVGTT was performed on the subjects. One of the relatives did not participate in the IVGTT. After a basal plasma sample was collected, subjects were administered 2 mL/kg 25% glucose intravenously and plasma samples were collected rapidly over the next 40 minutes. Plasma samples were analyzed for glucose and insulin. First-phase insulin release and insulin sensitivity were calculated from these data.[21] First-phase insulin release was calculated as the insulin area above basal over 0 to 10 minutes divided by the glucose peak above basal. Insulin sensitivity was determined by the glucose disappearance rate divided by the area under the insulin curve for the 40-minute test. Insulin sensitivity calculated in this way correlates well with insulin sensitivity calculated using either a clamp or IVGTT minimal-model analysis.[21] The plasma C-peptide level was also measured 1 minute after the IVGTT.

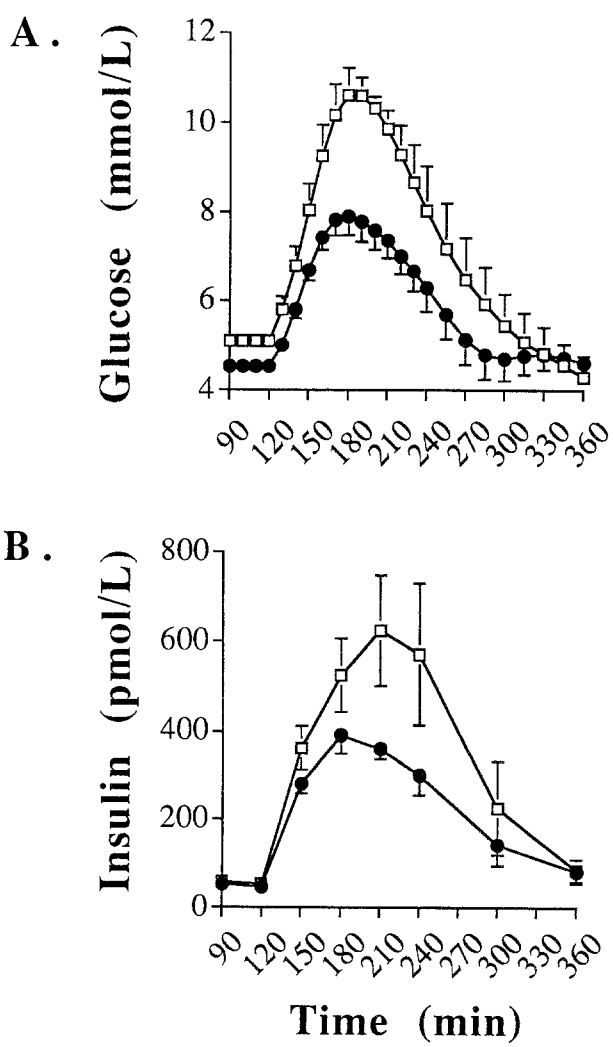

Fig 1. Plasma glucose (A) and insulin (B) in relatives (□) and controls (●) under basal conditions and during an OGTT at 120 minutes.

Statistical Analysis

The results are expressed as the mean ± SEM. Repeated-measures ANOVA was used to compare time-course data between relatives and controls. A two-tailed Student *t* test was used when single comparisons were made between groups. Statistical analysis was performed using SPSS for Windows 6.1 (SPSS, Chicago, IL). For all statistically significant differences reported herein, the probability of a type II error is less than 12% (ie, the power of the test is ≥88%).

RESULTS

Plasma glucose and insulin for the subjects under basal conditions and during the OGTT are shown in Fig 1. Fasting plasma glucose was not significantly different in relatives versus controls (5.0 ± 0.2 *v* 4.5 ± 0.1 mmol/L). In the relatives, the peak plasma glucose value was 2.5 mmol/L higher than in the controls ($P < .01$), but returned to normal by the end of the 4-hour OGTT. Basal insulin was not significantly different between the subject groups. Insulin levels during the OGTT were not significantly different in the relatives versus controls, although there was a trend for higher values. FFA and glucagon levels under basal conditions and when suppressed during the OGTT were also similar in the relatives and controls (Fig 2A and B).

Figure 3A and B shows that there was no significant difference in the basal MCR and basal endogenous glucose production between subject groups. During the OGTT, hyperglycemia in the relatives was not the result of reduced MCR or increased endogenous glucose production (Fig 3A and B). The MCR and endogenous glucose production were also compared in relatives and controls after dividing these values by the prevailing plasma insulin concentration, since there was a trend for insulin levels to be slightly higher in the relatives. This resulted in identical data curves for relatives and controls (data not shown), showing that the insulin-stimulated MCR and insulin-suppressed endogenous glucose production were the same in relatives and controls. The abnormality that caused impaired glucose tolerance in these relatives was an increase in the rate of gut-derived glucose absorption (Fig 3C), which was due to a 36% decrease in the rate of hepatic glucose uptake (17.9 ± 2.8 *v* 28.1 ± 2.3 g, $P < .02$). The defects in hepatic glucose uptake correlated well with the peak plasma glucose for all subjects ($r = .75$, $P < .01$; Fig 4). Figure 5 shows that the relatives also had a pronounced defect in first-phase insulin secretion (110 ± 12 *v* 211 ± 18 pmol · L^{-1} · min per mmol · L^{-1}, $P < .001$) during the IVGTT. C-peptide levels measured 1 minute after the IVGTT were also significantly lower in the relatives (1.3 ± 0.1 *v* 2.3 ± 0.3 nmol/L, $P < .05$). Insulin sensitivity over the 40-minute IVGTT was the same in relatives and controls (3.04 ± 0.65 *v* 2.33 ± 0.38 min^{-1} per μmol ·

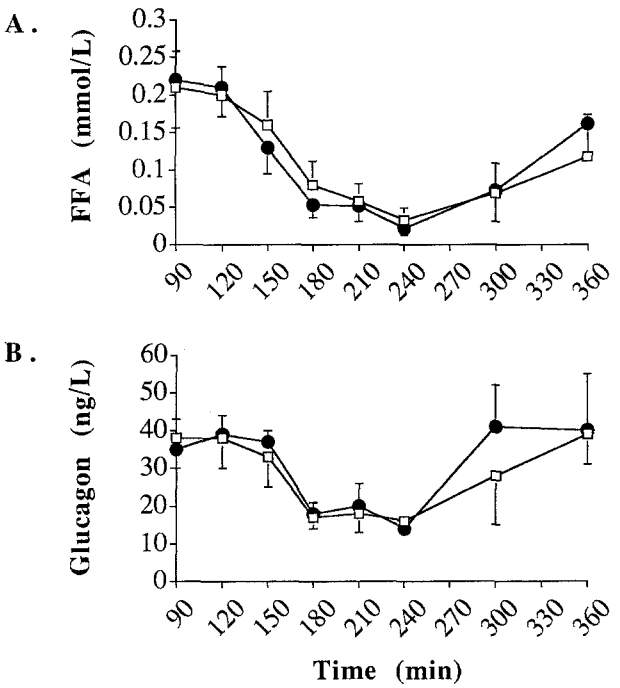

Fig 2. Plasma FFA (A) and glucagon (B) in relatives (□) and controls (●) under basal conditions and during an OGTT at 120 minutes.

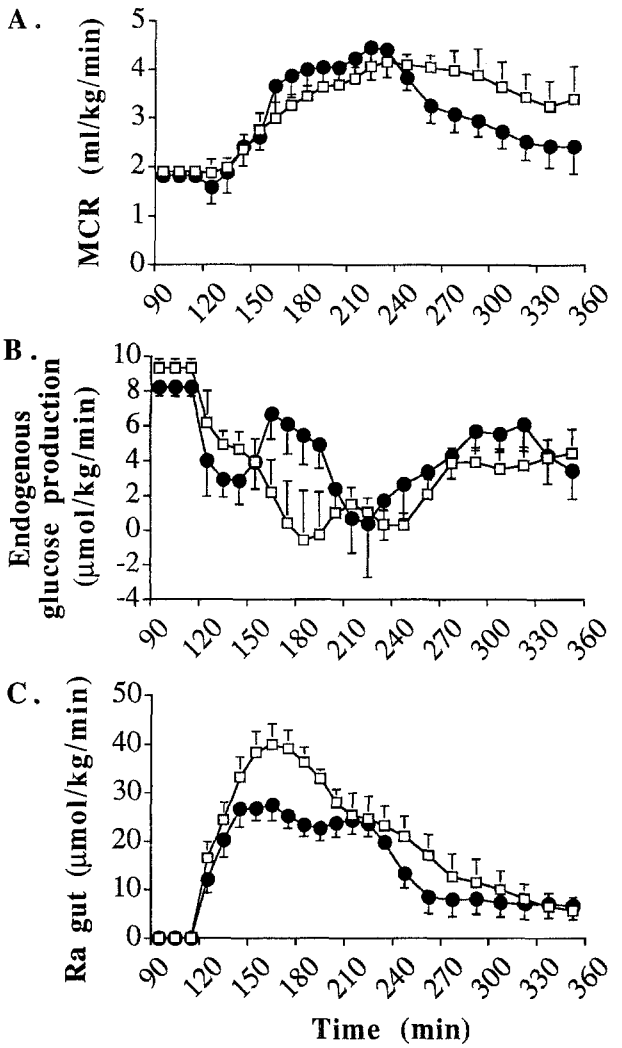

Fig 3. MCR of glucose (A), endogenous glucose production (B), and rate of gut-derived glucose absorption (C) in relatives (□) and controls (●) under basal conditions and during an OGTT at 120 minutes.

$L^{-1} \cdot$ min). A strong correlation was found between first-phase insulin secretion during the IVGTT and hepatic glucose uptake during the OGTT ($r = .81$, $P < .001$; Fig 6).

DISCUSSION

Our study shows that reduced glucose utilization in peripheral tissues is not an early cause of hyperglycemia in all NIDDM-prone subjects. We have shown using both an OGTT and an IVGTT that insulin sensitivity in diabetes-prone Southern Italian subjects is not reduced. Instead of a defect in peripheral tissue glucose clearance, we found impaired hepatic glucose uptake and reduced first-phase insulin secretion in Southern Italian subjects who had both parents with NIDDM. Therefore, diabetes-prone Southern Italians, like diabetes-prone Koreans,[22] appear to have normal insulin sensitivity in peripheral tissues but reduced insulin secretion, whereas Finnish, Danish, and Mexican-American first-degree relatives of NIDDM subjects have reduced insulin sensitivity but normal insulin secretion.[3-7] Another example of the disparate results obtained in different ethnic groups is illustrated when the results for diabetes-prone Southern Italians are compared with our previous findings in young diabetes-prone Australian Aboriginal subjects.[23] The prevalence of NIDDM in adult Aborigines (aged 20 to 50 years) is greater than 10 times the rate in Australians of European descent.[24] In diabetes-prone Aborigines, we found a significantly reduced Ra gut, in stark contrast to the increased Ra gut observed in the Italian group, indicating that reduced hepatic glucose uptake is not the cause of hyperglycemia in the young Aboriginal subjects. When viewed together, these findings suggest that the genetic basis of NIDDM may differ between different ethnic groups.

The heterogeneity and different prevalence rate of NIDDM in different populations suggest that NIDDM is indeed polygenic.[25] A "thrifty" gene that enables fat to be deposited efficiently may be responsible for the high prevalence rate of obesity and NIDDM in some ethnic populations that have undergone extreme life-style changes within the last 200 years (eg, Pima Indians, Pacific Island populations, African-Americans, and Australian Aborigines). It has been proposed that the prevalence of such a gene should be lower in European populations exposed to high-carbohydrate diets for a long period.[26] This would explain the different prevalence rates of NIDDM between non-European and European populations, but not the different early metabolic abnormalities found in different European populations at risk of developing NIDDM as described earlier. It is probable that this is due to other genes and ethnicity determines what these genes are.

The liver is known to play a major role in the disposal of an oral glucose load. The fractional extraction of glucose by the liver was 37% in our control group. This is well within the range of values reported in the literature.[17-20] Although absorption was not complete by the end of the study in some of our subjects, these values are unlikely to be significant overestimates, since Kalant et al,[19] Kelley et al,[20] and Mitrakou et al[17] reported

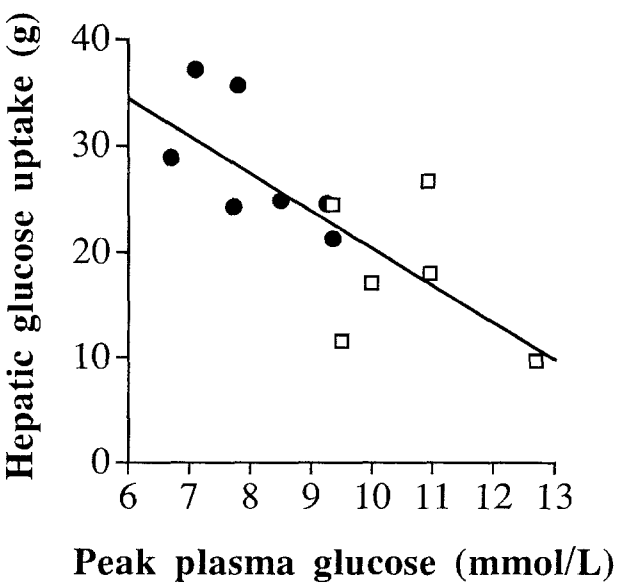

Fig 4. Relationship between peak plasma glucose and hepatic glucose uptake during an OGTT in relatives (□) and controls (●) ($r = .75$, $P < .01$).

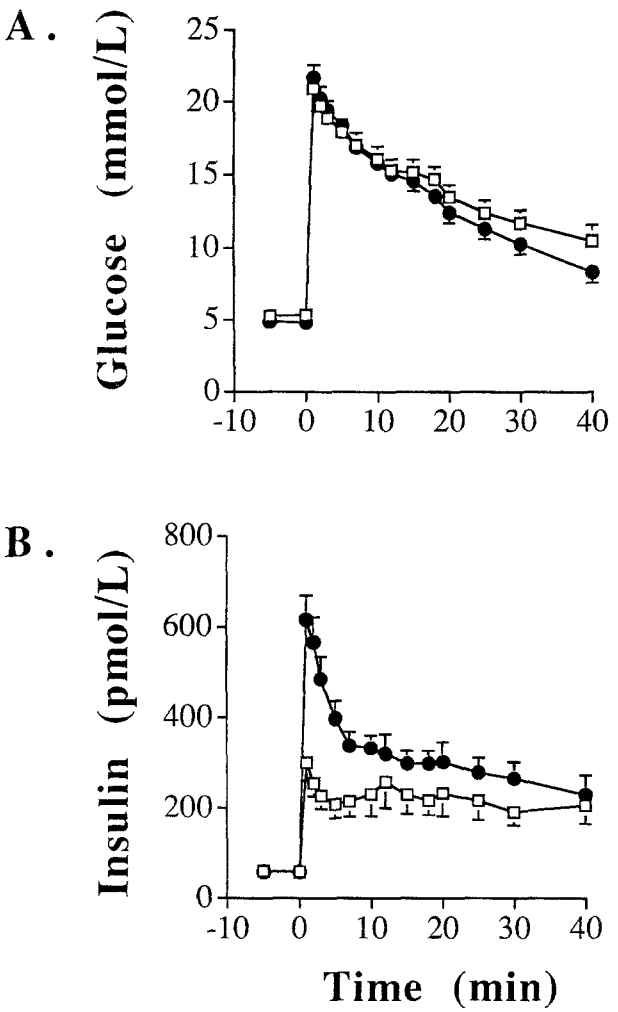

Fig 5. Plasma glucose (A) and insulin (B) in relatives (□) and controls (●) under basal conditions and during an IVGTT at 0 minutes.

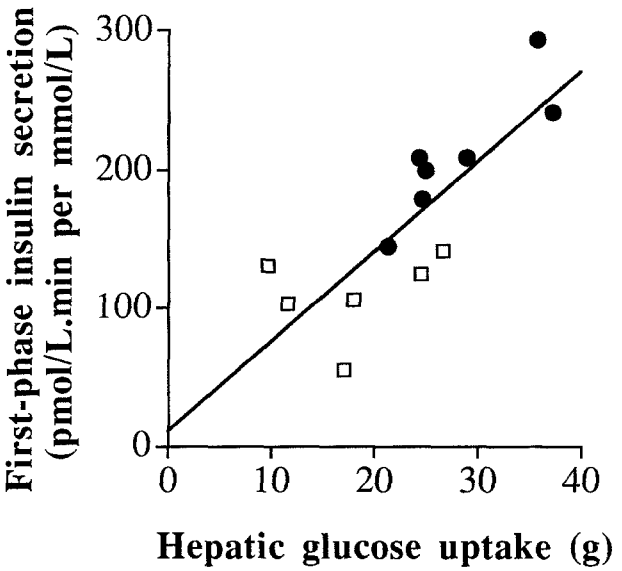

Fig 6. Relationship between first-phase insulin secretion during an IVGTT and hepatic glucose uptake during an OGTT in relatives (□) and controls (●) ($r = .81$, $P < .001$).

similar values (between 29% and 43%) after absorption of the oral load was complete. Our study is the first to measure hepatic glucose uptake in diabetes-prone subjects. We found that the fractional extraction of glucose by the liver was only 24% in the Southern Italian relatives, one third less than the value found in controls. Twenty years ago, Felig et al[27] suggested that a greater proportion of an ingested glucose load escapes hepatic uptake and enters the systemic circulation in NIDDM subjects. Since then, reduced hepatic glucose uptake has been reported in some studies[17,18,28] but not all studies[19,29] in subjects with NIDDM. This may be because it is a feature of some populations and not others.

The defects observed in both hepatic glucose uptake and glucose-stimulated insulin secretion in the Southern Italian subjects, and the fact that a good correlation exists between the magnitude of the defects in the two tissues, may indicate that the same genetic abnormality operates in both the liver and pancreatic islets. The most obvious candidates include defective β-cell glucose transporter, glucokinase, or the regulatory protein controlling the activity of glucokinase. These are all common components of the glucose-sensing apparatus of both the liver and β cells. Although mutations in glucokinase and GLUT 2 have not been found generally in diabetes, it is possible that they exist in selected populations such as our Southern Italian subjects. However, we cannot rule out the possibility that either defective insulin secretion or defective hepatic glucose uptake occurs first and induces the other abnormality.

We found no increase in basal FFA levels and no defect in the suppression of FFAs in our diabetes-prone subjects, nor did they have any evidence of increased adiposity (as measured by the waist to hip ratio). This agrees with some[5] but not all[4,30,31] other studies in subjects at risk of developing NIDDM. A close inspection of the data reported on subjects at risk of developing NIDDM shows that in general, subjects that have a predisposition to NIDDM are likely to have increased body fat,[30-32] increased serum triglyceride levels,[32,33] and impaired suppression of lipid oxidation and FFAs[4] once fasting plasma insulin begins to increase. Therefore, the reason for the differences between our study and others may be that our subjects were studied earlier in the progression of the disease before basal insulin levels were elevated.

NIDDM has long been known to show familial, geographic, and ethnic differences, but this study illustrates that the ethnic differences may be more widespread than previously thought. Our data show that NIDDM may be a disease that begins with a defect in glucose uptake into skeletal muscle in some ethnic groups, while in others, the initial defect may occur as a defect in the way glucose is taken up into liver and β cells. This draws attention to the importance of controlling for ethnicity when searching for genetic mutations that may cause NIDDM.

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