Increased Basal Glucose Production and Utilization in Nondiabetic First-Degree Relatives of Patients With NIDDM

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To characterize the abnormalities in basal glucose homeostasis in people who are at increased risk for non-insulin-dependent diabetes mellitus (NIDDM), we measured the rates of basal hepatic glucose output (HGO), glucose disappearance, and metabolic clearance of glucose (MCR) in 27 nondiabetic first-degree relatives of NIDDM patients and 16 age-, sex-, and weight-matched healthy control subjects with no family history of NIDDM. Mean fasting plasma glucose was significantly lower ($P < 0.05$) in control subjects (mean ± SE 77 ± 2 mg/dl) than in relatives (84 ± 2 mg/dl). Mean basal insulin levels were not significantly different between relatives and control subjects (10.0 ± 1.5 vs. 7.7 ± 1.0 μU/ml). Mean basal HGO was significantly lower in control subjects compared with relatives (1.83 ± 0.07 vs. 2.20 ± 0.10 mg · kg^{-1} · min^{-1}, $P < 0.05$). Mean MCR was similar in relatives (2.58 ± 0.12 mg · kg^{-1} · min^{-1}) and control subjects (2.35 ± 0.09 mg · kg^{-1} · min^{-1}). In summary, this study demonstrates that basal hepatic glucose production and glucose utilization are increased in glucose-tolerant first-degree relatives compared with healthy control subjects. We conclude that impaired basal hepatic glucose regulation rather than glucose disposal is present as an early defect in glucose-tolerant first-degree relatives of NIDDM patients.
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Non-insulin-dependent diabetes mellitus (NIDDM) is an insidious and progressive disease. The established disease is usually characterized by peripheral insulin resistance, excessive hepatic glucose production, and β-cell dysfunction (1–3). Although the exact etiology of NIDDM is uncertain, peripheral insulin resistance or impaired insulin action has been suggested as the possible primary lesion underlying the disease (1,2). In contrast, there is evidence to suggest that β-cell dysfunction may be the primary defect, and both hepatic glucose overproduction and insulin resistance are secondary (4). It is conceivable, however, that the liver defect, whatever its etiology, may occur early and could be the primary lesion that results in excessive hepatic glucose production in some diabetic patients. Because of the exquisite sensitivity of hepatic glucose output (HGO) to the suppressive effects of insulin, the absolute HGO values are usually normal in patients with mild diabetes and impaired glucose tolerance with compensatory hyperinsulinemia. In this regard, DeFronzo et al. (5) have shown that the absolute basal HGO is normal in patients with mild diabetes (fasting plasma glucose [FPG] ≤140 mg/dl). However, this apparently normal HGO occurs at fasting plasma insulin and FPG concentrations approximately twofold greater than the age-, sex-, and weight-matched control subjects. Furthermore, Efendic et al. (6) have demonstrated that basal HGO and intrahepatic glucose cycling are markedly increased in patients with mild diabetes. Thus, in addition to impaired total glucose disposal, the regulation of basal HGO even in mild diabetic patients is clearly defective.

Because hyperglycemia and β-cell dysfunction often coexist at the time of diagnosis, another approach to study the primary lesion of NIDDM patients without the confounding variable of hyperglycemia and altered insulin secretion is to investigate genetically predisposed but glucose-tolerant subjects who are at risk for the disease. In this regard, previous studies have demonstrated that cotwins, siblings, offspring, and other first-degree relatives of NIDDM patients have increased risk for and prevalence of the disease (7–9). These prediabetic subjects have abnormalities in FPG and insulin concentrations. We have previously demonstrated that basal and postmeal hepatosplanchnic glucose appearance rates are greater in the offspring despite greater insulin levels (10,11). Furthermore, Proietto et al. (12) have reported a greater basal HGO and impaired suppressibility of endogenous glucose production after oral glucose load in young Australian Aborigines. This is qualitatively similar

C-peptide	1 nM = 3.02 ng/ml	Insulin	1 pM = 0.167 μU/ml
Glucose	1 mM = 18 mg/dl		

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to the impaired endogenous glucose suppressibility found in patients with impaired glucose tolerance. Thus, in addition to insulin insensitivity in peripheral tissues in the offspring and first-degree relatives reported by Leslie et al. (13) and Eriksson et al. (14), it could be inferred that the regulation of HGO is disturbed even in glucose-tolerant first-degree relatives of NIDDM patients (15).

Thus, the objective of this study was to evaluate the basal glucose homeostasis in nondiabetic subjects at risk for NIDDM. To this end, isotopically derived rates of basal HGO, glucose disappearance (R_d), and metabolic clearance of glucose (MCR) were measured in 27 healthy glucose-tolerant first-degree relatives of NIDDM patients. Their results were compared with 16 age-, sex-, and weight-matched healthy control subjects with no family history of diabetes.

RESEARCH DESIGN AND METHODS

Twenty-seven healthy first-degree relatives (offspring and siblings) of patients with NIDDM as defined by the National Diabetes Data Group (NDDG) criteria (16) were recruited for the study. To ensure ascertainment of the disease, first-degree relatives were selected only if their diabetic relatives were currently receiving antidiabetic drug therapy (oral agents or insulin) and developed diabetes after 40 yr of age. Sixteen age-, sex-, and weight-matched healthy subjects with socioeconomic status and physical activity comparable to those of the relatives served as nondiabetic control subjects. Both groups were also matched for body mass index (BMI) as closely as possible. Control subjects were selected only if both parents were >50 yr old, had no diabetes themselves, and had no family history of diabetes. This approach was adopted to ensure that the likelihood of the control subjects developing NIDDM was minimal. Subjects with kidney, thyroid, liver, and heart disease were excluded from the study. Also, pregnant women and people who participated in endurance exercise training or received medications that influence glucose tolerance were not recruited for the study. Informed written consent approved by the Human Research Review Committee of the University was obtained at the Clinical Research Center after the risk involved in the study was thoroughly explained.

Subjects reported to the Clinical Research Center of The Ohio State University Hospitals at 0700 on the day of study. All subjects ingested at least 300 g of carbohydrate in their usual diet for 3 consecutive days before the day of study. They refrained from strenuous exercise for 48 h before the study. The studies were performed after a 10- to 12-h overnight fast.

Oral glucose tolerance test. Subjects ingested 75 g of oral glucose (Koladex, Custom, Baltimore, MD) over a 2-min period. Blood samples for plasma glucose were obtained before and after oral glucose load at 30, 60, 120, and 180 min. By the NDDG criteria, all the nondiabetic subjects were found to have normal glucose tolerance.

Determination of basal HGO and glucose clearance. All the subjects voided at 0730. With subjects in supine position, a 19-gauge scalp vein needle was inserted in an antegrade manner into a forearm vein for tracer infusion. The primed (35 μCi) continuous (0.35 μCi/min) tracer (D-[3-^{3}H]glucose) dissolved in 0.9% saline was infused throughout the study period of 200 min. An angiocatheter was inserted in a retrograde manner into a dorsal vein of the contralateral hand and kept patent with 0.9% saline. The hand was then inserted in a thermoregulated heat box (70 ± 2°C) for arterialization of venous blood. After 180 min of continuous tracer infusion for equilibration and labeling of glucose pool, five blood samples were obtained at 5-min intervals for 20 min for glucose and glucose specific-activity (SA) determinations. The glucose SA reached a steady state in both groups after a 180-min equilibration period (Fig. 1). The coefficient of variation of SA between the intervals was <2% in each group. Basal plasma insulin and C-peptide levels were obtained at 10-min intervals for 20 min. Urine samples were collected at the end of the study for determination of urinary glucose excretion.

Chemical analyses. Plasma and urine glucose concentrations were measured by the glucose oxidase method with a glucose analyzer (Beckman, Fullerton, CA). Glycosylated hemoglobin (HbA_{1c}) was measured by the cationic microcolumn chromatographic technique (Isolab, Akron, OH). Glucose SA was estimated by the perchloric acid–precipitation method as previously described (17). Plasma insulin and C-peptide were measured by the double-antibody radioimmunoassay technique (18). The sensitivities of the assays were 2.5 μU/ml for insulin and 0.47 ng/ml for C-peptide. The intra- and interassay coefficients of variation were 6 and 10% for insulin and 6 and 13% for C-peptide.

The rate of glucose appearance (R_a) and R_d was calculated by the steady-state Steele equation (19). In the steady postabsorptive state, R_a equals the basal hepatic glucose production. Also, basal R_a equals R_d. In the presence of glycosuria, the rate of glucose uptake (R_u) by the tissues is equal to R_d minus the rate of urinary glucose excretion. All the nondiabetic subjects were aglycosuric; thus, R_u is equal to R_d. Because R_d is influenced by the mass-action effect of

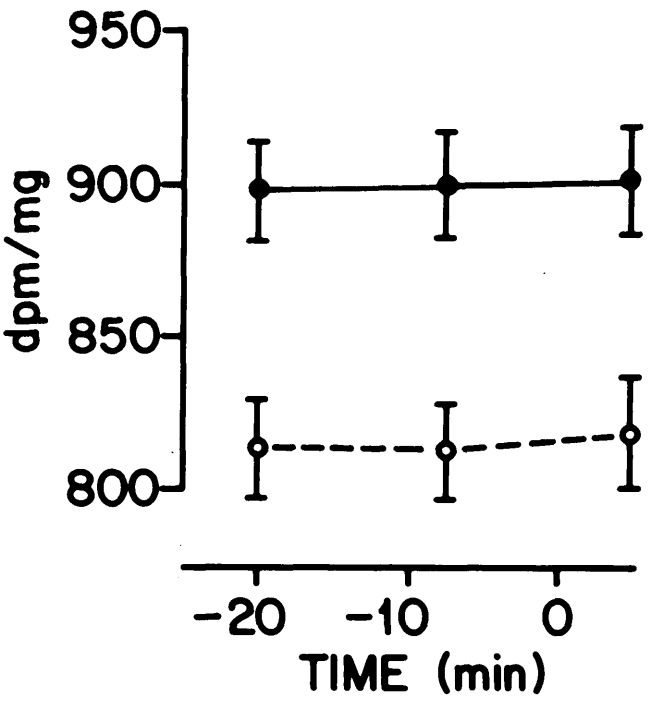

FIG. 1. Mean ± SE steady-state glucose specific activity in nondiabetic first-degree relatives (○) and healthy control subjects (●).

glucose per se, the MCR was also used to represent glucose disposal. MCR was calculated by dividing R_d by the plasma glucose concentration (20).

Statistical analysis. Results are means ± SE unless otherwise stated. Comparison between groups was made by unpaired Student's *t* test and analysis of variance where appropriate. Linear regression and correlation coefficients were calculated by the least-squares method. Because of the disproportionate sex ratios in the groups, we examined the effects of sex on the basal glucose turnover rates and biochemical parameters with analysis of covariance. No statistical differences were observed in any of the groups. Thus, the data in both sexes were pooled in each group for statistical analyses. $P < 0.05$ was considered significantly different.

RESULTS

There were 22 women and 5 men in the relatives group and 8 women and 8 men in the control group. Mean age, body weight, and BMI were not significantly different between relatives and control subjects (Table 1). There were no significant differences in the HbA_{1c} values in relatives compared with control subjects.

Mean FPG was significantly greater in relatives compared with control subjects (84 ± 2 vs. 77 ± 2 mg/dl, $P < 0.05$; Fig. 2*A*). Mean fasting plasma insulin levels were slightly but not significantly greater in relatives compared with control groups (10.0 ± 1.5 vs. 7.7 ± 1.0 μU/ml, NS; Fig. 2*B*). Plasma C-peptide was significantly greater ($P < 0.05$) in relatives than in control subjects (Table 1).

Mean basal HGO was significantly greater ($P < 0.05$) in relatives compared with control subjects (2.20 ± 0.10 vs. 1.83 ± 0.07 mg · kg^{-1} · min^{-1}; Fig. 3). The mean MCR was not significantly different between relatives and control subjects (2.58 ± 0.12 vs. 2.35 ± 0.09 mg · kg^{-1} · min^{-1}, respectively). We did not find any relationships between either HGO or MCR and plasma insulin, C-peptide, body weight, BMI, or HbA_{1c} in any of the groups.

DISCUSSION

Previous studies established that NIDDM is a disease with strong genetic and familial components (7–9,16). Despite strong evidence for the role of genetic inheritance (exemplified by ~100% concordance rate in monozygotic twins), metabolic markers for the disease remain controversial. In most population studies, elevated fasting and/or 2-h postprandial insulin and glucose levels have been found to strongly predict future development of NIDDM. However, these findings have been inconsistent because the disease is heterogenous. Isotopically derived studies were not used in most of these previous studies.

Previous investigators have observed several metabolic abnormalities in nondiabetic offspring and relatives of NIDDM patients (10–15,21–24). The bulk of evidence indicates insulin resistance and impaired glucose disposal in both glucose-tolerant and -intolerant first-degree relatives of NIDDM patients. In this regard, Eriksson et al. (14) demonstrated a reduced nonoxidative glucose metabolism as the mechanism of the decreased glucose disposal in first-degree relatives of NIDDM patients, regardless of glucose-tolerance status.

In our study, we found that FPG was slightly but significantly greater (albeit within normal limits) in relatives than in control subjects. This occurred despite slightly but insignificantly higher plasma insulin levels in the relatives. Several previous studies have found basal hyperinsulinemia in first-degree relatives and offspring of NIDDM patients in ethnic groups with a high propensity for the disease (23,24). However, in White first-degree relatives, variable fasting and poststimulation plasma insulin levels have been reported (9,10,13–15,22). In this regard, some investigators found decreased basal and postglucose insulin levels in nondiabetic cotwins of dizygotic diabetic patients (21) and relatives of NIDDM patients (9). Because the plasma C-peptide level was greater in the relatives in this study, it can be inferred that the actual portal insulin concentration was much greater in relatives than in control subjects. This will attest to the severity of the hepatic insulin insensitivity in first-degree relatives. Thus, our results might have been more impressive if the relatives were studied at an insulin level similar to that of control subjects.

Increased basal HGO, inappropriate for the insulin and glucose concentrations, is a characteristic feature of patients with NIDDM. Elevated HGO is an important determinant of both fasting and postprandial hyperglycemia in patients with diabetes and impaired glucose tolerance (5). We found that mean basal HGO was 25% greater in relatives than in control subjects in agreement with some previous studies (12). These basal HGO values were, however, within conventionally accepted normal limits (1.6–2.5 mg · kg^{-1} · min^{-1}). The greater HGO occurred in the face of slightly higher peripheral insulin, C-peptide, and FPG levels in the relatives. Thus, our

TABLE 1
Clinical and biochemical characteristics of subjects

Groups	Age (yr)	*n* (F/M)	Body weight (kg)	Body mass index (kg/m^2)	HbA_{1c} (%)	Fasting plasma glucose (mg/dl)	Fasting plasma insulin (μU/ml)	Fasting plasma C-peptide (ng/ml)
Nondiabetic relatives	32 ± 2 (28–44)	22/5	71 ± 3 (55–91)	25.3 ± 0.9 (19–39)	6.5 ± 0.2 (5.100–7.822)	84 ± 2 (72–109)	10.0 ± 1.5 (3.0–26.4)	1.45 ± 0.20 (0.60–3.56)
Control subjects	29 ± 2 (22–45)	8/8	73 ± 4 (56–92)	24.6 ± 0.8 (20.6–33.0)	6.3 ± 0.2 (4.8–7.5)	77 ± 2* (71–97)	7.7 ± 1.0 (3–15)	0.96 ± 0.09* (0.49–1.60)

Values are means ± SE. Ranges are given in parentheses. Normal body mass index <25 kg/m^2 for women and <27 kg/m^2 for men. Normal HbA_{1c} 4.5–8.5%.
*$P < 0.05$.

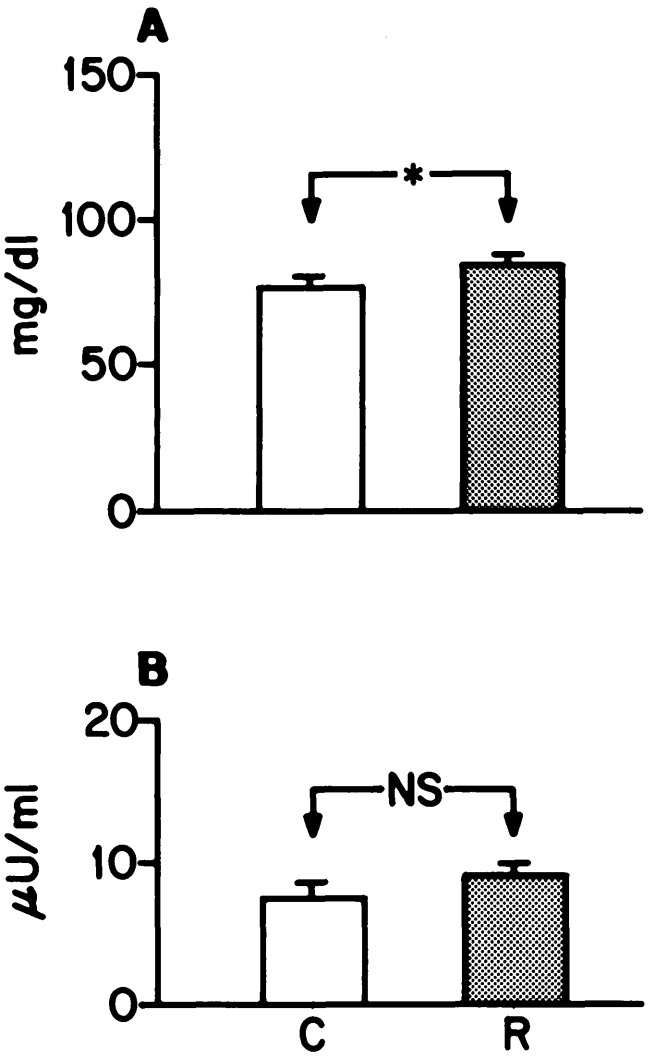

FIG. 2. Mean ± SE fasting plasma glucose (*A*) and insulin (*B*) in healthy control subjects (C) and relatives of non-insulin-dependent diabetic patients (R). *$P < 0.05$.

study indicates that glucose-tolerant relatives have an impaired insulin- and/or glucose-induced suppressibility of basal HGO. This may be qualitatively similar to the hepatic glucose abnormality found in NIDDM patients. We observed an extensive overlap between relatives and control subjects in the measurements of basal HGO. This could explain the similar basal HGO values found in previous studies by our laboratory (10,11) and that of Eriksson et al. (14) that involved a small number of subjects.

Impaired insulin-mediated peripheral glucose disposal, predominantly in skeletal muscle, is a characteristic feature of insulin resistance states found in patients with established diabetes, impaired glucose tolerance, obesity, and hypertension. Several investigators have demonstrated a similar defect in first-degree relatives regardless of their glucose-tolerance status. Therefore, we assessed the basal glucose disposal rate in our subjects. The basal glucose disposal expressed as MCR was not different between relatives and control subjects. However, in the basal postabsorptive state, R_d was equal to HGO. Thus, the absolute R_d was increased in the relatives. Because the subjects were aglycosuric, total tissue glucose uptake was also probably enhanced. However, this finding should not be misconstrued as evidence against insulin resistance or decreased insulin-mediated glucose disposal in peripheral tissues because non–insulin-mediated glucose transport accounts for 70% of basal glucose disposal in humans.

In conclusion, this study demonstrates that an impaired basal hepatic glucose regulation may be an early defect in young glucose-tolerant first-degree relatives of patients with NIDDM. This occurs in the face of a normal or an enhanced total glucose disposal. However, the mechanism of the early hepatic glucose abnormalities in first-degree relatives remains to be elucidated. We speculate that this defect may

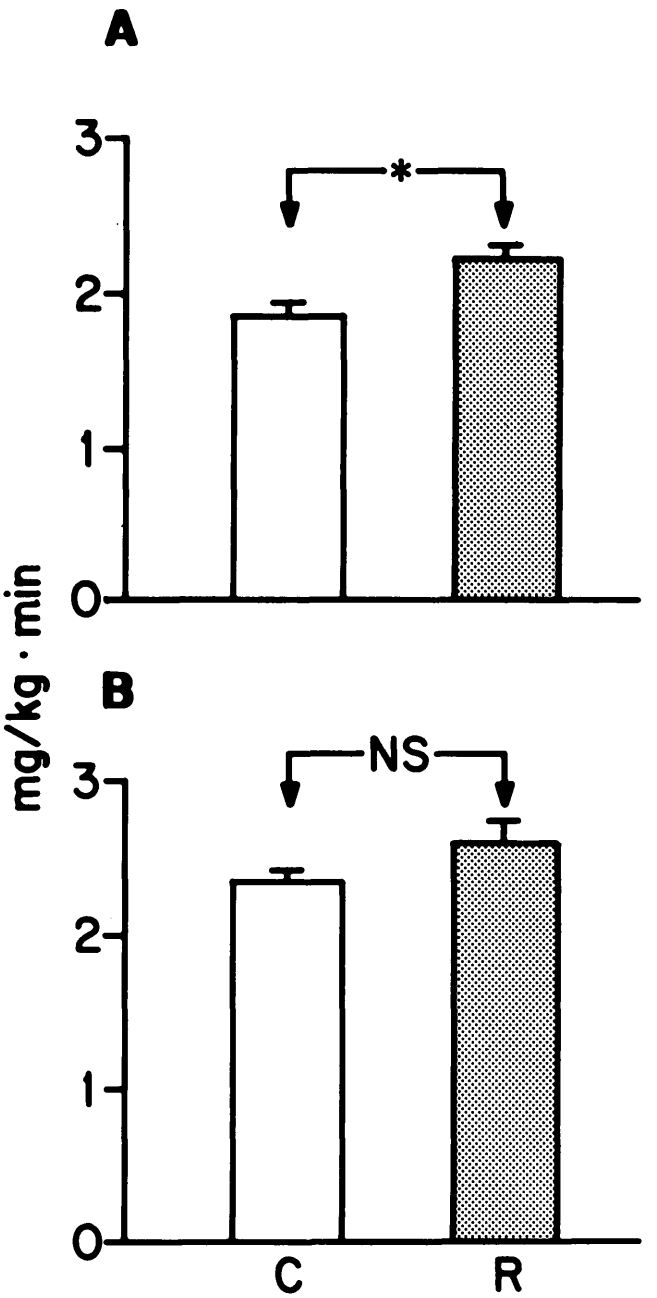

FIG. 3. Mean ± SE basal hepatic glucose output (*A*) and glucose clearance (*B*) in healthy control subjects (C) and relatives of non-insulin-dependent diabetic patients (R). *$P < 0.05$.

be a manifestation of the global insulin resistance in subjects at risk for NIDDM. Whether increased HGO is a harbinger for future NIDDM can only be ascertained in longitudinal studies of nondiabetic people at increased risk for NIDDM.

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