Similar Insulin Sensitivity in NIDDM Patients with Normo- and Microalbuminuria

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OBJECTIVE — To investigate whether insulin resistance and microalbuminuria are associated in non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS — Insulin sensitivity was assessed using a hyperinsulinemic euglycemic clamp in 11 normoalbuminuric and 9 microalbuminuric NIDDM patients matched for sex, age, body composition, glycemic control, diabetes duration, and therapy.

RESULTS — Isotopically determined glucose disposal was similar in normo- and microalbuminuric patients in the basal state (mean ± SD; 3.30 ± 1.01 vs. 3.46 ± 0.82 mg · kg lean body mass [LBM]$^{-1}$ · min^{-1}; NS) and during hyperinsulinemia (7.16 ± 2.65 vs. 6.63 ± 2.88 mg · kg LBM^{-1} · min^{-1}; NS). No difference was observed in nonoxidative glucose disposal or lipid oxidation. Endogenous glucose production was equally suppressed by insulin (−0.08 ± 0.99 vs. 0.30 ± 1.12 mg · kg^{-1} LBM · min^{-1}; NS). Glucose oxidation tended to be lower in the normoalbuminuric patients in the basal state (1.16 ± 0.37 vs. 1.41 ± 0.36 mg · kg LBM^{-1} · min^{-1}) and during hyperinsulinemia (2.35 ± 0.72 vs. 2.90 ± 0.77 mg · kg LBM^{-1} · min^{-1}; both $P < 0.15$). Urinary albumin excretion rate correlated with the insulin-stimulated glucose oxidation rate ($r = 0.59$, $P = 0.0064$), and a similar trend was seen in the basal state ($r = 0.42$, $P = 0.063$). Protein oxidation was higher in normoalbuminuric patients (1.6 ± 0.5 vs. 1.0 ± 0.4 mg · kg LBM^{-1} · min^{-1}; $P = 0.017$) and correlated inversely with albuminuria ($r = -0.70$, $P = 0.0007$). Serum growth hormone increased during insulin infusion; however, the increase was significantly greater in microalbuminuric patients. Plasma lipoproteins, maximal aerobic capacity, and 24-h ambulatory blood pressure were similar in the two groups.

CONCLUSIONS — Basal and insulin-stimulated glucose uptakes are comparable in carefully matched normo- and microalbuminuric NIDDM patients, and glucose oxidation may be positively related to albuminuria. The inverse relation between protein oxidation and albuminuria may be due to higher growth hormone levels during daily life perturbations in glucose in microalbuminuric patients.

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Received for publication 19 September 1994 and accepted in revised form 5 January 1995.

ACE, angiotensin-converting enzyme; ANOVA, analysis of variance; BMI, body mass index; DELFIA, dissociation-enhanced lanthanide immunoassay; LBM, lean body mass; IGF-I, insulin-like growth factor I; NEFA, nonesterified fatty acid; NIDDM, non-insulin-dependent diabetes mellitus; SHBG, sex hormone–binding globulin; UAE, urinary albumin excretion; WHR, waist-to-hip ratio.

A reduced sensitivity to the actions of insulin (i.e., insulin resistance) has been described in a number of conditions (1,2). A compensatory increase in plasma insulin concentration (i.e., hyperinsulinemia) often preserves a normal glucose homeostasis for some time, but progressive deterioration may eventually lead to glucose intolerance or even outright non-insulin-dependent diabetes mellitus (NIDDM) (3). The frequent association of insulin resistance and established cardiovascular risk factors (dyslipidemia, upper body obesity, and hypertension) to some extent supports the suggestion that insulin resistance (or secondary hyperinsulinemia) may be a common denominator, which may explain the increased cardiovascular morbidity and mortality of NIDDM (4–7).

Microalbuminuria (i.e., a urinary albumin excretion [UAE] rate of 20–200 μg/min), often found in NIDDM, has been shown to predict premature cardiovascular disease and progression to clinical nephropathy (UAE >200 μg/min) in NIDDM (8–10). It has been suggested that microalbuminuria may be a feature of the prediabetic state (11) to be added to the aforementioned markers of the so-called insulin resistance syndrome, which may also be found in confirmed prediabetic individuals (12–15). Recent reports even propose a further reduction in insulin sensitivity in microalbuminuric NIDDM patients compared with normoalbuminuric (UAE <20 μg/min) patients (16–18), thus linking these two factors of cardiovascular risk. Although allowances were made for some confounders (sex, age, and hypertension), these observations could partly be the result of other factors capable of modifying insulin sensitivity and/or albuminuria, such as differences in glycemic control, body composition, or physical fitness (19–21).

To test this hypothesis, we compared insulin-stimulated glucose uptake in two groups of NIDDM patients with normo- and microalbuminuria. The

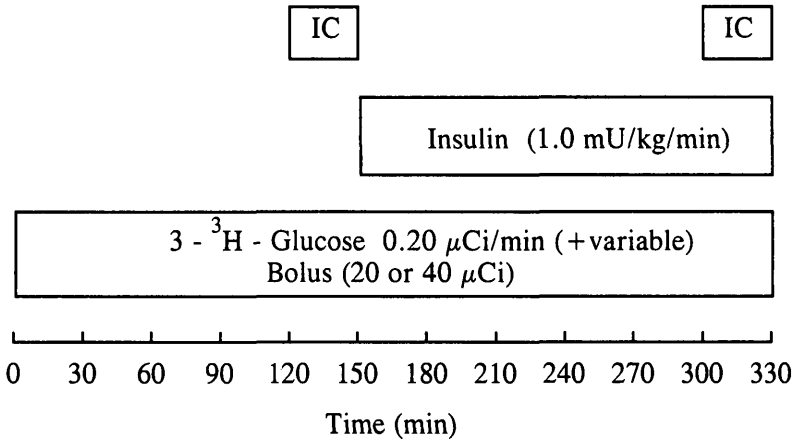

Figure 1—*Design of the hyperinsulinemic euglycemic clamp. IC, indirect calorimetry.*

groups were matched for sex, age, body composition, glycemic control, diabetes duration, and therapy. Furthermore, we assessed 24-h ambulatory blood pressure, plasma lipoproteins, and Vo_{2max} to minimize confounding by external modulators of insulin sensitivity or albuminuria.

RESEARCH DESIGN AND METHODS

— Twenty NIDDM patients (11 with normoalbuminuria and 9 with microalbuminuria) were selected from the outpatient clinic. The patients were matched for sex, age, diabetes duration, body composition (body mass index [BMI], lean body mass [LBM], and waist-to-hip ratio [WHR]), antidiabetic therapy, antihypertensive therapy, and smoking. Additional criteria for inclusion were the following: age 45–70 years, normal serum creatinine level, HbA_{1c} <9.5%, and blood pressure ≤160/100 mmHg. Sodium intake was unrestricted, and none of the patients followed a low-protein diet.

The patients were examined twice, with an interval of 1 week. At the first visit, Vo_{2max} was assessed using a standardized bicycle ergometer (Monark Ergomedic 829E, Copenhagen, Denmark) test as described by Åstrand (22). During this procedure, an individual workload is applied, leading to a submaximal and stable heart rate (125–135 beats/min) after 5 min. After 6 min, automatic measurements of heart rate and workload are used for computation of Vo_{2MAX}.

At the second visit, UAE was measured by radioimmunoassay (23) and assessed as the mean of three timed overnight collections. Moreover, the urine samples were used for determination of 24-h excretion rates of sodium, potassium, and creatinine. Fasting blood samples were taken for determination of plasma glucose, serum fructosamine was measured by a spectrophotometric technique (24), and HbA_{1c} was measured by high-performance liquid chromatography (25). Moreover, measurements of serum cholesterol by continuous flow analysis (26), serum triglycerides by an enzymatic technique (27), serum high-density lipoprotein cholesterol by a dextran sulfate-Mg^{2+} precipitation procedure (28), and serum creatinine by a modified Jaffe's reaction (29) were all adapted to the Technicon CHEM 1 analyzer. Sex hormone–binding globulin (SHBG) was measured in duplicate using an immunofluorometric sandwich assay with two monoclonal antibodies (dissoci-

Table 1—*Clinical characteristics of NIDDM patients by albuminuria*

	Normoalbuminuria	Microalbuminuria
n	11	9
Sex (M/F)	6/5	6/3
Age (years)	56 ± 6	62 ± 8
Diabetes duration (years)	9.1 ± 4.6	13.2 ± 8.8
BMI (kg/m^2)	27.5 ± 3.4	26.2 ± 3.3
LBM (kg)	53.2 ± 11.1	51.9 ± 9.6
WHR	0.96 ± 0.05	0.99 ± 0.04
Fasting plasma glucose (mmol/l)	10.7 ± 2.9	11.3 ± 2.9
Serum fructosamine (mmol/l)	386 ± 78	389 ± 73
HbA_{1c} (%)	8.3 ± 1.5	9.1 ± 1.3
Fasting serum C-peptide (nmol/l)	0.79 ± 0.27	0.98 ± 0.47
Total cholesterol (mmol/l)	5.6 ± 0.8	6.2 ± 1.7
Triglycerides (mmol/l)	1.61 ± 0.54	1.44 ± 0.38
High-density lipoprotein cholesterol (mmol/l)	1.33 ± 0.40	1.22 ± 0.26
Serum creatinine (μmol/l)	83 ± 16	86 ± 13
SHBG (nmol/l)	44 ± 12	46 ± 20
Serum albumin (g/l)	39 ± 6	38 ± 2
Urinary sodium (mmol/24 h)	145 ± 50	179 ± 61
Urinary potassium (mmol/24 h)	49 ± 26	51 ± 19
Urinary creatinine (mmol/24 h)	11.6 ± 3.2	9.8 ± 4.1
$VO_{2\ max}$ (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)	27.1 ± 0.9	21.6 ± 4.4
Antidiabetic treatment (d/o/i)	1/6/4	2/4/3
Antihypertensive treatment (yes/no)	2/9	4/5

Data are means ± SD. All NS. d, diet; o, oral agents; i, insulin.

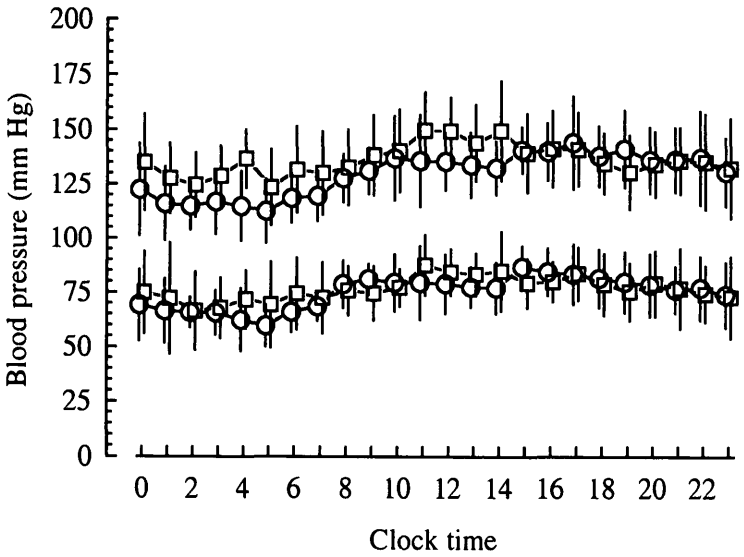

Figure 2—*Diurnal systolic and diastolic blood pressures in normoalbuminuric (○) and microalbuminuric (□) NIDDM patients. There was no difference between the groups (ANOVA).*

ation-enhanced lanthanide immunoassay [DELFIA] SHBG kit, Wallac, Turku, Finland). BMI was calculated as weight divided by height squared (kg/m^2) and used as an index of overall obesity. The WHR was used as a measure of body fat distribution. LBM was measured by means of bioimpedance (Animeter, HTS Engineering, Odense, Denmark) (30).

A hyperinsulinemic euglycemic clamp was performed in all patients (Fig. 1). The examination was initiated at 0800 after an overnight fast, and the patients were not allowed to take oral hypoglycemic drugs or insulin within 24 h before the clamp. During the basal period (t = 0–150 min) and the hyperinsulinemic period (t = 150–330 min), 3-[^{3}H]glucose (Du Pont-NEN, Boston, MA) was infused in a primed (20–40 μCi, depending on the fasting plasma glucose concentration), continuous manner (0.20 μCi/min) for the determination of glucose turnover rates (hepatic glucose production and total peripheral glucose disposal [R_d]). Moreover, to minimize rapid dilution of the labeled glucose pool with unlabeled glucose, 3-[^{3}H]glucose was also added to the glucose infused during the clamp (200 μCi/l, 20%) (31). Insulin (Actrapid, Novo Nordisk, Gentofte, Denmark) was infused at a rate of 1.0 mU · kg^{-1} · min^{-1}. In the hyperglycemic patients, plasma glucose was allowed to decline slowly to 5 mmol/l and was subsequently clamped at this level by infusion of glucose.

Every 10 min, plasma glucose was measured in duplicate immediately after sampling (Beckman, Palo Alto, CA). Blood samples for determination of glucose-specific activity and growth hormone were drawn every 30 min during the basal and the hyperinsulinemic periods and every 10 min during the steady-state periods (t = 120–150 and 300–330 min). Levels of insulin, glucagon, and nonesterified fatty acids (NEFAs) were measured at 120, 150, 300, and 330 min. The non-steady-state equation of Steele, as modified by DeBodo et al. (32), was used for calculation of glucose appearance and disposal rates (R_a and R_d). A pool fraction of 0.65 was used. Respiratory exchange ratios were assessed by indirect calorimetry (33) (Deltatrack metabolic monitor, Datex, Helsinki, Finland) performed during the last 30 min of the basal and hyperinsulinemic periods. Net lipid and glucose oxidation rates were computed from the above measurements, and protein oxidation rates were estimated from urinary carbamide excretion collected during the investigation. Net nonoxidative glucose disposal (i.e., glucose storage) was calculated by subtracting the glucose oxidation rate from the rate of disappearance. Serum insulin and plasma glucagon were measured by radioimmunoassay as described by Ørskov et al. (34) with minor modifications. Serum growth hormone was measured us-

Table 2—*Day- and nighttime values during 24-h blood pressure (mmHg) and heart rate recordings*

	Normoalbuminuria	Microalbuminuria
n	11	9
Systolic blood pressure (mmHg)		
Diurnal	131 ± 12	134 ± 11
Daytime	138 ± 12	140 ± 15
Nighttime	116 ± 11	128 ± 13
Diastolic blood pressure (mmHg)		
Diurnal	75 ± 9	75 ± 11
Daytime	80 ± 10	80 ± 11
Nighttime	64 ± 9	70 ± 14
Heart rate (beats/min)		
Diurnal	76 ± 16	81 ± 7
Daytime	81 ± 16	87 ± 8
Nighttime	65 ± 14	72 ± 5

Data are means ± SD. All NS.

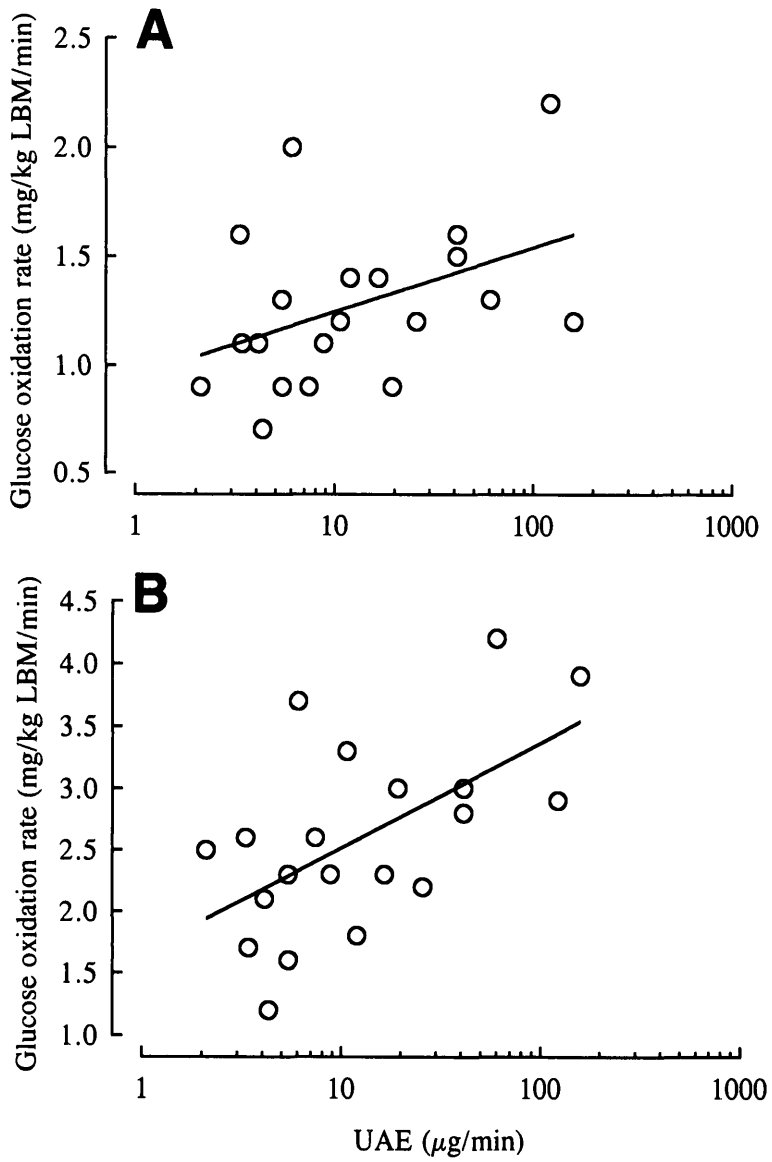

Figure 3—*Glucose oxidation rates as related to UAE rate in the basal state (A) and during insulin stimulation (B). Basal:* r = *0.42,* P = *0.063; insulin stimulation:* r = *0.59,* P = *0.0064.*

ing an immunofluorometric sandwich assay with two monoclonal antibodies (DELFIA hGH kit, Wallac). Insulin-like growth factor I (IGF-I) was assessed using an in-house time-resolved immunofluorometric assay based on the DELFIA principle (Wallac). The noncompetitive assay used two monoclonal antibodies directed against different sites on human recombinant IGF-I. The detection limit was 2.5 ng/l, and the standard response was linear up to 2.5 μg/l. Serum levels were measured after acid ethanol extraction. Mean intra-assay and interassay coefficients of variation are <5 and <10%, respectively (35). Serum NEFAs were determined by a colorimetric method (Wako, Neuss, Germany). Plasma C-peptide was measured by a radioimmunoassay kit (Immuno Nuclear, Stillwater, MN).

After termination of the glucose clamp, each patient was equipped with a portable automatic blood pressure monitor (model 90202, SpaceLabs, Redmond, WA) using oscillometry for estimation of 24-h ambulatory blood pressure (36). The device was programmed to measure blood pressure every 20 min between 0600 and 2400 and every hour during the night. Patients recorded actual time for going to bed and rising in the morning for accurate appraisal of day and night blood pressures.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all patients participating in the study.

Statistical analysis

Values are given as means ± SD or as median values (25th–75th percentiles). UAE was log-transformed because of the positively skewed distribution and is presented as the geometric mean ×/÷ antilog SD. Groups were compared using Student's *t* test, the Mann-Whitney two-sample test, and Fisher's exact test for dichotomous variables. Correlations were evaluated using Pearson's *r* or Spearman's ρ analysis. Between-group comparisons of changes during the clamp were analyzed by repeated-measures analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

RESULTS — Table 1 shows the clinical characteristics of the patients in the two groups. The overnight UAEs in normo- and microalbuminuric patients were (geometric mean ×/÷ antilog SD) 4.8 ×/÷ 1.6 and 38.9 ×/÷ 2.4 μg/min, respectively. Patients with microalbuminuria tended to be older ($P = 0.07$) than patients with normoalbuminuria. Chronic antihypertensive treatment was used by two normoalbuminuric (angiotensin-converting enzyme [ACE] inhibitors) and by four microalbuminuric (two ACE inhibitors, 1 thiazide, and 1 loop diuretic) patients. Only NPH insulin was used in all patients receiving insulin treatment.

Figure 2 summarizes the 24-h

Table 3—*Basal and insulin-stimulated (clamp) rates of glucose and lipid metabolism during the last 30 min of the basal period and the glucose clamp*

	Normoalbuminuria	Microalbuminuria
n	11	9
Basal rates (mg · kg LBM^{-1} · min^{-1})		
Isotopically determined glucose disposal	3.30 ± 1.01	3.46 ± 0.82
Glucose oxidation	1.16 ± 0.37	1.41 ± 0.36
Glucose storage	2.15 ± 1.00	2.08 ± 0.92
Lipid oxidation	1.37 ± 0.32	1.41 ± 0.18
Hepatic glucose production	3.09 ± 0.81	3.48 ± 0.66
Clamp rates (mg · kg LBM^{-1} · min^{-1})		
Glucose infusion rate	6.49 ± 3.59	6.62 ± 3.17
Isotopically determined glucose disposal	7.16 ± 2.65	6.63 ± 2.88
Glucose oxidation	2.35 ± 0.72	2.90 ± 0.77
Glucose storage	4.79 ± 2.37	3.74 ± 2.51
Lipid oxidation	0.81 ± 0.26	0.69 ± 0.34
Hepatic glucose production	−0.08 ± 0.99	0.30 ± 1.12

Data are means ± SD. All values are NS.

ambulatory blood pressure recordings. Diurnal blood pressure and daytime and nighttime blood pressures (Table 2) were comparable in the two groups.

Isotopically determined R_d and the glucose infusion rate were similar in normo- and microalbuminuric patients both during the basal state and during insulin stimulation (Table 3). Basal energy expenditure was comparable in the two groups (normoalbuminuric vs. microalbuminuric: 33.6 ± 3.7 vs. 32.5 ± 2.7 kcal · kg LBM^{-1} · 24 h^{-1}, NS) and was not altered during the clamp. No differences were found in nonoxidative glucose disposal or oxidation rates of glucose and lipids. Glucose oxidation tended to be higher in patients with microalbuminuria both in the basal state (normoalbuminuric vs. microalbuminuric: 1.16 ± 0.37 vs. 1.41 ± 0.36 mg · kg LBM^{-1} · min^{-1}) and during insulin stimulation (2.35 ± 0.72 vs. 2.90 ± 0.77 mg · kg LBM^{-1} · min^{-1}), although not significantly (both $P < 0.15$). UAE correlated significantly with the insulin-stimulated glucose oxidation rate ($r = 0.59$, $P = 0.0064$), and a similar tendency was seen in the basal state (Fig. 3). The endogenous glucose production was equally suppressed by insulin (normoalbuminuric vs. microalbuminuric: −0.08 ± 0.99 vs. 0.30 ± 1.12 mg · kg LBM^{-1} · min^{-1}; NS). Conversely, protein oxidation rate, as estimated from urinary carbamide excretion rate, was significantly higher in normoalbuminuric than in microalbuminuric patients (normoalbuminuric vs. microalbuminuric: 1.6 ± 0.5 vs. 1.0 ± 0.4 mg · kg LBM^{-1} · min^{-1}, $P = 0.017$), and a significant inverse correlation between the protein oxidation rate and UAE (Fig. 4) was observed ($r = -0.70$, $P = 0.0007$). Voided urinary volume, as well as urinary creatinine excretion, was similar in the two groups. Moreover, levels of insulin, glucagon, and NEFAs were comparable in the two groups (Table 4). Although plasma glucose was lowered very slowly, serum growth hormone rose significantly during insulin infusion ($P = 0.0022$). However, the increase was significantly higher in microalbuminuric patients ($P = 0.044$, repeated-measures ANOVA). Basal concentrations of serum IGF-I were similar (normoalbuminuric vs. microalbuminuric: 129 ± 99–197 vs. 134 ± 83–162 μg/l, NS [reference value for the age-group: 116 ± 83–145 μg/l]).

CONCLUSIONS — This study shows that the level of insulin sensitivity is similar in carefully matched NIDDM patients with normo- and microalbuminuria. The study also suggests a positive relation between UAE and glucose oxidation, especially during insulin stimulation, and an inverse relation between UAE and protein oxidation.

Previous studies have suggested

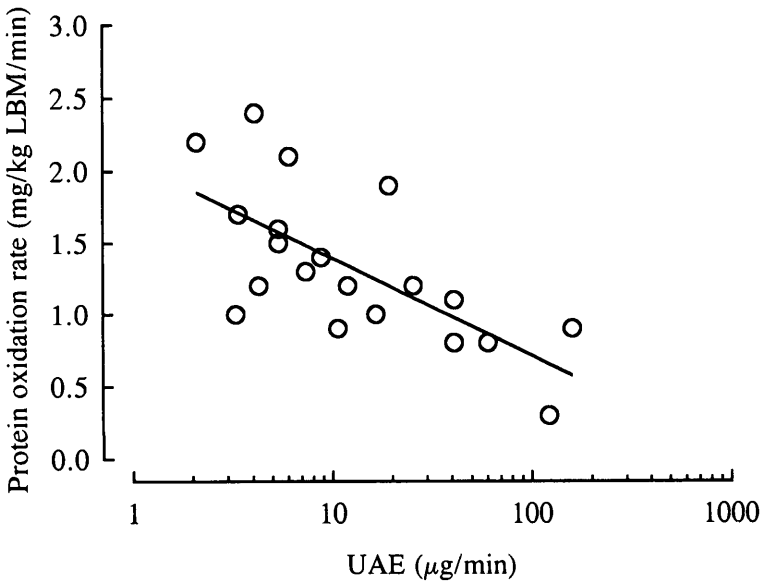

Figure 4—*Protein oxidation rate as related to UAE.* r = −0.70; P = 0.0007.

Table 4—*Basal and insulin-stimulated (clamp) hormone levels*

	Normoalbuminuria	Microalbuminuria
n	11	9
Basal		
Insulin (mU/l)	11 (9–22)	14 (9–17)
Glucagon (ng/l)	65 (44–79)	52 (46–96)
Growth hormone (μg/l)	0.14 (0.08–0.50)	0.06 (0.03–0.26)
NEFAs (μmol/l)	574 (487–848)	724 (615–885)
Clamp		
Insulin (mU/l)	83 (78–95)	92 (87–113)
Glucagon (ng/l)	39 (35–69)	49 (39–88)
Growth hormone (μg/l)	0.66 (0.18–0.83)	1.55 (0.72–2.69)*†
NEFAs (μmol/l)	64 (29–84)	56 (52–133)

Data are medians (25th–75th percentile). * $P < 0.05$ vs. normoalbuminuria; † $P < 0.05$ increase from basal (vs. normoalbuminuria).

that insulin resistance and microalbuminuria may be associated in NIDDM (16–18). Thus, total insulin-stimulated glucose uptake was reported to be more reduced in patients with elevated UAE than in patients with normoalbuminuria. Furthermore, Groop et al. (16) found that the reduction was due to a decrease in nonoxidative glucose disposal. A link between these two markers of cardiovascular disease could provide additional insight into the pathophysiological mechanisms underlying the increased cardiovascular morbidity and mortality in patients with increased albuminuria. Insulin resistance and microalbuminuria are both associated with hypertension in NIDDM (37,38), and prospective studies have shown that both conditions are predictive of atherogenic lipoprotein changes (13,39). However, apart from genetic determinants, a number of predominantly environmental factors, such as poor glycemic control, elevated blood pressure, obesity, physical fitness, and use of antihypertensive drugs, are known to influence insulin sensitivity (and in some cases also albuminuria) (19–21,37,40,41). As noted, our patients were matched according to these pivotal confounders. To minimize overmatching, other putative modulators of insulin sensitivity were assessed during the study. As shown in Tables 2 and 3, these parameters were similar in the two groups. In a study by Niskanen and Laakso (17), the group of microalbuminuric patients had significantly higher diastolic blood pressure and higher HbA_{1c}, in addition to being more obese and including more men; all conditions that favor reduced insulin sensitivity. Although statistical adjustments were made for some of these factors, the data were not controlled for the significantly poorer glycemic control in the microalbuminuric patients, which to some extent may explain the findings. In the study by Nosadini et al. (18), BMI varied considerably, but insulin sensitivity was lower in normotensive microalbuminuric patients than in normotensive normoalbuminuric patients with comparable BMI. However, indirect calorimetry was not performed. Moreover, in both studies, as well as in the study by Groop et al. (16), estimation of blood pressure was based on clinical blood pressure measurements and not on 24-h ambulatory blood pressure recordings, which may modify classification of blood pressure (42). Furthermore, none of the studies reported detailed information on body composition, physical fitness, or kidney function. It is established that upper-body (android) obesity is associated with insulin resistance and predicts the development of NIDDM (20,43,44). Moreover, physical training is known to increase insulin sensitivity considerably in both nondiabetic and NIDDM patients (21,45,46). Recently, prospective studies have demonstrated that the incidence of NIDDM is inversely related to the level of physical activity (47,48). A sedentary lifestyle (e.g., resulting from illness, such as ischemic heart disease) could partly explain both the reduced insulin sensitivity and the increased albuminuria. In our study, both age and physical fitness (estimated by Vo_{2max}) would, if anything, favor a lower insulin sensitivity in the microalbuminuric group. In addition, dietary sodium (estimated as urinary sodium excretion) and SHBG, factors both known to be associated with altered insulin action (49,50), were similar in the two groups.

The tendency for a higher glucose oxidation rate among microalbuminuric patients and the positive correlation with UAE are difficult to reconcile. The observations may, however, be parallel to the observations of Groop et al. (16) (i.e., a reduction in the glucose oxidation:nonoxidative glucose disposal ratio in the microalbuminuric patients). Groop et al. (16) also described a significant inverse correlation between total insulin-stimulated glucose uptake and UAE, but not between nonoxidative glucose disposal and UAE.

Protein oxidation, as determined from the urinary carbamide excretion rate, was significantly higher in normoalbuminuric than in microalbuminuric patients and correlated inversely with UAE. Urinary carbamide excretion has previously been found to be elevated in NIDDM associated with poor metabolic control and to be partly normalized during improvement of the hyperglycemia (51). Glucagon is a main determinant of urea excretion through increased gluconeogenesis and hepatic amino acid conversion during poor metabolic control (51,52). However, plasma glucagon, as well as glycemic control, was similar in our patients. There were no indications of more pronounced cystopathia in the microalbuminuric patients; the voided urinary volume and the urinary creatinine

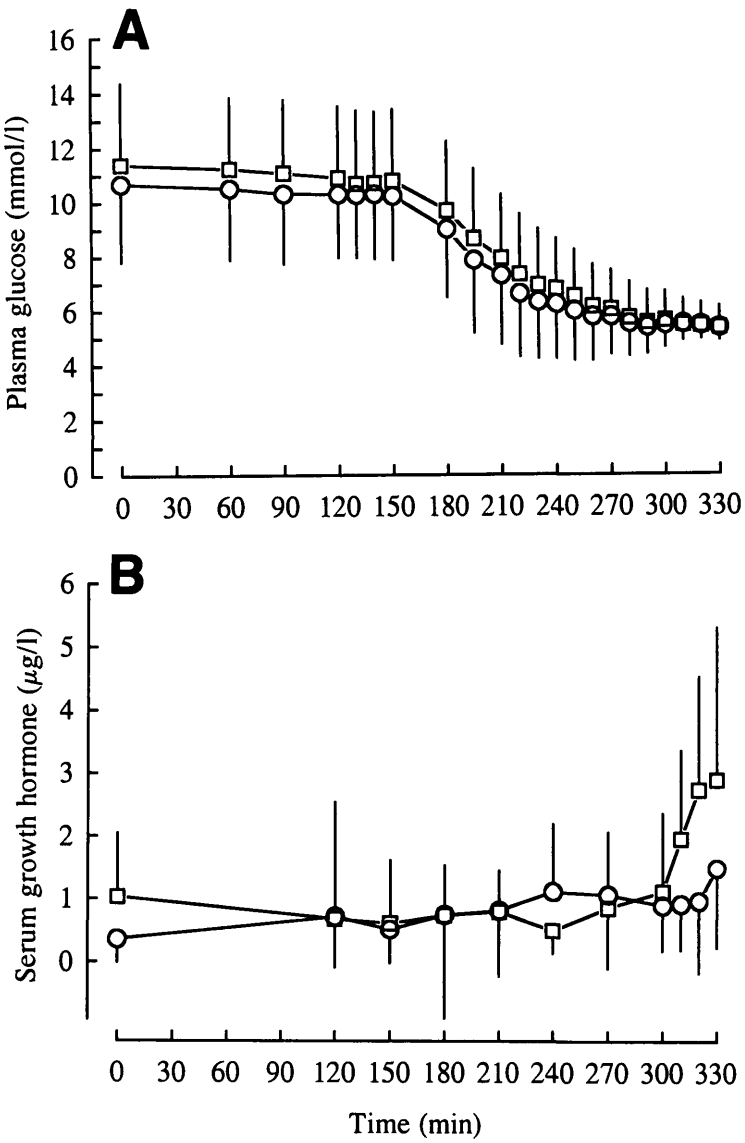

Figure 5—A: *Plasma glucose during the hyperinsulinemic euglycemic clamp in normoalbuminuric (○) and microalbuminuric (□) patients. Basal period: 0–150 min; insulin infusion: 150–330 min.* B: *Serum growth hormone. Normo- vs. microalbuminuria,* $P < 0.05$, *ANOVA.*

excretion during the investigation were comparable to those of normoalbuminuric patients. Quantitatively, the amount of nitrogen excreted through urinary albumin is insignificant compared with that of urea, accounting for <1% of the total nitrogen excretion. Serum growth hormone rose during insulin infusion; however, the increase was significantly greater in the microalbuminuric group (Table 4). There was no difference in the rate of decline in plasma glucose during the hyperinsulinemic period (Fig. 5), suggesting that the observed difference in growth hormone elevations was not caused by differences in counterregulatory stimuli. Previous reports have shown that decreases in plasma glucose, even without reaching hypoglycemic levels, promote growth hormone secretion, and other studies have demonstrated that diabetes is associated with an augmented growth hormone response during exercise, which may be especially evident in patients with microvascular complications (i.e., retinopathy) (53–55). Whether abnormal albuminuria in NIDDM is associated with more frequent oscillations in growth hormone is presently unknown, but it is established that diurnal levels are higher compared with those of healthy control subjects (53,56).

In conclusion, our study suggests equal levels of basal and insulin-stimulated total glucose uptake in matched groups of normo- and microalbuminuric patients with NIDDM. Whether glucose oxidation and protein oxidation are associated with UAE needs further investigation. The increased cardiovascular morbidity and mortality among microalbuminuric NIDDM patients may not primarily be a consequence of more pronounced levels of hyperinsulinemia or insulin resistance, but the influence of environmental factors may aggravate resident insulin resistance, elevate albuminuria, and contribute in itself to an increased cardiovascular risk.

Acknowledgments— We wish to thank A. Mengel, M. Møller, N. Rosenquist, I. Bisgaard, and K. Nygaard for excellent technical assistance.

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