

Microalbuminuria Is Associated With Insulin Resistance in Nondiabetic Subjects

The Insulin Resistance Atherosclerosis Study

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Microalbuminuria is associated with excess cardiovascular mortality in both diabetic and nondiabetic subjects. Patients with NIDDM and microalbuminuria are more insulin resistant than those without microalbuminuria. However, the relationship between insulin resistance and microalbuminuria in patients with NIDDM could be due to hyperglycemia, which can cause both insulin resistance and an increase in albumin excretion rate. Little is known about microalbuminuria and insulin resistance in nondiabetic subjects. Therefore, we examined, cross-sectionally, the relationship of insulin sensitivity ($S_i \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$), estimated by a frequently sampled intravenous glucose tolerance test and the minimal model and fasting plasma insulin concentration, to microalbuminuria (albumin-to-creatinine ratio $\geq 2 \text{ mg/mmol}$) in 982 nondiabetic subjects aged 40–69 years. Altogether, 15% of the subjects had microalbuminuria, and 32% had hypertension. Subjects with microalbuminuria had a lower degree of insulin sensitivity (means \pm SE, 1.70 ± 0.11 vs. 2.25 ± 0.07 , $P = 0.003$) and higher fasting insulin concentrations (17.4 ± 1.1 vs. $15.7 \pm 0.5 \text{ mU/l}$, $P = 0.059$) compared with subjects without microalbuminuria. In logistic regression analysis, an increasing degree of insulin sensitivity was related to a decreasing prevalence of microalbuminuria (odds ratio = 0.86, 95% CI: 0.79–0.94, $P < 0.001$). Although this relationship attenuated after adjustment for age, sex, ethnicity, hypertension, fasting glucose, and BMI, it still remained significant. The association between insulin sensitivity and microalbuminuria was shown not to be different between normotensive and hypertensive subjects. Our results suggest a relationship between insulin resistance and

microalbuminuria in nondiabetic subjects that is partially dependent on blood pressure, glucose levels, and obesity. *Diabetes*: 47:793–800, 1998

Microalbuminuria is a strong risk factor for diabetic nephropathy in patients with IDDM (1,2). Although microalbuminuria is predictive of clinical proteinuria in patients with NIDDM (3), it is more a marker of increased risk of cardiovascular mortality than a predictor of future end-stage renal disease in these patients (4–6). Microalbuminuria is also associated with excess cardiovascular mortality in nondiabetic subjects (7–9). Three studies (10–12) have shown that patients with NIDDM and microalbuminuria are more insulin resistant than those without microalbuminuria; in one study, however, NIDDM patients with and without microalbuminuria did not differ with regard to the degree of insulin resistance (13). Furthermore, first-degree relatives of NIDDM patients having microalbuminuria were more insulin resistant than relatives without microalbuminuria (14). Both insulin resistance (15–19) and microalbuminuria (20–23) are associated with hypertension and atherogenic changes in lipoproteins. Therefore, the increased cardiovascular risk in NIDDM patients with microalbuminuria could be mediated by insulin resistance, which leads to adverse changes in cardiovascular risk factors.

In patients with manifest diabetes, insulin resistance can develop secondary to chronic hyperglycemia (“glucotoxicity”) (24). Furthermore, hyperglycemia can increase albumin excretion rate (AER) in NIDDM patients without diabetic nephropathy (25). Thus, the relationship between insulin resistance and microalbuminuria in patients with overt NIDDM could be due to hyperglycemia. Few data, however, are available on insulin resistance and microalbuminuria in nondiabetic subjects. Forsblom et al. (14) investigated the association between microalbuminuria and insulin resistance in normoglycemic first-degree relatives of NIDDM patients. In many studies, however, individuals genetically predisposed to NIDDM have been insulin resistant (26–28).

Little is known about microalbuminuria and insulin resistance in nondiabetic populations. Therefore, we investigated, cross-sectionally, the relationship between insulin sensitivity and microalbuminuria in nondiabetic subjects participating in a large population-based study of insulin resistance and cardiovascular risk (the Insulin Resistance Atherosclerosis Study [IRAS]).

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ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; dBp, diastolic blood pressure; FPG, fasting plasma glucose; FSIGTT, frequently sampled intravenous glucose tolerance test; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; OGTT, oral glucose tolerance test; OR, odds ratio; sBP, systolic blood pressure; S_i , insulin sensitivity index; WHR, waist-to-hip ratio.

RESEARCH DESIGN AND METHODS

The IRAS is a multicenter epidemiological study aiming to explore relationships among insulin resistance, cardiovascular risk factors, and disease in African-Americans, Hispanics, and non-Hispanic whites across a broad range of glucose tolerance. A full description of the design and methods of the IRAS has been published (29). In brief, this study was conducted at four clinical centers. Clinical centers in Oakland and Los Angeles, California, studied non-Hispanic whites and African-Americans recruited from Kaiser Permanente, a nonprofit health maintenance organization. Clinical centers in San Antonio, Texas, and San Luis Valley, Colorado, studied non-Hispanic whites and Hispanics recruited from two ongoing population-based studies (the San Antonio Heart Study [30] and the San Luis Valley Diabetes Study [31]). Recruitment was tailored to yield approximately equal numbers of participants by ethnicity, sex, and glucose tolerance categories (NIDDM, impaired glucose tolerance [IGT], and normal glucose tolerance). To recruit an adequate number of subjects with IGT, sampling strategies were focused on methods that would maximize the number of IGT participants. San Antonio and San Luis Valley centers drew random samples from participant lists from their respective ongoing population studies, which resulted in selection of a disproportionate number of participants with previously diagnosed IGT. Oakland and Los Angeles centers enriched their samples of people with IGT by oversampling from lists of nondiabetic people with elevated levels of fasting plasma glucose (FPG) (i.e., 6.1–7.2 mmol/l). A total of 3,416 potential participants were contacted to obtain the final sample of 1,625, for an overall recruitment rate of 48%. However, despite the oversampling of IGT subjects, nondiabetic subjects in the IRAS have FPG levels similar to those of the corresponding ethnic group in the population-based NHANES (National Health and Nutrition Examination Survey) and HHANES (Hispanic Health and Nutrition Examination Survey) surveys (29).

The final study sample included 613 non-Hispanic whites, 548 Hispanics, and 464 African-Americans. Individuals with normal glucose tolerance comprised the largest segment of the study sample (44%), followed by diabetic subjects (33%) and people with IGT (23%). Diabetic subjects were not included in the current report because the aim of this report is to investigate the relationship between insulin resistance and microalbuminuria in nondiabetic subjects. Thus, the study population of this report comprised 982 nondiabetic subjects, aged 40–69 years, of whom 143 had microalbuminuria. Among these 143 subjects, urinary albumin-to-creatinine ratio (ACR) was ≥ 2 and < 20 mg/mmol in 133 subjects and 20 mg/mmol in 10 subjects.

The IRAS examination required two visits (~1 week apart [range 2–28 days]), each lasting ~4 h. An oral glucose tolerance test (OGTT) and a frequently sampled intravenous glucose tolerance test (FSIGTT) were performed during the first and second visits, respectively. Participants were asked before each visit to fast for 12 h, to abstain from heavy exercise and alcohol for 24 h, and to refrain from smoking the morning of the examination. For the OGTT, a 75-g glucose load (Orangedex; Custom Laboratories, Baltimore, MD) was administered over a period of < 10 min. Blood was collected before ingestion and at 2 h after the glucose load. Glucose tolerance status was based on the World Health Organization criteria (32).

Plasma glucose was measured with the glucose oxidase technique on an automated autoanalyzer (YSI, Yellow Springs, OH). Insulin was measured using the dextran-charcoal radioimmunoassay (33). Glucose and insulin for all samples were measured at the central IRAS laboratory at the University of Southern California.

Insulin sensitivity was assessed by the FSIGTT (34) with minimal model analyses (35). Two modifications of the original protocol were used. An injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance (36). This was because of the blunted or absent insulin response in diabetic subjects. Also, the reduced sampling protocol (which required 12 rather than 30 plasma samples and shows results similar to the full protocol [37]) was used because of the large number of subjects. Glucose in the form of a 50% solution (0.3 g/kg) and regular human insulin (0.03 U/kg) were injected through an intravenous line at 0 and 20 min, respectively. Blood was collected at -5, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min for plasma glucose and insulin concentrations. Insulin sensitivity, expressed as the insulin sensitivity index (S_i), was calculated by mathematical modeling methods (MINMOD, version 3.0 [1994]). This modified version of the FSIGTT protocol used in the IRAS has recently been compared with the hyperinsulinemic euglycemic clamp and shown to be a valid measure of insulin resistance (38). The distribution of insulin sensitivity in nondiabetic participants of the IRAS has been described previously (39).

Urinary albumin concentration was assessed in a random morning spot urine sample. Urinary albumin was measured from samples stored at -20°C by a commercial immunoprecipitation assay (Incstar SPQ test system, Stillwater, MN) with a sensitivity of 5.8 mg/l and intra- and interassay coefficients of variation of 1.46 and 1.77%, respectively. Urinary creatinine was determined by a modified Jaffe method (40). Urinary albumin and creatinine for all samples were measured at the central IRAS laboratory at the Medlantic Research Institute in Washington, DC. We have external quality control data of urinary albumin and creatinine measurements in the IRAS. From 170 blind duplicate specimens, the external coefficient

of variation for urinary albumin measurements was 12% and for urinary creatinine measurements was 17%; correlation between the two blind duplicate measurements for urinary albumin was 0.82 and for urinary creatinine was 0.71. The urinary ACR (albumin in milligrams per liter and creatinine in millimoles per liter) was used as a measure of albumin excretion. Overnight ACR correlates well with AER (41,42), and ACR measured in a single untimed urine specimen has been shown to be an effective means for identifying diabetic patients who are at risk of developing overt nephropathy (43). An overnight ACR ≥ 2 mg/mmol predicts an AER > 30 $\mu\text{g}/\text{min}$ with a high sensitivity and specificity (41).

Race and ethnicity were assessed by self-report. Hispanic ethnicity was defined by the U.S. census question, "Are you of Spanish or Hispanic origin or descent?" Height, weight, and girths (waist at the umbilicus and hip) were measured following a standardized protocol. BMI (weight/height² [kg/m²]) was used as an estimate of overall adiposity. The ratio of waist-to-hip circumferences (WHR) was used as an estimate of body fat distribution. Blood pressure was measured in the sitting position with a mercury sphygmomanometer after a 5-min rest. Three readings were taken, and the average of the second and third was used in statistical analyses. Hypertension was defined as a systolic blood pressure (sBP) of > 140 mmHg, a diastolic blood pressure (dBp) of > 90 mmHg, or current use of medicine for hypertension. A family history of diabetes was regarded positive if at least one parent or sibling was reported as having NIDDM.

Statistical methods. Means, SDs, and other basic descriptive statistics were calculated to describe the study population (Table 1). A natural logarithm transformation of ACR was required to satisfy statistical assumptions for partial correlations of ACR with anthropometric and metabolic measurements (Table 2). Partial correlations were computed as full partial correlations. For subsequent analyses (Tables 3–7), subjects were divided into those with microalbuminuria (ACR ≥ 2 mg/mmol) and those without microalbuminuria (ACR < 2 mg/mmol). Fasting and 2-h insulin concentrations were not normally distributed, and, therefore, a log transformation was used for statistical testing.

Multiple logistic regression was used to relate the prevalence of microalbuminuria to S_i and to fasting insulin concentration (log transformed) adjusted for potentially confounding variables. Odds ratios (ORs) for the prevalence of microalbuminuria in relation to S_i and to fasting insulin concentration were assessed by four models (Tables 4–6) adjusted for 1) age, sex, ethnicity, and clinic; 2) age, sex, ethnicity, clinic, and hypertension; 3) age, sex, ethnicity, clinic, hypertension, and FPG; and 4) age, sex, ethnicity, clinic, hypertension, FPG, and BMI. We also examined the relationship between risk factors and the prevalence of microalbuminuria using incremental logistic regression models (Table 7). In these models, microalbuminuria was the dependent variable and independent variables were 1) age, sex, ethnicity, and clinic; 2) age, sex, ethnicity, clinic, and hypertension; 3) age, sex, ethnicity, clinic, and S_i ; and 4) age, sex, ethnicity, clinic, and fasting insulin concentration (log transformed). Significance of individual model parameters was assessed by likelihood ratio test. The strength of the association between the prevalence of microalbuminuria and independent variables was assessed by calculating the R^2 statistics discussed by Hosmer and Lemeshow (44). Values for R^2 were calculated by forming the ratio of the model χ^2 value to the -2 log likelihood for the null (intercept only) model. R^2 values for individual covariates were calculated by squaring the quantity (β/SE) for each coefficient. For both S_i and fasting insulin models, estimated changes in the prevalence of microalbuminuria were calculated given an increase in S_i or fasting insulin concentration from the 25th to the 50th percentile. ORs and 95% CIs corresponding to these changes in S_i and fasting insulin were compared to assess the differences in impact on the prevalence of microalbuminuria between changing S_i and fasting insulin concentration.

Hypertensive subjects have increased AERs (45–47). Furthermore, hypertension is an insulin-resistant condition, at least in some ethnic groups (15,17,48). Therefore, we investigated whether the association between insulin sensitivity and fasting insulin concentration and microalbuminuria was different in normotensive and hypertensive subjects by entering an interaction term of $S_i \times$ hypertension or \log_e (fasting insulin) \times hypertension into a multiple logistic regression model. Furthermore, antihypertensive medication may influence insulin sensitivity as well as AER. In the present report, 222 subjects were on antihypertensive medication. We investigated whether the association between insulin sensitivity and fasting insulin concentration and microalbuminuria was different in subjects on antihypertensive medication compared with those not on antihypertensive medication by entering an interaction term of $S_i \times$ antihypertensive medication or \log_e (fasting insulin) \times antihypertensive medication into a multiple logistic regression model.

All statistical analyses were performed using SAS statistical software (PROC LOGISTIC and PROC GENMOD) (49,50).

RESULTS

Characteristics of the study population are shown in Table 1. The mean age of the subjects was 54.8 years, and 44.8% were men. Altogether, 26.3% of subjects were black, 33.8% were His-

panics, and 39.9% were non-Hispanic whites. The prevalence of hypertension was 32.3%, and the prevalence of IGT was 33.1%. Altogether, 14.6% of the subjects were found to have microalbuminuria (ACR ≥ 2 mg/mmol).

Table 2 shows partial correlations of ACR (log transformed), S_i , and fasting insulin (log transformed) with anthropometric and metabolic variables. ACR correlated positively with age, BMI, WHR, sBP and dBP, and fasting and 2-h insulin levels. There was an inverse correlation between ACR and insulin sensitivity (S_i). ACR was not related to fasting or 2-h glucose levels in these nondiabetic subjects. S_i correlated inversely with age, indexes of obesity, blood pressure, glucose concentrations, and insulin concentrations. Fasting insulin concentration correlated positively with indexes of obesity, blood pressure, glucose concentrations, and 2-h insulin concentration. There was an inverse correlation between fasting insulin concentration and S_i .

We further investigated the association between ACR and S_i by linear regression analysis and by calculating partial correlation, adjusting for age, sex, hypertension, FPG, BMI, ethnicity, and clinic. After adjusting for these variables, the partial correlation of ACR (log transformed) with S_i was -0.076 ($P < 0.05$).

Characteristics of subjects, according to the presence or absence of microalbuminuria, are shown in Table 3. Subjects with microalbuminuria were more obese (high BMI) and had higher sBP and dBP and a higher prevalence of hypertension compared with those without microalbuminuria. Furthermore, subjects with microalbuminuria had a significantly lower S_i ; in other words, they were more insulin resistant compared with subjects without microalbuminuria. In addition, fasting and 2-h insulin levels were higher in subjects with microalbuminuria compared with those without microalbuminuria, but this difference was not statistically significant. Subjects with microalbuminuria did not differ from those without microalbuminuria with regard to age, WHR, blood glucose levels, glucose tolerance status, or family history of diabetes. After adjusting for age, ethnicity, and clinic, these results remained similar except for WHR, which was significantly higher after these adjustments in subjects with microalbuminuria compared with those without microalbuminuria.

We further examined the relationship between microalbuminuria and insulin sensitivity and fasting insulin concentration by logistic regression analyses (Tables 4–7). An increase in S_i from the 25th to the 50th percentile (from 0.89 to $1.61 \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$) was related to an OR of 0.86 for having microalbuminuria (Table 4, model 1). In other words, increasing insulin sensitivity was associated with a significant decrease in the prevalence of microalbuminuria. This relationship was independent of age, sex, ethnicity, clinic, hypertension, FPG, and obesity (BMI) (model 4). However, after further adjustment for hypertension, FPG, and obesity, the association between microalbuminuria and insulin sensitivity was attenuated, which is depicted by a 33% decrease in the β -coefficient (model 4 vs. model 1). An increase in fasting insulin concentration from the 25th to the 50th percentile (from 9.0 to 13.0 mU/l) was related to an OR of 1.12 for having microalbuminuria (Table 5, model 1), meaning that increasing fasting insulin concentration was associated with an increase in the prevalence of microalbuminuria. However, after adjustment for hypertension in model 2, fasting

TABLE 1
Demographic, clinical, and metabolic characteristics of the study population

	Mean \pm SD	Median
Age (years)	54.8 \pm 8.4	54.0
BMI (kg/m ²)	28.4 \pm 5.6	27.4
WHR	0.932 \pm 0.076	0.942
Men (%)	44.8 (440)	
Ethnicity		
Black (%)	26.3 (258)	
Hispanic (%)	33.8 (332)	
Non-Hispanic white (%)	39.9 (392)	
sBP (mmHg)	123 \pm 17	121
dBP (mmHg)	78 \pm 9	78
Hypertension (%)	32.3 (317)	
FPG (mg/dl)	99 \pm 11	97
2-h glucose (mg/dl)	125 \pm 34	123
Fasting insulin (mU/l)	15.9 \pm 15.1	13.0
2-h insulin (mU/l)	99.6 \pm 92.9	79.0
S_i ($\times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$)	2.17 \pm 2.03	1.61
IGT (%)	33.1 (325)	
Urine albumin (mg/l)	15.0 \pm 44.3	6.2
ACR (mg/mmol)	1.64 \pm 4.59	0.74
Microalbuminuria (%)	14.6 (143)	

Microalbuminuria was defined as urine ACR ≥ 2 mg/mmol. $n = 982$.

insulin concentration was no longer significantly associated with the prevalence of microalbuminuria.

We present the full logistic regression model with all of the covariates (model 4) in Table 6 to depict the relative strength of the association of different covariates with microalbuminuria. Hypertension was the strongest determinant of microalbuminuria in the model that included insulin sensitivity as a covariate as well as in the model that included fasting insulin concentration as a covariate. Insulin sensitivity was the only other variable, in addition to hypertension, that was independently related to microalbuminuria. The relationship between insulin sensitivity and microalbuminuria was

TABLE 2
Partial correlation coefficients of urine ACR, insulin sensitivity (S_i), and fasting insulin concentration (F-insulin) with anthropometric and metabolic variables

	ACR	S_i	F-insulin
Age	0.06*	-0.07^*	-0.02
BMI	0.11†	$-0.38†$	0.48‡
WHR	0.10†	$-0.39†$	0.37‡
sBP	0.25‡	$-0.19†$	0.14‡
dBP	0.13‡	$-0.11†$	0.15‡
FPG	-0.01	$-0.30†$	0.36‡
2-h glucose	0.03	$-0.43†$	0.30‡
Fasting insulin	0.06*	$-0.53†$	—
2-h insulin	0.08*	-0.55	0.56‡
S_i	$-0.13†$	—	$-0.53†$

Partial correlation coefficients were adjusted for sex and ethnicity \times clinic by linear regression. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$. $n = 982$.

TABLE 3
Characteristics of subjects according to presence of microalbuminuria

	Microalbuminuria		Unadjusted <i>P</i> value	Adjusted <i>P</i> value
	Yes	No		
<i>n</i>	143	839		
Demographic				
Age (years)	54.8 ± 0.7	54.8 ± 0.3	0.918	0.932
BMI (kg/m ²)	30.0 ± 0.5	28.2 ± 0.2	0.001	0.002
WHR	0.94 ± 0.006	0.93 ± 0.003	0.095	0.019
Blood pressure				
sBP (mmHg)	130 ± 1	121 ± 1	<0.001	<0.001
dBP (mmHg)	81 ± 1	77 ± 0.3	<0.001	<0.001
Hypertension (%)	50.0	30.0	<0.001	<0.001
Glucose				
FPG (mg/dl)	100 ± 1	99 ± 0.4	0.425	0.350
2-h glucose (mg/dl)	126 ± 3	125 ± 1	0.619	0.635
Family history of diabetes (%)	42.7	38.6	0.360	0.346
IGT (%)	31.5	33.4	0.655	0.607
Insulin sensitivity				
Fasting insulin (mU/l)	17.4 ± 1.1	15.7 ± 0.5	0.059	0.058
2-h insulin (mU/l)	116.5 ± 9.1	96.8 ± 3.1	0.053	0.049
<i>S</i> ₁ (×10 ⁻⁴ min ⁻¹ · μU ⁻¹ · ml ⁻¹)	1.70 ± 0.11	2.25 ± 0.07	0.003	0.002

Data are means ± SE. Unadjusted *P* values of Student's *t* test (continuous variables) or logistic regression (categorical variables). *P* values were adjusted for age and ethnicity × clinic by regression models for continuous variables and by logistic regression for categorical variables.

stronger than the association between BMI or FPG concentration and microalbuminuria. In contrast to insulin sensitivity, fasting insulin concentration was not significantly associated with microalbuminuria after adjustment for hypertension, FPG concentration, and BMI. Figure 1 depicts ORs for microalbuminuria by octiles of insulin sensitivity, adjusted for age, sex, ethnicity, clinic, hypertension, FPG, and BMI.

To examine the relative strength of the associations of microalbuminuria with insulin sensitivity, fasting insulin concentration, and hypertension, we did additional logistic regression analyses with microalbuminuria as a dependent variable using incremental models (Table 7). All *R*² values were low. Age, sex, ethnicity, and clinic (model 1) explained 1.3% of the variance in the prevalence of microalbuminuria. Addition of hypertension in the model increased the variance explained by 2.4%. Addition of insulin sensitivity in the model increased the variance explained by 1.7%. Finally, addition of fasting insulin in the model increased the variance explained by 0.5%. Thus, the relation between hypertension and microalbuminuria was somewhat stronger than the relation between insulin sensitivity and microalbuminuria. The association of fasting insulin con-

centration and microalbuminuria was much weaker compared with the association between insulin sensitivity and microalbuminuria. Accordingly, the change in *R*² for the insulin sensitivity model was three-fourths of the change in *R*² for the hypertension model. The change in *R*² for the fasting insulin model was only one-fifth of that for the hypertension model.

An interaction term of *S*₁ × hypertension was entered into a multiple logistic regression model in the pooled population; this interaction term was not statistically significant (*P* = 0.84), suggesting that the effect of insulin sensitivity on microalbuminuria was not different in hypertensive and nonhypertensive subjects. Similarly, an interaction term of log_e(fasting insulin) × hypertension was not statistically significant (*P* = 0.20), suggesting that the effect of fasting insulin concentration on microalbuminuria was not different in hypertensive and nonhypertensive subjects. Furthermore, an interaction term of *S*₁ × antihypertensive medication was not statistically significant (*P* = 0.302), suggesting that the effect of insulin sensitivity on microalbuminuria was not different in subjects taking antihypertensive medication compared with those not taking antihypertensive medication.

TABLE 4
Change in the prevalence of microalbuminuria associated with change in *S*₁ from the 25th to the 50th percentile

Model	Adjusted for	OR (95% CI)	<i>P</i> value	β	SE(β)	<i>R</i> ² (<i>S</i> ₁)
1	Age, sex	0.86 (0.79–0.94)	< 0.001	-0.150	0.045	0.017
2	Age, sex, hypertension	0.89 (0.82–0.98)	0.012	-0.114	0.045	0.010
3	Age, sex, hypertension, FPG	0.88 (0.80–0.97)	0.009	-0.124	0.048	0.010
4	Age, sex, hypertension, FPG, BMI	0.90 (0.82–0.997)	0.044	-0.100	0.050	0.006

For *S*₁, 25th percentile = 0.89 and 50th percentile = 1.61 × 10⁻⁴ min⁻¹ · μU⁻¹ · ml⁻¹. ORs were calculated by multiple logistic regression analyses. All models also included ethnicity × clinic coded as dummy variables. *R*²(*S*₁) is partial *R*² for insulin sensitivity. *n* = 982.

TABLE 5

Change in the prevalence of microalbuminuria associated with change in fasting plasma insulin concentration from the 25th to the 50th percentile

Model	Adjusted for	OR (95% CI)	<i>P</i> value	β	SE(β)	R^2 (I)
1	Age, sex	1.12 (1.00–1.24)	0.043	0.110	0.054	0.006
2	Age, sex, hypertension	1.07 (0.96–1.20)	0.203	0.072	0.056	0.003
3	Age, sex, hypertension, FPG	1.08 (0.96–1.22)	0.187	0.080	0.060	0.002
4	Age, sex, hypertension, FPG, BMI	1.03 (0.90–1.17)	0.662	0.029	0.067	0.004

For fasting plasma insulin, 25th percentile = 9.0 and 50th percentile = 13.0 mU/l. ORs were calculated by multiple logistic regression analyses. All models also included ethnicity \times clinic coded as dummy variables. R^2 (I) is partial R^2 for fasting insulin. $n = 982$.

Similarly, an interaction term of $\log_e(\text{fasting insulin}) \times$ antihypertensive medication was not statistically significant ($P = 0.467$), suggesting that the effect of fasting insulin concentration on microalbuminuria was not different in subjects on antihypertensive medication compared with those not on antihypertensive medication.

We repeated all the analyses reported above after excluding subjects with ACR ≥ 20 mg/mmol ($n = 10$), and the results were essentially similar to including all subjects (corresponding ORs and 95% CIs [as in Table 4] were 0.86 and 0.79–0.94, $P = 0.001$, for model 1, and 0.90 and 0.82–0.997, $P = 0.044$, for model 4).

DISCUSSION

Microalbuminuria has been shown to be a marker of increased risk of cardiovascular disease in both NIDDM patients (4–6) and nondiabetic subjects (7–9). One mediator of the increased cardiovascular risk in subjects with microalbuminuria could be insulin resistance. Previous data on the association between insulin resistance and microalbuminuria are from studies in NIDDM patients (10–13) and their relatives (14). Because hyperglycemia in NIDDM patients and genetic susceptibility to NIDDM in first-degree relatives of NIDDM patients per se are associated with insulin resistance, we tested this hypothesis by investigating the relationship between insulin sensitivity and fasting insulin concentration and microalbuminuria in nondiabetic subjects. We found that nondiabetic subjects with microalbuminuria were more insulin resistant and had higher fasting insulin concentrations

than subjects without microalbuminuria. These results suggest that insulin resistance may indeed play a role in the increased cardiovascular risk in subjects with microalbuminuria.

In the present study, nondiabetic subjects with microalbuminuria had higher sBP and dBP and a higher prevalence of hypertension compared with those without microalbuminuria. Although the role of hyperinsulinemia in hypertension has been debated (51–53), there is evidence that hypertension is associated with insulin resistance at least in some lean populations (15,17,54,55). In addition, subjects with essential hypertension have been shown to have increased urinary AER (45). Therefore, hypertension among nondiabetic subjects with microalbuminuria could explain the association between microalbuminuria and insulin resistance in the present study. Adjustment for hypertension indeed attenuated the relationship between microalbuminuria and insulin resistance. Nevertheless, this association remained significant even after adjustment for hypertension (Table 4). Furthermore, the relation between microalbuminuria and insulin resistance was not different in hypertensive compared with nonhypertensive subjects or in subjects taking antihypertensive medication compared with those not taking antihypertensive medication. These findings mean that hypertension did not fully account for the observed relation between microalbuminuria and insulin resistance.

In the present study, nondiabetic subjects with microalbuminuria were also more obese than subjects without microalbuminuria. Obese people, particularly if they have abdominal obesity, have increased urinary AER even when

TABLE 6

Full model of multiple logistic regression analysis on the association of microalbuminuria with other variables

Covariate	Model A (S_1)				Model B (F-insulin)			
	β	SE(β)	<i>P</i> value	R^2	β	SE(β)	<i>P</i> value	R^2
Age (per 10 year increase)	-0.118	0.119	0.320	0.003	-0.103	0.118	0.385	0.002
Male sex (yes/no)	-0.214	0.198	0.277	0.003	-0.194	0.197	0.322	0.002
Hypertension (yes/no)	0.796	0.206	<0.001	0.017	0.836	0.206	<0.001	0.019
FPG (per 10 mg/dl increase)	-0.080	0.092	0.383	0.0003	-0.049	0.093	0.596	0.00003
BMI (per 5 kg/m ² increase)	0.111	0.092	0.231	0.001	0.162	0.093	0.085	0.003
S_1 (per increase from 25th to 50th percentile)	-0.100	0.050	0.031	0.006	—	—	—	—
F-insulin (per increase from 25th to 50th percentile)	—	—	—	—	0.029	0.067	0.662	0.0004
Full model				0.048				0.042

Independent variables are the same as those in model 4 of Table 4, including ethnicity \times clinic coded as dummy variables. *P* values were calculated by likelihood ratio test. For S_1 , 25th percentile = 0.89 and 50th percentile = $1.61 \times 10^{-4} \text{ min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{ml}^{-1}$. For fasting plasma insulin (F-insulin), 25th percentile = 9.0 and 50th percentile = 13.0 mU/l.

TABLE 7
Incremental logistic regression models on the relationship between the prevalence of microalbuminuria and risk factors

Model	Adjusted for	Added variable	R ²	Change in R ²
1	Age, sex	—	0.013	—
2	Age, sex	Hypertension	0.037	0.024
3	Age, sex	S ₁	0.030	0.017
4	Age, sex	Fasting insulin	0.018	0.005

All models also included ethnicity × clinic coded as dummy variables.

they are normotensive (56). Obesity and abdominal obesity are also characterized by insulin resistance (57,58). Thus, it is possible that the association between insulin resistance and microalbuminuria in the present study may be a reflection of the relation between obesity and microalbuminuria. Indeed, adjustment for both hypertension and BMI decreased the significance of the association between microalbuminuria and insulin sensitivity to a borderline level (Table 4). The OR, however, remained unchanged, indicating that hypertension and obesity did not fully explain the relationship between microalbuminuria and insulin resistance.

Hypertension was the strongest determinant of microalbuminuria (Table 6). Relative to hypertension, insulin sensitivity was a weaker correlate of microalbuminuria. However, insulin sensitivity was the only other variable in addition to hypertension that was independently associated with microalbuminuria. The relationship between insulin sensitivity and microalbuminuria was stronger than the association between BMI or FPG level and microalbuminuria.

We also investigated the relationship between fasting insulin concentration and microalbuminuria. In the present study, nondiabetic subjects with microalbuminuria had higher fasting plasma insulin concentrations compared with those without microalbuminuria, although this difference did not quite reach statistical significance. This is in accordance with two previous reports (22,23). However, nondiabetic subjects with microalbuminuria did not have increased fasting insulin concentrations in the study of Forsblom et al. (14). In the present study, fasting insulin concentration was associated with microalbuminuria only in a multiple regression analysis model adjusting for age, sex, ethnicity, and clinic (Table 5, model 1) but not in models adjusting for hypertension and BMI. Thus, the relationship between insulin resistance and microalbuminuria was much stronger compared with that between fasting insulin concentration and microalbuminuria.

What could be the mechanisms relating insulin resistance to microalbuminuria? Insulin resistance is accompanied by hyperinsulinemia in subjects who do not have impaired insulin secretion capacity. Our study population included both normoglycemic subjects and subjects with IGT; our subjects did not have overt hyperglycemia, indicating that their insulin secretion capacity was not decreased. Insulin has effects on renal hemodynamics. Acute hyperinsulinemia caused renal vasodilatation, resulting in increased plasma flow and increased glomerular hydrostatic pressure gradient in normal rats (59) and renal vasodilatation and increased glomerular filtration rate in the isolated perfused rat kidney (60). Localized elevated pressure in the glomerular vessels possibly is involved in increased albumin excretion (61). The

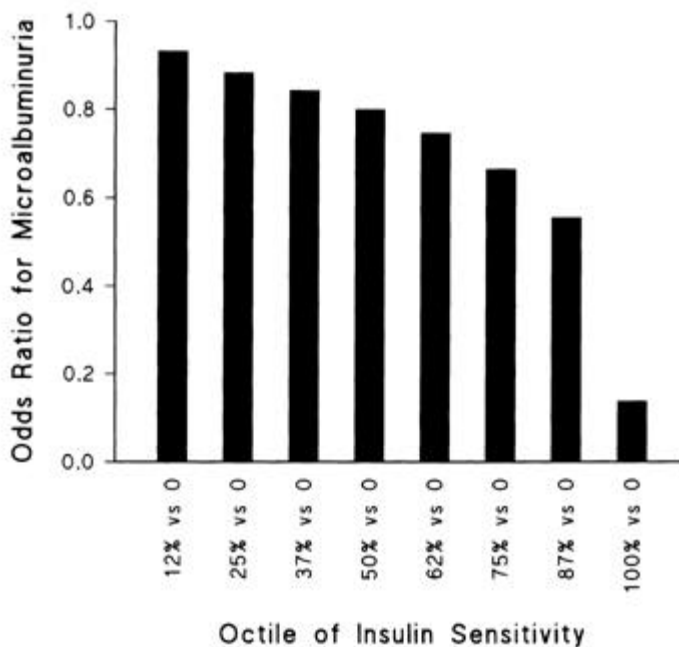


FIG. 1. ORs for microalbuminuria by octiles of insulin sensitivity, adjusted for age, sex, ethnicity, clinic, hypertension, FPG, and BMI.

long-term effects of hyperinsulinemia on renal hemodynamics are not known. Another possibility is that there may be no causal relationship between insulin resistance and hyperinsulinemia and microalbuminuria but that both may be related to a third, as yet unknown, factor.

A limitation of the IRAS is that the study sample was not randomly selected from the general population but instead was recruited from identified subgroups of ethnicity and glucose tolerance status to allow valid comparisons among and within these subgroups. The IRAS population was drawn from existing population-based studies (San Antonio Heart Study and San Luis Valley Diabetes Study) or from health maintenance organization populations (Oakland and Los Angeles, CA) that were basically representative of the general population. Furthermore, the focus of the present report is on the relationship of microalbuminuria and insulin sensitivity, both of which were measured in the study participants, rather than a description of the distribution of these factors in the general population. Therefore, we think that the results of the present study are applicable to a wider community beyond the IRAS population.

In conclusion, our results suggest that microalbuminuria is associated with insulin resistance in nondiabetic subjects. This relationship was partially dependent on blood pressure and obesity. Because this is a cross-sectional study, we do not know the temporal relation between ACR and insulin sensitivity. It is possible that insulin resistance may mediate, in part, the increased cardiovascular risk in subjects with microalbuminuria.

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