PRELIMINARY REPORT

Lack of a Relationship Between Urinary Albumin Excretion Rate and Insulin Resistance in Patients With Non–Insulin-Dependent Diabetes Mellitus

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The study was performed to determine the relationship between urinary albumin excretion (UAE) and resistance to insulin-mediated glucose disposal in patients with non–insulin-dependent diabetes mellitus (NIDDM). Twenty-five non-obese male patients were enrolled; UAE rates were determined on two 24-hour urine collections, and resistance to insulin-mediated glucose disposal was quantified by measurement of steady-state plasma glucose (SSPG) and steady-state plasma insulin concentrations during the last 30 minutes of a 180-minute infusion of somatostatin, insulin, and glucose. Twenty-four-hour urine UAE rates varied from 6 to 112 μg/min, and microalbuminuria (> 20 μg/min) was present in seven of 25 patients. SSPG concentration ranged from 158 to 419 mg/dL, and there was no relationship between UAE rates and SSPG concentration (r = .16, P = NS). Furthermore, the mean SSPG concentration was not significantly different in seven patients with microalbuminuria compared with 18 normoalbuminuric subjects (318 ± 20 *v* 298 ± 17 mg/dL). Thus, resistance to insulin-mediated glucose disposal occurs in patients with NIDDM in the absence of microalbuminuria, and we could not detect any relationship between UAE and insulin resistance in this population.

THE CURRENT STUDY was initiated to extend our evaluation of the relationship, if any, between microalbuminuria and resistance to insulin-mediated glucose disposal in patients with non–insulin-dependent diabetes mellitus (NIDDM). Although there is considerable evidence that insulin resistance is a common finding in patients with NIDDM and in their nondiabetic first-degree relatives,[1-11] evidence has recently been published suggesting that resistance to insulin-mediated glucose disposal in patients with NIDDM is primarily a function of the coexistence of microalbuminuria.[12-14] Since these findings seemed to conflict with our experience over the past 20 years that insulin resistance is present in the vast majority of patients with NIDDM, we recently compared the insulin resistance in normal volunteers with that in NIDDM patients without microalbuminuria.[15] In this report, we broaden the scope of our inquiry by including microalbuminuric patients with NIDDM, as well as changing the ethnicity of the study group from Chinese patients to individuals of European ancestry.

SUBJECTS AND METHODS

The study population consisted of 25 consecutive male patients with NIDDM who volunteered for the study and satisfied the following criteria: currently under sulfonylurea treatment, with a fasting plasma glucose of less than 200 μg/dL; (2) body mass index less than 30 kg/m^2; (3) normotensive; and (4) negative result on dip-stick test for proteinuria. The mean age of the subjects was 57 years (range, 40 to 66), and they had a mean body mass index of 25.7 kg/m^2 (range, 24.3 to 29.4).

The study was approved by the Institutional Review Board of Stanford Medical Center, and informed consent was provided by all participants.

Resistance to insulin-mediated glucose disposal was determined by a modification of the insulin suppression test.[16] Briefly, each subject received a 180-minute continuous intravenous infusion of somatostatin (300 μg/h), insulin (25 mU/m^2/min), and glucose (240 mg/m^2/min). Venous blood samples were obtained before and after 30, 60, 90, 120, 150, 160, 170, and 180 minutes after starting the infusion for measurement of plasma glucose and insulin levels.[16] The mean value of the four measurements made during the last 30 minutes of the test was used to calculate steady-state plasma insulin (SSPI) and steady-state plasma glucose (SSPG) correlations. Given the similarity of the steady-state plasma insulin levels, the SSPG concentration provides a measure of insulin-mediated glucose disposal, ie, the higher the SSPG, the more insulin-resistant the subject. Blood drawn before the insulin suppression test was also used for determination of plasma lipid and lipoprotein concentrations, as described previously.[16] Finally, all participants collected two 24-hour urine samples for determination of urinary albumin excretion (UAE) rate.[17]

RESULTS AND DISCUSSION

Microalbuminuria was present in seven of 25 subjects, a prevalence comparable to that seen in several published studies reviewed recently.[18] The SSPG concentration (mean ± SEM) in these seven individuals was 318 ± 20 mg/dL, as compared with 298 ± 17 mg/dL in the other 18 subjects; this difference was not statistically significant. To put the degree of insulin resistance present in these 25 patients in perspective, the mean value ± 2 SD of the last 240 normoglycemic individuals studied by our group was 119 ± 68 mg/dL; only one of the patients studied had an SSPG concentration (158 mg/dL) within the 95% confidence limits of the normal population.

Figure 1A shows the relationship between UAE rate and SSPG concentration in these 25 patients with NIDDM. It is apparent that there was no significant relationship between the two variables. Since patients with NIDDM often have high plasma triglyceride (TG) and low high-density lipopro-

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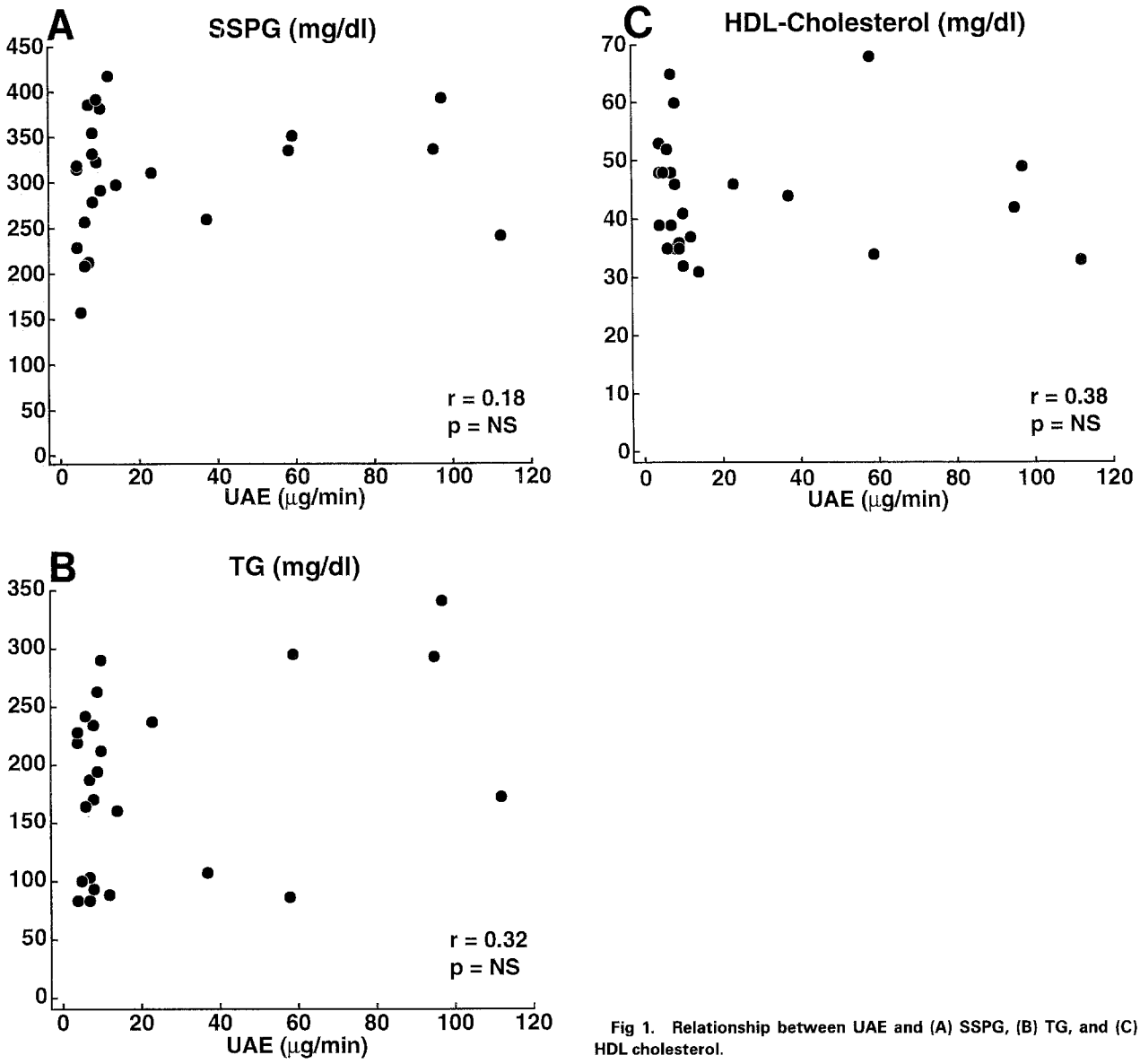

Fig 1. Relationship between UAE and (A) SSPG, (B) TG, and (C) HDL cholesterol.

tein (HDL) cholesterol concentrations, we also investigated the association between UAE and these two variables. These relationships are shown in Fig 1B and C, respectively, and it is apparent that the variables were not significantly correlated with UAE rate. Furthermore, there were no differences between patients with and without microalbuminuria with regard to plasma TG (218 ± 37 *v* 172 ± 16 mg/dL) and HDL cholesterol (43 ± 2 *v* 45 ± 3 mg/dL) concentrations.

These results offer evidence that insulin resistance is present in NIDDM patients of European ancestry regardless of whether they have microalbuminuria. Furthermore, in this population, the magnitude of insulin resistance was unrelated to variations in UAE rates. As such, these data support similar results recently described by Nielsen et al,[19] as well as our observations in Chinese patients with NIDDM.[15] Finally, the characteristic changes in lipid metabolism seen in patients with NIDDM were also unrelated to UAE rates.

The fact that we have been unable to define an association between UAE rates and insulin resistance in two disparate ethnic groups suggests that our results can be generalized, and differences in ethnicity do not provide an explanation for the disparity between our results and those of others.[12-14] Furthermore, although we used the insulin suppression test to assess insulin-mediated glucose disposal,[16] as compared with the euglycemic clamp technique used in the other studies, we have previously shown[20] that these two methods are highly correlated ($r > .9$). Thus, the differences in methods of assessing insulin resistance cannot account for the disparity in the results. Perhaps the method of patient selection provides the most likely explanation for differences in the data. Specifically, three studies[12-14] in which a relationship between insulin resistance

and microalbuminuria was demonstrated were performed on patients selected because they had high blood pressure, microalbuminuria, or both. The potential impact of this selection process on the study results is not immediately apparent, but a closer inspection of the data reveals some interesting findings. For example, in the report by Groop et al,[12] glucose disposal rates in 52 patients with NIDDM were reduced by 36% as compared with control values (n = 19), in contrast to differences of more than 50% as reported by other investigators.[3-8] Although Niskanen and Laakso[13] did not compare glucose disposal rates in their NIDDM patients versus a control population, values in subjects with or without microalbuminuria were both lower than estimates for normal volunteers reported by many other groups using the clamp technique.[3-8] Furthermore, since the mean 24-hour UAE was 131 mg, with a range that included patients excreting 3.8 g albumin/d, a proportion of the patients they studied cannot be classified as microalbuminuric. Unfortunately, creatinine clearance measures were not included, and it is not possible to know if any of these subjects also had a decrease in glomerular filtration rate, a variable that could also contribute to the greater degree of insulin resistance in the proteinuric group.

In conclusion, the results of this study in 25 non-obese NIDDM patients of European ancestry support the view that insulin resistance and dyslipidemia can be found in patients with NIDDM independently of variations in UAE rates. The results neither support nor rule out the possibility that the magnitude of insulin resistance and dyslipidemia is accentuated in patients with NIDDM who are also microalbuminuric.

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