Microalbuminuria: Potential Marker for Increased Cardiovascular Risk Factors in Nondiabetic Subjects?

Steven M. Haffner, Michael P. Stern, M. Katherine Kozlowski Gruber, Helen P. Hazuda, Braxton D. Mitchell, and Judith K. Patterson

Microalbuminuria is associated with progression to renal disease in insulin-dependent diabetes and with increased mortality in noninsulin-dependent diabetes. In contrast, few studies have addressed the effect of microalbuminuria on cardiovascular risk in nondiabetics. We, therefore, determined the level of microalbuminuria in 316 nondiabetic subjects from the San Antonio Heart Study, a population-based study of diabetes and cardiovascular risk factors. Microalbuminuria (≥30 mg/l) was found in 42 of these 316 subjects (13%). Subjects with microalbuminuria had significantly higher blood pressure, triglyceride concentration, sum of insulin concentrations during a glucose tolerance test, and prevalence of hypertension and of self-reported myocardial infarction than subjects without microalbuminuria. When subjects with hypertension were excluded (n=27), normotensive subjects with microalbuminuria (n=31) still had significantly higher triglyceride concentrations and insulin sum than normotensive subjects without microalbuminuria (n=258), suggesting that an increased atherogenic risk factor pattern exists even in normotensive subjects with microalbuminuria. Microalbuminuria may be a marker for cardiovascular risk, although it is not certain whether microalbuminuria causes these metabolic changes or results from some metabolic disturbance such as insulin resistance.

(Microalbuminuria has been associated with progression to renal disease in type I diabetes.1,2 Microalbuminuria predicts mortality.4 Microalbuminuria has also been associated with increased blood pressure,5,6 increased very low density lipoprotein (VLDL) cholesterol, and decreased high density lipoprotein (HDL) cholesterol7 in subjects with insulin-dependent diabetes mellitus. Few data exist, however, on whether microalbuminuria is a marker for increased cardiovascular risk in nondiabetic subjects. Yudkin et al.4 reported that subjects with microalbuminuria had increased peripheral and coronary heart disease. In the present report, we examined the relationship of microalbuminuria (≥30 mg/l)4 to lipids, lipoproteins, blood pressure, glucose, and insulin concentrations in nondiabetic subjects from the San Antonio Heart Study (SAHS), a population-based study of diabetes and cardiovascular risk factors.

Methods

The SAHS was conducted in two phases: the first phase extended from October 1979 to October 1982 and the second phase, from October 1984 to October 1988. The sampling design has been previously described in detail for both phases.9,10 Briefly, households were randomly sampled from three socioeconomicl.y distinct neighborhoods: low, middle, and high income. All 25- to 64-year-old men and nonpregnant women residing in the selected households were considered eligible to participate. A total of 2217 Mexican Americans and non-Hispanic whites were examined in phase I of the study, and 2957 Mexican Americans and non-Hispanic whites, in phase 2. The overall response rate for both phases combined was 65.3%. Mexican Americans were defined as individuals whose ancestry and cultural traditions derived from a Mexican national origin.11 Anthropometric measurements (height, weight, waist, and hip circumference) were made after each participant had removed his or her shoes and upper garments and had donned an examination gown. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. The ratio of waist-to-hip circumference (WHR) was chosen as a measure of upper body adiposity. A glucose tolerance test was performed in the morning on each participant with a 75 g glucose equivalent load (Koladex or Orangedex, Custom Laboratories, Baltimore, MD). Individuals were instructed to fast for 12 to 14 hours before the test. After obtaining a fasting blood specimen, additional specimens were drawn one-half, 1, and 2 hours after administration of the glucose load. Plasma glucose concentrations were measured with an Abbott Bichromatic Analyzer (South Pasadena, CA). Serum insulin concentrations were measured with a commercial
coated tube radioimmunoassay. Lipid and lipoprotein methodology have been previously described.

Diabetes was diagnosed according to the plasma glucose criteria of the National Diabetes Data Group (fasting plasma glucose ≥140 mg/dl and/or both 1- and 2-hour post-glucose load plasma glucose ≥200 mg/dl). Individuals who did not meet these criteria were also considered to be diabetic if they were currently taking either oral antidiabetic agents or insulin.

Urine specimens were obtained on all diabetic subjects (364 Mexican Americans and 80 non-Hispanic whites) and on a matched set of nondiabetic controls from phase II of the SAHS. Analyses in this report are restricted to the nondiabetic subjects, who were matched on age, sex, ethnic group, and neighborhood of residence to diabetic subjects. Since only one of 54 nondiabetic non-Hispanic white subjects had microalbuminuria and only two had clinical proteinuria, only Mexican Americans are considered in this report. Urine specimens were not obtained from 39 of the 369 nondiabetic Mexican American subjects, leaving 330 subjects available for analysis.

Both clinical proteinuria and microalbuminuria were assessed in an early morning spot urine specimen. These samples were usually, but not always, the first voided urine specimen. Clinical proteinuria was measured by Albustix (Ames, Elkhart, IN). Of 330 nondiabetic Mexican American subjects, 14 had 1+ or greater proteinuria and were excluded from this report, leaving 316 subjects who were free of clinical proteinuria. After determination of clinical proteinuria, urine specimens were stored at −70°C. Microalbuminuria was determined an average of 12 months later by a quantitative immunoturbidimetric method (Ames, Slough, England). Previous studies have shown that an early morning spot urine gives a good estimate of the 24-hour urinary excretion of albumin.

Systolic (first phase) and diastolic (fifth phase) blood pressures were measured with a random-zero sphygmomanometer (Hawksley-Gelman) on the right arm of the seated participant after at least a 5-minute rest. Three readings were obtained on each subject, and the average of the second and third reading was defined as the patient’s blood pressure. Hypertension was defined according to the Hypertension Detection and Follow-up Program criteria (diastolic blood pressure >95 mm Hg and/or currently taking antihypertensive medications).

Analysis of variance was used with the presence or absence of microalbuminuria as the grouping variable. The dependent variables were lipids, lipoproteins, blood pressure, and glucose and insulin concentrations. For hypertension prevalence and self-reported myocardial infarction, a χ² test was used to evaluate the association with microalbuminuria. Glucose and insulin sum were calculated by summing the fasting, one-half-hour, 1-hour, and 2-hour values. The relationship between cardiovascular risk factors and level of albuminuria in microalbuminemic subjects was evaluated by multiple linear regression. All statistical analyses were performed using the SAS statistical software.

Table 1 shows the clinical characteristics of subjects with and without microalbuminuria. Forty-two of 316 sub-

Table 1. Cardiovascular Risk Factors in Nondiabetic Subjects with and without Microalbuminuria

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Microalbuminuria</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>N</td>
<td>42</td>
<td>274</td>
</tr>
<tr>
<td>Men</td>
<td>14 (33%)</td>
<td>103 (37.6%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>49.6±1.6</td>
<td>51.0±0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.2±0.8</td>
<td>28.5±0.3</td>
</tr>
<tr>
<td>WHR</td>
<td>0.885±0.02</td>
<td>0.883±0.01</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>129.3±2.8</td>
<td>124.2±1.1</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.0±1.4</td>
<td>73.5±0.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>26.2%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>160.7</td>
<td>131.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>(137.8, 187.6)</td>
<td>(124.1, 140.0)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210.9±7.0</td>
<td>205.7±2.7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>133.9±6.6</td>
<td>129.2±2.5</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>44.0±2.2</td>
<td>48.5±0.8</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>87.7±1.8</td>
<td>87.3±0.7</td>
</tr>
<tr>
<td>Glucose sum (mg/dl)</td>
<td>498.6±14.5</td>
<td>491.9±10.5</td>
</tr>
<tr>
<td>Fasting Insulin (μU/ml)</td>
<td>17.3±2.5</td>
<td>13.0±0.9</td>
</tr>
<tr>
<td>Insulin sum (μU/ml)</td>
<td>423.0±38.3</td>
<td>337±15</td>
</tr>
<tr>
<td>% with myocardial infarction</td>
<td>7.1%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Microalbuminuria present = >30 mg/l, microalbuminuria absent = <30 mg/l. BMI = body mass index, WHR = ratio of waist circumference to hip circumference, BP = blood pressure, CI = confidence interval, LDL = low density lipoprotein, HDL = high density lipoprotein.
jects had microalbuminuria (≥30 mg/l). There were no significant differences in age, gender, body mass index, WHR, total cholesterol, low density lipoprotein (LDL) cholesterol, fasting glucose, or glucose sum according to microalbuminuria status. Blood pressure, hypertension prevalence, triglyceride concentration, insulin sum, and the proportion of subjects reporting myocardial infarction were greater in subjects with microalbuminuria than in subjects without microalbuminuria. Additionally, fasting insulin was higher and HDL cholesterol was lower in subjects with microalbuminuria, although these differences achieved only borderline statistical significance (0.05<p<0.10). The Spearman correlation coefficient between albumin excretion and insulin sum in the overall population was highly statistically significant (r=0.30, p<0.001). However, no significant correlation existed between glucose sum and albumin excretion (r=0.08, p>0.30).

We also examined whether cardiovascular risk factors differed by level of microalbuminuria among the 42 subjects with microalbuminuria as defined by Mogensen. 4 In general, there were no significant trends (p>0.25) in the pattern of cardiovascular risk factors with increasing microalbuminuria (data not shown), but this could have been due to the small sample size.

Hypertension has been associated with insulin resistance 18-21 and dyslipidemia. 18-19 21 Moreover, antihypertensive medications, especially thiazides and beta blockers, have been associated with increased triglyceride concentrations, insulin resistance, and decreased HDL concentrations. 22-26 Therefore, we excluded the 27 subjects with hypertension to determine whether the more adverse pattern of cardiovascular risk factors in subjects with microalbuminuria was independent of hypertension and/or antihypertensive therapy. Triglyceride concentrations and insulin sum remained significantly higher in subjects with microalbuminuria (Table 2). Fasting insulin and blood pressure were also higher and HDL cholesterol was lower in subjects with microalbuminuria, although these differences were only borderline statistically significant (0.05<p<0.10). There were no significant differences in total cholesterol, LDL cholesterol, fasting glucose, or glucose sum, or in the proportion of subjects reporting myocardial infarction in subjects with and without microalbuminuria.

Discussion

We have shown that nondiabetic subjects with microalbuminuria have a more adverse pattern of cardiovascular risk factors than nondiabetic subjects without microalbuminuria. These changes were most marked for triglyceride, HDL cholesterol, insulin concentration, and blood pressure. Since hyperinsulinemia has been associated with an adverse pattern of cardiovascular risk factors, 18-21 it may be that insulin resistance underlies the adverse risk pattern of subjects with microalbuminuria. Our results are consistent with the worse pattern of lipids and lipoproteins in insulin-dependent diabetic subjects 8 and the increased mortality in nondiabetic subjects 8 with microalbuminuria. In the latter report, microalbuminuria was also associated with coronary heart and peripheral vascular disease in multivariate analysis. However, insulin concentrations were not measured in this study. The association of microalbuminuria with elevated insulin concentrations reported in this study suggests an explanation for its association with vascular disease as described by Yudkin et al. 4 since in previous reports, hyperinsulinemia has been associated with increased coronary disease in nondiabetics. 20,27,28

It is of interest that when we excluded subjects with hypertension, the same pattern of adverse risk factors was observed even though, with the smaller sample size, some of these differences were no longer statistically significant. In the report by Yudkin et al., microalbuminuria was no longer related to vascular disease once hypertensive subjects were excluded.
Since our study was cross-sectional, we cannot determine whether the microalbuminuria causes the adverse pattern of cardiovascular risk factors or whether some common factor causes both abnormalities. The latter possibility is attractive since insulin resistance has been associated with at least two other abnormalities in renal function. DeFronzo has shown an association between increased sodium reabsorption distal to the proximal tubule and insulin resistance. Recently, Scholey and Meyer have shown in a diabetic Munich Wistar rat model that administration of insulin normalized glomerular capillary pressure although the glomerular ultrafiltration rate remained elevated as a consequence of a rise in the ultrafiltration coefficient. The authors concluded that glomerular hypertension in diabetes was a result of insulin deficiency rather than glomerular hypertrophy. If insulin resistance (i.e., lack of effective insulin action) occurs at the level of the kidney as well as in the muscle and liver, it could contribute to increased intraglomerular pressure, which in turn could lead to increased microalbuminuria. At present, microalbuminuria should be considered as a marker for cardiovascular disease rather than an etiologic agent.

Recently, angiotensin converting enzyme (ACE) inhibitors have been shown to both increase insulin sensitivity [29] and decrease albumin excretion. Our study suggests that these potentially beneficial effects of ACE inhibitors could be linked. Clinical studies of pharmacologic agents that improve insulin sensitivity should be performed in subjects with microalbuminuria to test directly whether improving insulin sensitivity will decrease albumin excretion.

Acknowledgments

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References

27. Ducimetiere P, Eschwege E, Richard J, Rosselin G, Claude JR. Clinical complications of coronary heart disease according to plasma insulin and glucose levels. A further

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