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Association Between Microalbuminuria and the Metabolic Syndrome: NHANES III

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Background: We investigated whether microalbuminuria was associated with the metabolic syndrome by comparing the strength of the association between microalbuminuria and the syndrome as a whole and its individual components.

Methods: This investigation included 5659 women and men aged 20 to 80 years from the cross-sectional, nationally representative, Third National Health and Nutrition Examination Survey (NHANES III: 1988–1994). Metabolic syndrome was defined as any three of the following: increased waist circumference, increased triglycerides, decreased HDL cholesterol, increased blood pressure, or high fasting glucose. Microalbuminuria was defined as urinary albumin/creatinine ratio of 30 to 300 mg/g.

Results: Microalbuminuria was present in 7.8% of women and 5.0% of men. Log linear analysis revealed a significant association between the metabolic syndrome and microalbuminuria in both genders (women $\chi^2 = 44.1$; men $\chi^2 = 59.6$; $P < .0001$ for both). Microalbuminuria was more common in both women (odds ratio [OR] = 2.2; 95% confidence interval [CI] 1.44, 3.34) and men (OR = 4.1; 95% CI 2.45, 6.74) with metabolic syndrome compared to those without it; 34% of women and 42% of men with microalbuminuria also had metabolic syndrome. After adjusting for other components of the metabolic syndrome, hypertension demonstrated the strongest association with microalbuminuria in both women (OR = 3.34; 95% CI 2.45, 4.55) and men (OR = 2.51; 95% CI 1.63, 3.86).

Conclusions: Microalbuminuria and metabolic syndrome are associated in a large, nationally representative cohort, possibly due to early renal effects of hypertension, and it may be useful to consider microalbuminuria as a component of the metabolic syndrome. Am J Hypertens 2003;16:952–958 © 2003 American Journal of Hypertension, Ltd.

Key Words: Metabolic cardiovascular syndrome, albuminuria, hypertension, population.

The term metabolic syndrome refers to an apparent clustering of several findings in patients: abdominal obesity, insulin resistance (elevated fasting glucose), hypertension, and dyslipidemia (elevated triglyceride and decreased HDL cholesterol levels).[1] In 2001 the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) report provided the first definition of the syndrome in national guidelines.[2] According to this definition more than 20% of adults have metabolic syndrome.[3] In 1998, the World Health Organization (WHO) had also proposed a unifying definition for the metabolic syndrome, which included the same components as the new ATP III definition, with the addition of microalbuminuria.[4]

The inclusion of microalbuminuria as part of the metabolic syndrome has been controversial because of its weak association with insulin resistance in some studies,[5] but not others.[6] There is also considerable evidence that microalbuminuria is a strong predictor of cardiovascular mortality.[7,8] It is well established that microalbuminuria is related to hypertension[9] and central adiposity,[10] both components of the metabolic syndrome. It is thought that microalbuminuria may be the renal expression of general vascular endothelial damage, specifically increased vascular permeability, and thus an early indicator of atherosclerosis.[11]

Previously, there has not been a standard definition of the metabolic syndrome to fully evaluate degree of association with microalbuminuria. Compared to previous definitions, the new ATP III guidelines define metabolic syndrome using lower fasting glucose, lower blood pressure (BP), and higher HDL criteria. It is important to assess whether microalbuminuria is associated with the metabolic syndrome when it is defined by these preclinical states. Previous observational studies evaluating the relationship between microalbuminuria and metabolic syn-

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drome have been limited in number of participants,[12,13] and done outside of US populations.[12,13] The current study assesses the relationship between the metabolic syndrome as defined by ATP III and microalbuminuria as defined by WHO in the large population-based Third National Health and Nutrition Examination Survey (NHANES III).

Methods

The Third National Health and Nutrition Examination Survey, conducted between 1988 and 1994 by the National Center for Health Statistics, was designed to assess the health status of the US civilian noninstitutionalized population ≥2 months of age. A representative sample of the population was recruited using a multistage, stratified sampling design. Survey participants were non-Hispanic white, African American, and Mexican-American aged 2 months and older, with oversampling of participants who were young, elderly, African American or Mexican-American to allow for more precise calculation of prevalence estimates of health behaviors in these groups. Demographic characteristics were collected during a standardized interview. Age was defined at the time of the household interview. Self-reported race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, or Mexican-American. Participants who did not identify with any of these categories were classified into an "other" race category.

The operation and procedures have been described.[14]

As detailed in the ATP III report[2], the metabolic syndrome is defined as three or more of the following characteristics: 1) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; 2) hypertriglyceridemia: ≥150 mg/dL (1.69 mmol/L); 3) low HDL cholesterol: <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women; 4) high BP: systolic BP ≥130 mm Hg and diastolic BP ≥85 mm Hg; and 5) high fasting glucose: ≥110 mg/dL (≥6.1 mmol/L).

Metabolic Syndrome Components

Participants underwent a detailed physical examination at a mobile examination center. Waist circumference was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest from participants at minimal respiration to the nearest 0.1 cm. The procedure for blood collection and processing has been described.[14] Serum samples were shipped to the Lipoprotein Analytical Laboratory at Johns Hopkins University, Baltimore, Maryland; serum triglycerides were measured enzymatically after hydrolyzation to glycerol (Hitachi 704 Analyzer; Hitachi, Tokyo, Japan) and total and HDL cholesterol were assessed using a Hitachi 737 Analyzer (Boehringer-Mannheim Diagnostics, Indianapolis, IN). Blood pressure was measured from seated participants three times during the household interview and three times at the mobile examination center; all available systolic and diastolic measurements were averaged. Participants who used hypertension control medications or reported a previous physician diagnosis (two or more occasions) were defined as having high BP. Plasma glucose was measured using a modified hexokinase enzymatic method (Cobas Mira assay; Roche, Basel, Switzerland). The interassay coefficient of variation was <4% during the 6 years of the survey. Participants who reported currently using antidiabetic medication (insulin or oral agents) were defined as having high fasting glucose.

Microalbuminuria

During the examination, a random untimed urine sample was obtained from participants using clean-catch techniques. Urine samples were frozen and shipped to a central laboratory for analysis. Urinary albumin concentration was measured by solid-phase fluorescent immunoassay[15] on thawed samples. Measurements were not performed on specimens with visible hematuria or on those testing positive for hemoglobin using qualitative test strips (Multistix; Bay Corp, Elkhart, IN). Urinary creatinine concentration was measured by the modified kinetic method of Jaffe,[16] using a Beckman Synchron AS/ASTRA analyzer (Beckman Instruments, Inc., Brea, CA). Interassay coefficients of variation were <16% and 10% for low (1.0 mg/L) and medium (7 mg/L) urinary albumin samples, respectively. Coefficients of variation for all levels of urinary creatinine were <8%. Microalbuminuria is defined as a urinary albumin-to-creatinine ratio (ACR) of 30 to 300 mg/g. Details about the laboratory procedures of all these tests are published elsewhere.[17]

Exclusions

Fasting blood specimens were obtained in 17,287 participants aged more than 20 years and less than 80 years. We excluded participants with missing values for glucose (2387), waist circumference (2458), HDL (2470), triglycerides (6248), systolic BP (249), diastolic BP (255), ethnicity (1508), and ACR (1744). We excluded participants who fasted for fewer than 8 hours (4022), those with serum creatinine >1.5 mg/dL and ACR >300 mg/g (298), and women who were pregnant (821). The sample for our analysis includes 5659 participants.

Data Analysis

Primary analyses, using linear models, were carried out in SUDAAN (Research Triangle Institute, Cary, NC), to adjust for the complex sample design of NHANES III (sampling weights are incorporated to adjust for unequal probabilities of selection). Analyses were stratified by gender. Means (standard deviations) and proportions of baseline characteristics were compared by ethnicity group using t-tests and χ^2 tests, respectively. We did not find differences in the association between metabolic syndrome and microalbuminuria by ethnicity, and further analyses were pooled. Log-linear models were used to test whether microalbuminuria and metabolic syndrome were statisti-

cally independent. Logistic regression was used to test the association between 1) metabolic syndrome and microalbuminuria; 2) individual components of the metabolic syndrome and microalbuminuria; and 3) individual components adjusted simultaneously for all components. Weighted proportions were derived from NHANES III using SUDAAN and extrapolated to the adult US population using Census 2000 data.[18]

Results

Characteristics of the population are shown in Table 1. Differences in the distributions of weight, body mass index, and components of the metabolic syndrome by ethnicity and gender have been reported previously.[3] Microalbuminuria was present in 7.8% of women and 5.0% of men, with African American men (8.7%) having a significantly higher prevalence than white (4.3%) and Mexican American (3.5%) men. The mean ACR was higher in women (6.7 mg/g) than in men (4.5 mg/g), reflecting the lower creatinine excretion found in women compared to men. Ethnicity interaction terms were not significant, and further analysis was separated on the basis of gender but not ethnicity.

The overall prevalence of metabolic syndrome is 19.8% in women and 17.2% in men. Table 2 shows the prevalence of each individual component of the metabolic syndrome by microalbuminuria status. The frequency of high glucose and high BP was significantly higher in those with microalbuminuria. In men with microalbuminuria, compared to those without, the frequencies of large waist circumference and of high triglycerides were also higher. Log linear analysis revealed a significant association between the metabolic syndrome and microalbuminuria in both genders (women $\chi^2 = 44.1$; men $\chi^2 = 59.6$; $P < .0001$ for both). The prevalence of microalbuminuria was higher in women (odds ratio [OR] = 2.2; 95% confidence interval [CI] 1.44, 3.34) and men (OR = 4.1; 95% CI 2.45, 6.74) with metabolic syndrome, as shown in Fig. 1.

Fig. 2 shows the age-adjusted odds ratios for microalbuminuria given specific components of the metabolic syndrome. Odds ratios were strongest for high fasting glucose and high BP. The age-adjusted odds ratios for microalbuminuria in metabolic syndrome overall are 1.9 in women and 2.6 in men.

Table 3 shows the odds ratios for microalbuminuria given specific components of the metabolic syndrome, controlling simultaneously for all other components. Even while concurrently adjusting for other components, the association between microalbuminuria and high glucose and high BP remains strong in both genders. Subsequent analyses (not shown) revealed that even while excluding hypertension as a component of the metabolic syndrome, the association between microalbuminuria and the metabolic syndrome remained significant (controlling for age: men OR = 2.3; 95% CI 2.1, 5.7 and women OR = 1.6; 95% CI 1.1, 3.1).

Table 1. Distribution of characteristics in the population

	Women			Men		
	Microalbuminuria*	Normoalbuminuria	*P*	Microalbuminuria	Normoalbuminuria	*P*
N	247	2558		198	2656	
White	74.9	75.8		63.7	75.9	
African-American	11.6	11.5		16.8	9.4	
Mexican-American	4.9	4.2		4.0	5.8	
Other	8.7	8.6		15.6	8.9	
Age	49.9 (1.6)	44.4 (0.7)	<.0001	53.6 (1.8)	40.5 (0.6)	<.0001
Weight (kg)	69.2 (1.3)	69.6 (0.7)	.5	84.0 (1.4)	82.3 (0.5)	.01
BMI	27.0 (0.6)	26.6 (0.3)	.5	27.6 (0.4)	26.6 (0.2)	.01
Waist circumference	89.9 (1.6)	88.1 (0.6)	.0003	100.1 (1.4)	94.6 (0.5)	<.0001
Triglycerides (mg/dL)	136.0 (6.4)	116.9 (2.8)	<.0001	180.0 (13.2)	136.0 (3.7)	.0005
HDL	57.8 (1.9)	54.9 (0.6)	.57	47.1 (1.7)	45.5 (0.6)	.23
DBP	75.0 (0.9)	72.1 (0.3)	<.0001	81.6 (1.1)	76.4 (0.4)	<.0001
SBP	131.6 (2.0)	118.4 (0.6)	<.0001	136.2 (1.7)	122.6 (0.6)	<.0001
Glucose (mg/dL)	108.7 (2.9)	95.1 (0.5)	<.0001	116.2 (4.3)	99.1 (0.4)	<.0001
ACR	73.6 (6.8)	7.4 (0.2)	<.0001	75.2 (4.9)	5.4 (0.2)	<.0001

* Microalbuminuria defined as urinary albumin to creatinine ratio (ACR) of 30 to 300 mg/g. Normoalbuminuria defined as ACR <30 mg/g.
BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 2. Distribution of the components of the metabolic syndrome

	Women			Men		
	Microalbuminuria	Normoalbuminuria	*P*	Microalbuminuria*	Normoalbuminuria	*P*
N	247	2558		198	2656	
Large waist (%)	52.5	45.1	.06	50.8	25.6	.0015
High triglycerides (%)	30.7	21.4	.02	50.0	30.0	.0019
Low HDL (%)	41.3	38.0	.45	35.4	35.0	.95
High BP (%)	40.3	15.4	<.0001	39.7	14.4	<.0001
High glucose (%)	21.6	8.2	.0002	32.2	11.3	.0005
Metabolic syndrome (%)	33.9	18.6	<.0001	41.5	15.9	.0005

* Microalbuminuria defined as urinary albumin to creatinine ratio (ACR) of 30 to 300 mg/g. Normoalbuminuria defined as ACR <30 mg/g.

FIG. 1. Prevalence of microalbuminuria by metabolic syndrome.

Estimates for metabolic syndrome and microalbuminuria based on US Census 2000 data are shown in Table 4. Including microalbuminuria as one of the components of metabolic syndrome increases the number of identified cases of metabolic syndrome by 7.5% in women and 5.6% in men. An additional 3.4 million women and 3.6 million men would be identified for treatment of the metabolic syndrome in the US.

Discussion

In this population-based analysis we found strong positive associations between microalbuminuria and the metabolic syndrome in both women and men. Within the population, high glucose and high BP were the components most

FIG. 2. Age-adjusted odds ratio and 95% confidence intervals of microalbuminuria by the components of the metabolic syndrome. All variables simultaneously in one model, except metabolic syndrome, which is only age adjusted. BP = blood pressure.

Table 3. Odds of microalbuminuria by components of the metabolic syndrome

	Women			Men		
	OR	**(95% CI)**	***P***	**OR***	**(95% CI)**	***P***
High glucose	2.24	(1.25–4.00)	.0047	2.51	(1.54–4.10)	.0001
Low HDL	0.89	(0.58–1.37)	.5868	0.76	(0.37–1.55)	.4338
High BP	3.34	(2.45–4.55)	<.0001	2.51	(1.63–3.86)	<.0001
High TG	1.17	(0.65–2.10)	.5789	1.61	(0.89–2.91)	.0995
Large waist	0.8	(0.59–1.08)	.1342	2.05	(1.12–3.75)	.0159

* OR = Odds ratios, adjusted for all other components in table.

strongly associated with microalbuminuria. The magnitude of this association persisted even after controlling for age and other components of the metabolic syndrome. These results indicate that microalbuminuria may be a component of the metabolic syndrome, supporting results from other epidemiologic studies.[6,13,19,20]

Hypertension has long been associated with microalbuminuria.[6,13,21,22] Increases in intraglomerular capillary pressure are thought to cause leakage of albumin.[23] Clinically, microalbuminuria may be an indicator of early vascular complications of hypertension. Yudkin[24] proposed in 1996 that the clustering of risk factors attributed to insulin resistance and microalbuminuria may all be features of damage to different aspects of endothelial function. Signs of early endothelial dysfunction as manifested by microalbuminuria may herald impending renal impairment, and may offer another focus for treatment of the metabolic syndrome.

The association between high glucose as defined by ATP III guidelines and microalbuminuria has not been previously examined. Prior studies have examined various surrogates for insulin resistance, including the homeostasis model index, fasting insulin levels, and more direct measures of insulin sensitivity such as frequently sampled intravenous glucose tolerance tests. The Hoorn study,[25] which used fasting hyperinsulinemia, insulin resistance (calculated from the formula of the homeostasis model assessment), and glucose intolerance showed no associations with microalbuminuria. The Insulin Resistance in Atherosclerosis Study[6] showed an increasing degree of insulin sensitivity was related to a decreasing prevalence of microalbuminuria using the minimal model and fasting plasma insulin concentration. A recent study of the Korean general population[26] also showed that subjects with microalbuminuria had a higher fasting plasma glucose than subjects without microalbuminuria. Our results indicate that a fasting plasma glucose level of >110 mg/dL is strongly associated with the presence of microalbuminuria.

Studies suggest that prevalence of microalbuminuria is greatest in populations with both hypertension and diabetes.[27–29] Our study extends these findings to even lower levels of BP and glucose. Microalbuminuria may reflect the chronicity of even mild BP and glucose elevations. These findings reinforce the concept that there is a vascular constellation of symptoms associated with these metabolic abnormalities.

Prior studies examining the relationships of metabolic syndrome factors have used different levels to designate abnormal values. This makes it difficult to compare the strength of association across studies. Researchers have divided studied populations into quartiles comparing the lowest to the highest, or have defined the 90th percentile as the cutpoint for "abnormal" factors. Differing measures for insulin resistance (as described here) and obesity (body mass index, waist to hip ratio, waist circumference) have

Table 4. Percentage of NHANES participants and US population-based estimates

	Percentage	**US Population in Millions***
Women with metabolic syndrome	20%	41.8
Men with metabolic syndrome	17%	36.3
Women with microalbuminuria	8%	16.5
Men with microalbuminuria	5%	10.5
Women with metabolic syndrome that have microalbuminuria	13%	5.6
Men with metabolic syndrome that have microalbuminuria	12%	4.4
Women with metabolic syndrome, if microalbuminuria is included as a component	21%	45.2
Men with metabolic syndrome, if microalbuminuria is included as a component	19%	39.9

* Based on 2000 census data, which reported 211,066,430 people in the US over the age of 18 years.

been used. Statistical methodology has also differed—comparisons of prevalences, odds ratios, and correlations have been variously used. This has lead to inconsistent reporting of hypertension,[12] obesity,[13] dyslipidemia,[30] and insulin resistance,[31] as the strongest associated risk factor to microalbuminuria. The ATP III definition will allow researchers to uniformly compare the strength of association and prediction of various metabolic syndrome components across populations.

Microalbuminuria is a well-known cardiovascular disease marker,[32] and has been a strong predictor of cardiovascular morbidity and mortality in several studies.[8,33] A recent European longitudinal study[20] of the individual components of the metabolic syndrome (WHO definition) and subsequent risk of cardiovascular disease death found that microalbuminuria conferred the strongest risk of cardiovascular disease death when compared to obesity, hypertension, and dyslipidemia. The finding of microalbuminuria along with other components of the metabolic syndrome may increase the specificity of this risk prediction tool, and may explain the increased cardiovascular disease risk seen with this syndrome.

In this epidemiologic survey, a spot urine ACR was used as an acceptable substitute for a timed urine albumin measurement. Studies comparing spot urine ACR to 24-h urine collections in diabetics have found kappas ranging from 0.49 to 0.57, indicating good agreement.[34] In addition, sensitivities range from 71% to 75%, and specificities are 96% to 98%.[34–36] Although use of urinary albumin excretion is the gold standard, spot urine ACR offers a good estimation in epidemiologic surveys and has been used in many other studies[13,19,32] evaluating microalbuminuria in populations. Use of spot urine ACR to estimate microalbuminuria would result in nondifferential misclassification bias, and this leads to bias toward the null. Thus, in our analysis, the actual strength of the association would be higher than we have estimated.

The prevalence of microalbuminuria as defined by ACR was higher in women than in men in our analyses. Previous studies estimating prevalence of microalbuminuria in NHANES III[37] and other populations[13] have used ACR of 30 to 300 mg/g as the definition of microalbuminuria in both sexes. Studies suggest that sex-specific cutoffs for ACR are necessary to adjust for higher urine creatinine excretion found in men[38,39] due to increased muscle mass. Various sex-specific cutoffs have been proposed,[38,39] but none have been universally adopted. We chose to define microalbuminuria as an ACR of 30 to 300 mg/g in our analyses to reflect the WHO definition for microalbuminuria,[4] which is gender insensitive. Using sex-specific cutoffs of 17 mg/g in men and 25 mg/g in women,[38] we find that the prevalence of microalbuminuria is similar in both sexes. Lower cutpoints for ACR increases the prevalence of microalbuminuria in men, and further strengthens the association of metabolic syndrome and its high BP and high blood glucose components with microalbuminuria in men. There were no differences identified in the association of microalbuminuria and the metabolic syndrome or its components between men and women.

The NHANES III study is one of the most comprehensive national surveys to date. Extensive data are available from both the home survey and medical examination, and response rates were high. Unlike many surveys, NHANES III is a representative sample of the US population and therefore the results are generalizable and can be extrapolated to estimate the prevalence in the population using US census data. The principal limitation relevant to the interpretation of these results is the use of cross-sectional data, which limits inferences about causal pathways. There was also a large number of missing values, which greatly limited sample size available for analysis. Previous analyses to approximate the US population prevalence of metabolic syndrome,[3] based estimates on an NHANES III population of 8814 adults. This significant reduction in sample size reflects a large number of missing values for triglyceride level, which requires a fasting blood draw. Our analyses required even further exclusions due to missing values for urinary microalbumin. These exclusions are necessary to create accurate prevalence estimates, and are in accord with prior metabolic syndrome analyses in this dataset.

In summary, we found that microalbuminuria was highly associated with the metabolic syndrome, specifically the high fasting glucose and high BP components. These results suggest that there may be clinically important renal dysfunction associated with the metabolic syndrome in many patients and physicians would be wise to measure urinary albumin in this setting. Further research in this area could investigate the longitudinal relationship and explore pathways between metabolic syndrome and microalbuminuria.

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