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Urinary Albumin and Cardiovascular Profile in the Middle-Aged Population

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The moderate increase in urinary albumin excretion defined as microalbuminuria is not rare and is associated with cardiovascular risk factors. Microalbuminuria prevalence is low in the absence of cardiovascular risk factors and progressively increases with the number cardiovascular risk factors. The main correlate of microalbuminuria is blood pressure, either systolic or diastolic pressure. The relation between blood pressure and microalbuminuria is continuous and graded because the microalbuminuria prevalence increases with the severity of hypertension. Among hypertensive patients on drug treatment, blood pressure control is associated with a low prevalence of microalbuminuria. Thus, blood pressure appears as a determinant of microalbuminuria rather than a mere correlate. For hypercholesterolemia, smoking, and diabetes, data are less strong but point to an independent positive association with microalbuminuria. Altogether, data indicate that microalbuminuria in the population reflects the presence of cardiovascular risk factors. Data on microalbuminuria and coronary heart disease support this idea. There is a continuous and graded relation between urinary albumin excretion and coronary heart disease prevalence. High urinary albumin excretion is likely a sign of vascular damage existing both at the renal and cardiac levels and induced by 1 or more uncontrolled cardiovascular risk factors.
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KEYWORDS microalbuminuria, cardiovascular risk, coronary heart disease, epidemiology, Gubbio Study

A relationship between proteinuria and mortality has been hypothesized since 1893[1] and later was proven by epidemiologic data on predictors of cardiovascular mortality.[2,3] The relationship between proteinuria and cardiovascular disease has been studied in recent years by analyses on the urinary excretion of albumin. Albumin, although it is usually the most abundant urinary protein, is not precisely measurable by standard urinalysis unless it increases above the normal range.[4,5] The kidneys control the level of urinary albumin excretion via the selective permeability of the glomerular filter and the albumin reabsorption in the proximal tubule.[4,5] The terms *microalbuminuria* and *macroalbuminuria* are used to define high urinary albumin excretion. Microalbuminuria is the term for the mild increase in urinary albumin excretion, a disorder that generally is detectable only by specific and sensitive measurements. Macroalbuminuria is the term for the large increase in urinary albumin excretion, a disorder that generally is considered a sign of overt renal disease detectable by standard urinalysis. Clinical and population-based data suggest that microalbuminuria is a marker of cardiovascular diseases.[6-17] Yet, it still is uncertain whether the relationship of microalbuminuria to cardiovascular disease is independent of other factors. Coronary heart disease (CHD) is a common form of cardiovascular disease that can be diagnosed by standardized measurements.[18] This article describes the relationships among cardiovascular risk factors, urinary albumin excretion, and CHD in middle-aged men and women from an Italian population sample.

Methods

The Gubbio Study is an ongoing investigation in a population sample of people ages 5 to 99 years residing in the Italian town of Gubbio. Information on the Gubbio Study for response rates, responders and nonresponders, time of examinations, and main characteristics of the population sample were reported previously.[19-22] This article discusses data col-

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lected only for men and women ages 45 to 64 years in the second examination of the study. For these people, the protocol included the administration of standardized questionnaires on medical history, drug or dietary treatment, smoking habits, and cardiovascular diseases;[18] the measurements of weight, height, and blood pressure; a standard 12-lead resting electrocardiogram (ECG) read by the Minnesota Code;[18] the collection of morning blood samples under fasting conditions, and of timed overnight urine.[23] Written instructions were given to have detailed information on the duration of overnight collection. The average blood pressure between second and third measurements was used for analysis. Urinary albumin level was measured by immunoturbidimetry preceded by ultrafiltration to concentrate samples with albumin concentration less than 7 μg/mL.[23] Automated procedures were used for measurements in serum (including glucose, total cholesterol, and creatinine) and urine (including creatinine).

Urinary albumin excretion was expressed as μg/min (urinary albumin concentration times urine flow rate). The urinary albumin/creatinine ratio was not used as an independent variable to avoid the confounding of creatininuria (ie, muscle mass).[23] Urinary albumin excretion was defined as normal when less than 20 μg/min, as microalbuminuria when in the range of 20 to 199 μg/min, and as macroalbuminuria when 200 μg/min or greater.[5] People with systolic pressure of 140 mm Hg or greater and/or diastolic pressure of 90 mm Hg or greater and/or antihypertensive drug treatment were defined as hypertensive. Hypercholesterolemia was defined as a plasma cholesterol level of 6.20 mmol/L or greater (240 mg/100 mL) and/or regular drug treatment for hypercholesterolemia. Diabetes mellitus was defined as a fasting plasma glucose level of 7.2 mmol/L or greater (130 mg/100 mL) and/or regular treatment with insulin and/or antidiabetic drugs. CHD was defined as myocardial infarction or myocardial ischemia on the basis of data for the coded ECG and for the questionnaire on cardiovascular disease.[18]

Prevalence and Correlates of Microalbuminuria

The sample of people ages 45 to 64 year in the Gubbio study comprised 715 men and 917 women with a high prevalence of major cardiovascular risk factors as expected for a middle-aged population from an industrialized country (40.8% for hypertension, 39.5% for hypercholesterolemia, 31.2% for cigarette smoking, and 5.3% for diabetes mellitus).[23-25] Microalbuminuria was approximately 10 times more prevalent than macroalbuminuria (4.2% and 0.4%, respectively). Sex was a correlate of high urinary albumin excretion because both microalbuminuria and macroalbuminuria were more prevalent in men than women (Fig 1). The prevalence of microalbuminuria was progressively higher with increasing blood pressure, and was higher in men than women at any level of blood pressure (Fig 2). Untreated hypertensive patients had a high prevalence of microalbuminuria either in the presence of an increase in the diastolic or systolic pressure

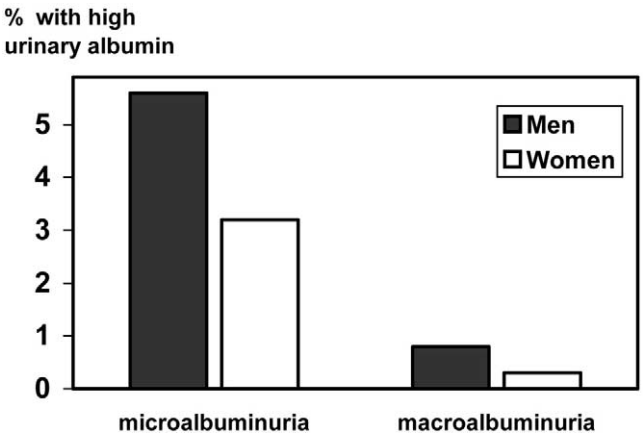

Figure 1 Percent prevalence of microalbuminuria (urinary albumin excretion 20-199 μg/min) and macroalbuminuria (urinary albumin excretion ≥200 μg/min) in the population of men and women ages 45 to 64 years.[23,25] ■, men; □, women.

(Fig 3). Hypertensive patients on regular antihypertensive drug treatment did not have a high prevalence of microalbuminuria if their hypertension was controlled (Fig 3). Hypercholesterolemia, smoking, and diabetes mellitus also were associated with a high prevalence of microalbuminuria independently of blood pressure and of each other (Fig 4). Thus, the prevalence of microalbuminuria was progressively higher with increasing the number of the individual's cardiovascular risk factors (Fig 5).

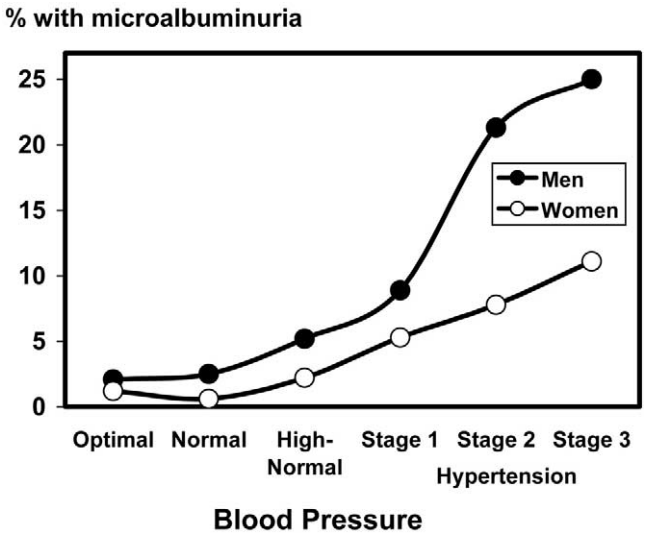

Figure 2 Percent prevalence of microalbuminuria (urinary albumin excretion 20-199 μg/min) by blood pressure level in the population of men and women ages 45 to 64 years.[23] (Blood pressure as mm Hg): OPTIMAL, systolic pressure less than 120 and diastolic pressure less than 80; NORMAL, systolic pressure 120 to 129 or diastolic pressure 80 to 84; HIGH-NORMAL, systolic pressure 130 to 139 or diastolic pressure 85 to 89; STAGE 1 HYPERTENSION, systolic pressure 140 to 159 or diastolic pressure 90 to 99; STAGE 2 HYPERTENSION, systolic pressure 160 to 179 or diastolic pressure 100 to 109; STAGE 3 HYPERTENSION, systolic pressure of 180 or greater or diastolic pressure of 110 or greater. ●, men; ○, women.

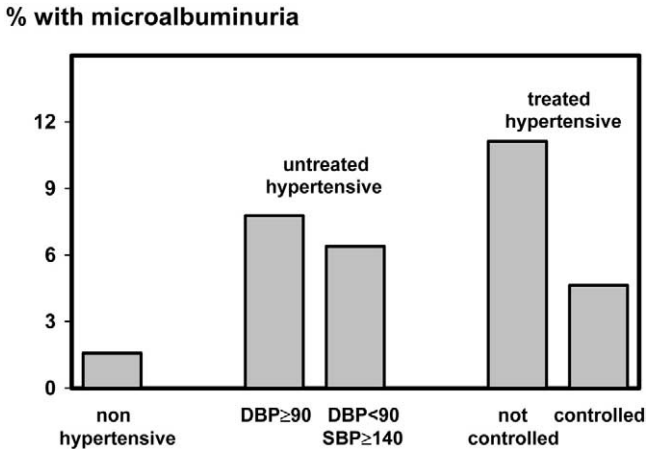

Figure 3 Percent prevalence of microalbuminuria (urinary albumin excretion 20-199 μg/min) by blood pressure status in the population of men and women ages 45 to 64 years.[24] (Blood pressure as mm Hg): NONHYPERTENSIVE, systolic pressure less than 140 and diastolic pressure less than 90 and no antihypertensive drug treatment; DBP ≥90, diastolic pressure of 90 or greater, any systolic pressure, and no antihypertensive drug treatment; DBP <90 SBP ≥140, diastolic pressure less than 90, systolic pressure of 140 or greater, and no antihypertensive drug treatment; NOT-CONTROLLED, on antihypertensive drug treatment with systolic pressure of 140 or greater or diastolic pressure of 90 or greater; CONTROLLED, on antihypertensive drug treatment with systolic pressure less than 140 and diastolic pressure less than 90.

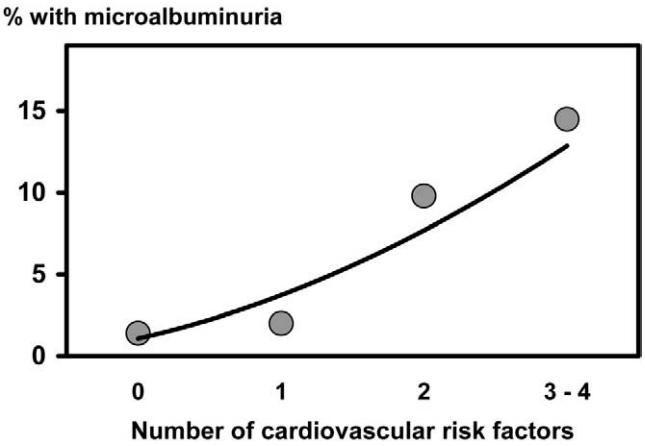

Figure 5 Percent prevalence of microalbuminuria (urinary albumin excretion 20-199 μg/min) by number of cardiovascular risk factors in the population, men and women, ages 45 to 64 year.[23] Factors in analysis: HYPERTENSION, systolic pressure of 140 mm Hg or greater and/or diastolic pressure of 90 mm Hg or greater and/or antihypertensive drug treatment; HYPERCHOLESTEROLEMIA, plasma cholesterol level of 6.20 mmol/L or greater (240 mg/100 mL) and/or regular drug treatment for hypercholesterolemia; SMOKING, reported information at questionnaire; DIABETES MELLITUS, fasting plasma glucose level of 7.2 mmol/L or greater (130 mg/100 mL) and/or regular treatment with insulin and/or antidiabetic drugs.

Urinary Albumin and CHD

The prevalence of CHD in the middle-aged population sample of the Gubbio study was 8.2% (5.6% for myocardial infarction, 2.6% for myocardial ischemia). People with normal urinary albumin excretion had a CHD prevalence of 7.5%, a rate that was lower than the rate of people with microalbuminuria (21.7%) or macroalbuminuria (33.3%). In comparison with those with normal urinary albumin excretion, the odds ratio of CHD was 3.44 in patients with microalbuminuria and 6.20 in patients with macroalbuminuria ($P < .01$). Findings were similar for myocardial infarction and myocardial ischemia (not shown). The positive association of urinary albumin excretion to CHD prevalence was present also in the range of normal urinary albumin as shown by Figure 6. Table 1 shows that the relationship between urinary albumin excretion and CHD statistically was independent of other variables. A difference as low as 10 μg/min in urinary albumin excretion was associated with a 31% difference in the prevalence of CHD with control for sex, age, hypertension, hypercholesterolemia, diabetes, and smoking.

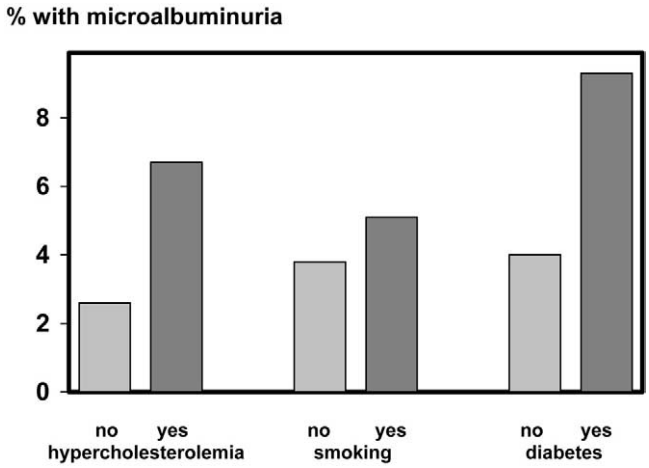

Figure 4 Percent prevalence of microalbuminuria (urinary albumin excretion 20-199 μg/min) by absence/presence (no/yes) of hypercholesterolemia, smoking, and diabetes mellitus in the population of men and women ages 45 to 64 years.[23] hypercholesterolemia = plasma cholesterol ≥6.20 mmol/L (240 mg/100 mL) and/or regular drug treatment for hypercholesterolemia; smoking = reported information at questionnaire; diabetes mellitus = fasting plasma glucose ≥7.2 mmol/L (130 mg/100 mL) and/or regular treatment with insulin and/or antidiabetic drugs.

Conclusions

Data from the Gubbio study indicate that, in the middle-aged population, the moderate increase in urinary albumin defined as microalbuminuria is not rare and is much more frequent than the severe increase defined as macroalbuminuria. Microalbuminuria is associated strongly with the presence of cardiovascular risk factors. Its prevalence is quite low in people with a favorable cardiovascular profile (nonsmokers without hypertension, hypercholesterolemia, and diabetes) and progressively increases with the increasing number of cardiovascular risk factors present in the individual. Blood pressure appears as the main correlate of microalbuminuria,

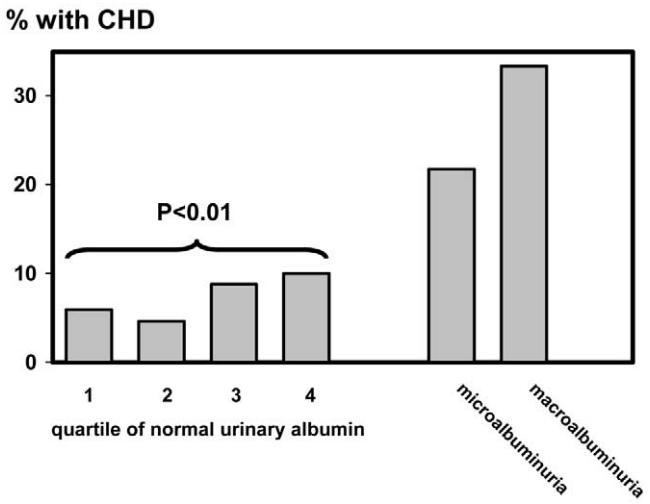

Figure 6 Percent prevalence of CHD (myocardial infarction or myocardial ischemia by coded electrocardiogram and reported symptoms) by level of urinary albumin excretion in the population of men and women ages 45 to 64 years.[25] QUARTILE OF NORMAL URINARY ALBUMIN, sex-controlled quartile for people with urinary albumin excretion less than 20 μg/min; MICROALBUMINURIA, urinary albumin excretion 20 to 199 μg/min; MACROALBUMINURIA, urinary albumin excretion of 200 μg/min or greater.

with similar findings for systolic or diastolic pressure. In fact, the prevalence of microalbuminuria is similar in untreated hypertensive patients with isolated systolic hypertension and untreated hypertensive patients with diastolic hypertension. Data indicate that the level of blood pressure increase plays a key role because the positive relationship between blood pressure and microalbuminuria is continuous and graded from high-normal blood pressure to hypertension stage 3. Thus, hypertensive patients with severe blood pressure increases have microalbuminuria more frequently than hypertensive patients with mild blood pressure increases. The same concept is supported by data in hypertensive patients on regular drug treatment in whom well-controlled blood pressure is associated with a low prevalence of microalbuminuria. Altogether, data support the interpretation that the level of blood pressure is a determinant rather than a mere correlate of microalbuminuria. For hypercholesterolemia, smoking, and diabetes, the findings are less strong but in the same direction, that is, a positive and independent association with microalbuminuria. It is not clear if treatment and control of these disorders also is associated with control of microalbuminuria. Clinical trials on this possibility either are inconsistent or missing. However, regardless of the possible mechanisms, this set of epidemiologic data indicates that microalbuminuria in this population could be used as a marker of cardiovascular risk because it is associated most often with uncontrolled hypertension and/or other cardiovascular risk factors. Data on the association between microalbuminuria and CHD further support this conclusion. There is a strong, continuous, graded, and independent relationship of urinary albumin excretion with CHD. The prevalence of CHD—assessed by ECG and reported symptoms—progressively increased over the entire range of urinary albumin excretion from about 5% in people with low-normal urinary albumin to about 35% in people with macroalbuminuria. It is likely that these data are an underestimate of the true strength of the relationship because some cases must have been misclassified for the use of a single measurement of urinary albumin excretion without urinalysis.[2,4] There are no reasons to suspect that an increase in urinary albumin excretion could be a determinant of CHD. According to a more reasonable explanation, a high albumin excretion could be a urinary sign of cardiorenal vascular damage secondary to 1 or more uncontrolled cardiovascular risk factors. The practical implication of the data are that the measurement of urinary albumin excretion is an important tool for prevention and control of CHD.

Table 1 Relationship of Urinary Albumin Excretion to Prevalence of CHD in Middle-Aged Men and Women

Independent variable	Referent Interval	Odds Ratio
Urinary albumin excretion	10 μg/min	1.31*
Hypertension	Yes versus no	1.67*
Diabetes	Yes versus no	1.80†
Hypercholesterolemia	Yes versus no	1.10
Smoking	Yes versus no	NS

NOTE. Odds ratio in multivariate logistic regression analysis. Data controlled for sex and age.[25]
Abbreviation: NS, not specified.
*$P < .001$, †$P = .06$

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