Low Muscular Mass and Overestimation of Microalbuminuria by Urinary Albumin/Creatinine Ratio

Massimo Cirillo, Martino Laurenzi, Mario Mancini, Alberto Zanchetti, Natale G. De Santo

Abstract—Microalbuminuria is a mild urinary albumin elevation and is associated with cardiovascular disease. Urinary albumin/creatinine ratio is recommended for microalbuminuria assessment, because it reflects urinary albumin excretion. Muscular mass could affect albumin/creatinine ratio, because urinary creatinine reflects muscular mass. The study investigated high albumin/creatinine ratio attributed to low urinary creatinine without microalbuminuria. The Gubbio Population Study for ages 45 to 64 collected data on weight, skinfold, urinary albumin, urinary creatinine, and coronary heart disease. Weight and skinfold thickness were used to calculate fat and nonfat mass and urinary creatinine as a marker of muscular mass. Microalbuminuria was defined as urinary albumin of 20 to 199 μg/min and high albumin/creatinine ratio as a ratio of 17 to 250 μg/mg in men and of 25 to 355 μg/mg in women. Persons with macroalbuminuria (urinary albumin ≥200 μg/min) were excluded to focus analyses on microalbuminuria. Coronary heart disease was defined by ECG and questionnaire. The target cohort consisted of 1623 men and women, ages 45 to 64. Prevalence was 8.5% for high albumin/creatinine ratio (n=138), 4.3% for microalbuminuria (n=69), 5.2% for high albumin/creatinine ratio without microalbuminuria (n=85), and 1.0% for nonhigh albumin/creatinine ratio with microalbuminuria (n=16). High albumin/creatinine ratio without microalbuminuria was inversely associated with nonfat mass and urinary creatinine (P<0.04). Compared with persons with a nonhigh albumin/creatinine ratio, coronary heart disease was more prevalent in persons with a high albumin/creatinine ratio and microalbuminuria (18.9% and 7.1%; P=0.002), not in persons with a high albumin/creatinine ratio without microalbuminuria (8.2% and 7.1%; P=0.706). A high albumin/creatinine ratio in persons with low muscle mass indicates low urinary creatinine more often than microalbuminuria and cardiovascular disease. (Hypertension. 2006;47:56-61.)

Key Words: albuminuria • body mass • muscles • coronary disease

A statement of the American Heart Association and guidelines of the National Kidney Foundation suggest that the moderate elevation in urinary albumin excretion (uAE) defined as microalbuminuria should be considered as a risk factor for cardiovascular disease.1,2 The urinary albumin/creatinine ratio (uACR) is recommended for the assessment of uAE, because uACR is an index of uAE than can be measured in untimed spot urine samples. In fact, the uACR can be calculated with use of the urinary concentration of albumin and creatinine without information on duration and volume of urine collection. The value of the uACR necessarily depends not only on the rate of uAE but also on the rate of urinary creatinine excretion that, in turn, reflects the interindividual differences in muscle mass.3,4 Gender-specific thresholds for the definition of high uACR were proposed to reduce the confounding because of an underestimate of microalbuminuria, that is, a normal uACR because of the combination of normal uAE with low urinary creatinine.5,6 Research data are missing on the opposite confounding, that is, on the overestimation of microalbuminuria caused by a high uACR because of the combination of normal uAE with low urinary creatinine excretion (ie, low muscle mass). Significant and independent associations were reported previously among uAE, cardiovascular risk factors, and coronary heart disease (CHD) in middle-age persons participating in the Gubbio Population Study.4,7,8 Data of the Gubbio Study were analyzed to investigate persons with high uACR and normal uAE, that is, on the elevation of the uACR because of low urinary creatinine excretion rather than high uAE. Analyses were focused on the prevalence of this trait, its association with CHD, and indices of body mass.

Methods

The Gubbio Study is an epidemiological investigation ongoing in the Italian city of Gubbio.9,10 The study adheres to the principles of the Declaration of Helsinki and the Title 45 of US Code of Federal Regulation. Study activities were approved by the local institutional review committee, and an informed consent was given by participants. All of the procedures were in accordance with institutional guidelines. The protocol for participants 45 to 64 years of ages included the collection of timed overnight urine,4 standardized
questionnaires on cardiovascular disease, blood pressure measurements, a 12-lead resting ECG read by the Minnesota Code, weight, and skinfold thickness.

As reported previously, blood pressure was measured by trained medical doctors using mercury sphygmomanometers and cuffs of appropriate size with the participant in the sitting position. The first measurement was done after 5 minutes of quiet rest after application of the cuff. The mean of second and third measurements was used for analysis. Albumin, creatinine, and urea were measured in urine samples: albumin by ultrafiltration immunoturbidimetry and creatinine and urea by automated biochemistry. The rate of uAE (in mg/min) was defined as nonhigh when <17 in men and <25 in women. Persons with macroalbuminuria were excluded from analyses to focus on uAE in the range of normalcy and microalbuminuria. Hypertension was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg and/or regular treatment with antihypertensive drug(s). CHD was analyzed as the most common clinical presentation of vascular disease and defined with use of ECG data combined with symptoms reported in the questionnaire as described previously. Myocardial infarction or ischemia were combined in analysis, because previous data showed that uAE is similarly and independently related to both disorders. Data of skinfold thickness (triceps and subscapular) and weight were used for the estimation of fat mass. Nonfat mass was calculated as weight minus fat mass. Urinary creatinine excretion (in mg/min) was used as index of dietary protein intake to control the confounding of diet composition on urinary creatinine.

Results

A total of 1684 persons were 45 to 64 years of age in the Gubbio population sample. Sixty-one persons were excluded from analyses because of missing ECG data (n=52) or macroalbuminuria (n=9). Thus, the study cohort was composed of 1623 persons. Table 1 shows descriptive statistics in the study cohort. Descriptive data on smoking, hypercholesterolemia, diabetes mellitus, infarction, and ischemia were reported previously. Differences between men and women were significant for nonfat mass, urinary creatinine excretion, and microalbuminuria prevalence. Urinary creatinine excretion correlated with weight and nonfat mass (R=0.403 and 0.504; P<0.001) but not with fat mass (R=0.022; P=0.379). Urinary creatinine also correlated with urinary urea (R=0.485; P<0.005). The correlation between urinary creatinine excretion and nonfat mass was also significant with control for urinary urea excretion (partial R=0.476; P<0.001). Findings were similar in analyses separate by gender (data not shown).

Agreement Between uACR and uAE

Individual values of uAE and uACR were significantly correlated in analysis for men and women combined together (rank correlation coefficient=0.884; P<0.001) and in analy-
TABLE 2. Prevalence of Microalbuminuria and Normal Urinary Albumin Excretion by Level of Urinary Albumin/Creatinine Ratio, Men and Women Combined, Ages 45 to 64 y

<table>
<thead>
<tr>
<th>Urinary Albumin/Creatinine Ratio</th>
<th>Microalbuminuria (n=69)</th>
<th>Normal (n=1554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (n=138)</td>
<td>53</td>
<td>85</td>
</tr>
<tr>
<td>Nonhigh (n=1485)</td>
<td>16</td>
<td>1469</td>
</tr>
</tbody>
</table>

Urinary albumin excretion: microalbuminuria = 20 to 199 µg/min; normal = <20 µg/min. Urinary albumin/creatinine ratio: high = ratio ≥17 g/mg in men and ≥25 µg/mg in women; nonhigh = ratio <17 µg/mg in men and <25 µg/mg in women.

Comparison of coronary heart disease prevalence between persons with nonhigh uACR (□, n=1485) and persons with high uACR. Persons with high uACR are analyzed as a whole group (high uACR, □, n=138) and as 2 subgroups: without microalbuminuria (high uACR without microalbuminuria, ■, n=85) and with microalbuminuria (high uACR with microalbuminuria, □, n=53). P values are by χ² analyses in comparison with persons with nonhigh uACR.

TABLE 3. Univariate Relation of Age and Indices of Body Mass to Prevalence of Cases With High Urinary Albumin/Creatinine Ratio Without Microalbuminuria: Logistic Analyses, 1607 Men and Women Combined, Ages 45 to 64 y

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Reference Interval</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>+5.6 y</td>
<td>1.43*</td>
<td>1.14 to 1.79</td>
</tr>
<tr>
<td>Weight</td>
<td>+12.9 kg</td>
<td>0.94</td>
<td>0.75 to 1.17</td>
</tr>
<tr>
<td>Non-fat mass</td>
<td>+10.0 kg</td>
<td>0.66†</td>
<td>0.46 to 0.96</td>
</tr>
<tr>
<td>Fat mass</td>
<td>+7.1 kg</td>
<td>1.08</td>
<td>0.87 to 1.33</td>
</tr>
<tr>
<td>Urinary creatinine excretion</td>
<td>+0.44 mg/min</td>
<td>0.04‡</td>
<td>0.02 to 0.07</td>
</tr>
</tbody>
</table>

High urinary albumin/creatinine ratio: ratio ≥17 µg/mg in men, ≥25 µg/mg in women. Without microalbuminuria: urinary albumin excretion <20 µg/min. Reference interval=1SD of independent variable for men and women combined. OR was not significant for weight and fat mass.

High uACR without microalbuminuria

Relation of uACR to CHD

FIGURE

Figure shows data for men and women combined on CHD prevalence in the group of persons with nonhigh uACR and the group of persons with high uACR. With age and indices of body mass (Table 3). Prevalence of high uACR without microalbuminuria was significantly associated with age, nonfat mass, and urinary creatinine excretion but not with weight and fat mass. The association was positive for age and negative for nonfat mass and urinary creatinine excretion. Findings were similar in analyses separate by gender: high uACR without microalbuminuria was associated in men and women directly with age (OR for +5.6 years =1.23 and 1.66, respectively; P=0.205 and 0.002, respectively), inversely with nonfat mass (OR for +10.0 kg =0.56 and 0.82, respectively; P=0.021 and 0.037, respectively) and urinary creatinine excretion (OR for +0.44 mg/min =0.07 and 0.01, respectively; P<0.001). Findings were similar also in analyses limited to hypertensive subjects: high uACR without microalbuminuria was associated directly with age (OR for +5.6 years =1.42; P=0.042) and inversely with nonfat mass (OR for +10.0 kg =0.82; P=0.088) and urinary creatinine excretion (OR for +0.44 mg/min =0.09; P<0.001).

A multivariate logistic analysis was done to assess whether the association of high uACR without microalbuminuria with age and nonfat mass was independent of urinary creatinine excretion (index of muscular mass). In the logistic model with age, nonfat mass, and urinary creatinine excretion included together as independent variables (men and women combined, whole cohort), high uACR without microalbuminuria was associated with urinary creatinine excretion (OR for +0.44 mg/min =0.03; P<0.001) but not with nonfat mass and age (P>0.4).

Relation of uACR to CHD

Differences by Level of uAE

The combination of high uACR with normal uAE and microalbuminuria by the level of uACR. The overall accuracy of uACR for the prediction of uAE was 93.8%. The negative predictive power of uACR was high (98.9%), because there was a substantial agreement for definitions of nonhigh uACR and normal uAE. The positive predictive power of uACR was much more prevalent than microalbuminuria (P<0.001 by McNemar test). The positive predictive power of uACR was similarly low in men and women (39.4% and 37.5%, respectively), as well as in analysis limited to hypertensive subjects (44.9%).

High uACR Without Microalbuminuria

Prevalence and Correlates in the Population

Relation of high uACR without microalbuminuria to urine albumin excretion (OR for 5.6 years =1.42; P=0.042) and inversely with nonfat mass (OR for +10.0 kg =0.82; P=0.088) and urinary creatinine excretion (OR for +0.44 mg/min =0.09; P<0.001).

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minuria. CHD prevalence was significantly higher in the high uACR group than in the nonhigh uACR group. Findings were similar for myocardial infarction (prevalence in high uACR group than in the nonhigh uACR group. Findings were similar in analyses by gender and fat mass.

The relation between nonfat mass and uAE in persons with high uACR was additionally investigated with use of nonfat mass tertiles. To control for the effect of gender on nonfat mass (shown in Table 1), cutoff points of tertiles were defined by analysis of nonfat mass distribution separately in men and women with high uACR. Table 5 shows that, among persons with high uACR, nonfat mass was linearly related to uAE (both prevalence of normal uAE and mean uAE), urinary creatinine excretion, and CHD in the absence of significant differences for gender and age. The relation of nonfat mass to CHD among persons with high uACR was explained by the confounding of uAE, because it was significant in univariate analysis (OR of CHD for +10 kg in nonfat mass, 2.24; 95% CI, 0.71 to 2.01) but not with control for uAE (OR of CHD for +10 kg in nonfat mass, 1.19; P=0.500, 95% CI, 0.71 to 2.01).

Discussion

The study reports new findings on the confounding because of the use of the uACR for assessment of microalbuminuria. First, the prevalence of microalbuminuria was overestimated with use of uACR, because ~60% of persons with high uACR do not have microalbuminuria. Second, persons with high uACR but without microalbuminuria did not have the excess of CHD prevalence typical of persons with microalbuminuria. Third, the combination of high uACR with normal uAE was associated with low nonfat mass or low muscular mass in analyses for the whole population sample and in analyses limited to persons with high uACR. Fourth, in

Analyses for Persons With High uACR

Differences by Level of uAE and by Nonfat Mass

Table 4 shows gender, age, and indices of body mass in the subgroup with high uACR (n=138) divided in the subgroups without microalbuminuria and with microalbuminuria. In comparison to the subgroup with microalbuminuria, the subgroup without microalbuminuria differed for higher age (difference with borderline significance), lower weight, lower nonfat mass, and lower urinary creatinine excretion but not for gender and fat mass.

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persons with low nonfat mass, high uACR reflected low urinary creatinine excretion rather than microalbuminuria and vascular disease.

Various methodological limitations could have affected the results of the study. The errors in urine collection precision, certainly frequent in a population-based study, should have diluted the results for uAE but not those for uACR, because the uACR calculation is independent of duration and volume of urine collection. Thus, because of this limitation, the results might underestimate the strength of the association between high uAE and CHD but not between high uACR and CHD. The use of a single urine sample likely caused errors in the classification of normal/high values because of daily variability in urinary albumin. This misclassification should have similarly influenced the results for uAE and uACR, because these 2 indices were measured in the same urine sample. The same should be true for the misclassification attributed to absence of urinalysis that could be of help for definition of persons with high urinary albumin secondary to urinary tract infection. The exclusion from analysis of data for other vascular diseases should have had only a minor role, unless urinary albumin and urinary creatinine (ie, muscular mass) were associated with those diseases differently than CHD. The use of skinfold data and of urinary creatinine could have caused an inaccurate assessment of muscular mass, although the finding of an independent relation between nonfat mass and urinary creatinine is against this possibility. A different preexamination mortality between persons with low and high muscular mass could have confounded some of the results. Finally, the cross-sectional design of the analysis did not exclude the possibility of changes in urine composition secondary to CHD, a point that was behind the aims of the study yet was important for the comprehension of the mechanisms underlying the association urinary albumin and CHD.

Taken together, study results indicate that interindividual differences in muscular mass substantially influence the value of the uACR via urinary creatinine excretion. Because of this influence, persons with low muscular mass often have the moderate uACR elevation used for the definition of microalbuminuria in the absence of a true elevation in absolute uAE. Thus, the uACR has a low predictive power for the definition of microalbuminuria implying the overestimation of the true prevalence of microalbuminuria in persons with low urinary creatinine because of low muscular mass. The finding that the group of persons with high uACR and low muscular mass was without an excess of CHD prevalence additionally supports this interpretation, because present and previous data consistently show an independent association between microalbuminuria and CHD. Within the middle-age sample of the Gubbio Population Study, the overestimation of microalbuminuria because of low urinary creatinine was found in 60% of persons with high uACR. Muscular mass and urinary creatinine excretion undergo parallel reductions during aging. Thus, a reasonable inference is that the frequency of the overestimation of microalbuminuria could progressively increase from young to older ages. The finding in this study of a positive relationship between age and the prevalence of overestimation of microalbuminuria supports this possibility. At variance with the low value of the positive predictive power, uACR appears to have a high negative predictive power, because a person with nonhigh uACR was unlikely to have microalbuminuria.

Perspectives

A practical implication of the study is that low muscle mass is an important confounder in the use of uACR as marker of microalbuminuria and cardiovascular disease in the population. Physicians should know that in persons with low muscular mass, a high uACR may be because of low urinary creatinine excretion rather than high uAE and may not be associated with vascular disease. The strong cross-sectional association between microalbuminuria and CHD in the middle-age population might explain, at least in part, the predictive power of microalbuminuria for the incidence of cardiovascular disease, because the presence of CHD is, per se, a predictor of cardiovascular events.

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References


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