Direct, Progressive Association of Cardiovascular Risk Factors With Incident Proteinuria

Results From the Korea Medical Insurance Corporation (KMIC) Study

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Background: Proteinuria is a major risk factor for the progression of kidney disease and the development of cardiovascular disease. Little is known, however, about risk factors for incident proteinuria.

Methods: We conducted a 10-year prospective cohort study of 104,523 Korean men and 52,854 women, aged 35 to 59 years, who attended Korea Medical Insurance Corporation health examinations and who did not have proteinuria at baseline. Incident proteinuria was assessed at biennial examinations during the next 10 years. We performed Cox proportional hazards analyses.

Results: During 10 years of follow-up, proteinuria developed in 3,951 men (3.8%) and 1,527 women (2.9%). The adjusted relative risk (RR) of proteinuria associated with diabetes was 3.27 (95% confidence interval [CI], 2.98-3.58) in men and 2.60 (95% CI, 1.98-3.43) in women; with body mass index (calculated as weight in kilograms divided by the square of height in meters), it was 1.43 (95% CI, 1.35-1.50) in men and 1.45 (95% CI, 1.35-1.55) in women per 5-U increment. Compared with subjects with serum cholesterol levels of less than 200 mg/dL (<5.18 mmol/L), the adjusted RRs associated with serum cholesterol levels of 200 to 239 mg/dL (5.18-6.19 mmol/L) and 240 mg/dL or more (≥6.22 mmol/L) were 1.13 (95% CI, 1.05-1.21) and 1.40 (95% CI, 1.27-1.54), respectively, in men and 1.14 (95% CI, 1.01-1.28) and 1.22 (95% CI, 1.00-1.37), respectively, in women. Persons with stages 1 and 2 hypertension had a greater adjusted RR of incident proteinuria compared with those with normal blood pressure (1.62 [95% CI, 1.47-1.79] and 2.06 [95% CI, 1.81-2.34], respectively, in men and 1.37 [95% CI, 1.14-1.65] and 2.10 [95% CI, 1.59-2.76], respectively, in women).

Conclusions: Fasting glucose and cholesterol levels, body mass index, and blood pressure were direct and independent predictors of incident proteinuria in Korean adults. These associations were present even at low levels of exposure, emphasizing the importance of early detection and management of these modifiable risk factors.

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Medical Insurance Corporation covered civil servants, private teachers, and their dependents. All insured workers and dependents were required to participate in biennial medical examinations performed by KMIC. In 1990 and 1992, 94.5% and 94.4%, respectively, completed biennial examinations. The cohort in the KMIC study is a systematic random sample of 115,695 men and 67,939 women, aged 35 to 59 years. Detailed characteristics of this cohort have been reported previously. Of the 183,634 original study enrollees, the 26,257 (14.3%) with incomplete data at baseline on proteinuria or any of the CVD risk factors studied (blood pressure, serum cholesterol and fasting blood glucose levels, body mass index [BMI], and smoking status) or with prevalent proteinuria were excluded, resulting in a final sample size of 157,377 (104,523 men and 52,854 women).

**DATA COLLECTION**

In 1990, initial visits and physical examinations were conducted following a standardized protocol at 416 hospitals. Subsequently, biennial examinations were conducted. In 1992, participants returned for repeated laboratory measurements and were asked to describe their current levels of physical activity, smoking, alcohol consumption, treatment of hypertension and diabetes, and medical history. Information on treatment for hypercholesterolemia was not collected. The 1990 and 1992 biennial medical examinations included measurements of weight, height, fasting serum levels of glucose and total cholesterol, and semiquantitative dipstick testing of urine for protein. Alcohol use at baseline was assessed by the question, “Do you drink alcohol regularly?” Physical activity was assessed by the question, “Do you exercise regularly?”

Blood pressure was measured in the seated position using a mercury sphygmomanometer or automatic (oscillometric) manometer. In the case of manual manometers, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured as the first and fifth Korotkoff sounds, respectively. Body mass index was calculated as the weight in kilograms divided by the square of height in meters.

Urine protein level was determined at each visit by results of a single urine dipstick semiquantitative analysis (Multistix; Ames Division of Miles Laboratory Inc, Elkhart, Ind). Dipstick results of 1+ and 2+ corresponded to protein levels of about 300 and 1000 mg/L, respectively. Reported specificity was 97.4% and sensitivity was 46.0%. Rates of false-negative findings were small (2.6%), whereas higher rates of false-negative findings were present at urine protein levels of 200 to 1000 mg/L, resulting in the potential for underdiagnosis of proteinuria. Dipstick urinalysis was performed on fresh, midstream urine samples collected in the morning. The results of the urine test were based on a color scale that quantified proteinuria as absent, trace, 1+, 2+, 3+, and 4+. Proteinuria was defined as a dipstick finding of 1+ or greater.

**VISIT SCHEDULE**

The percentages of participants who were examined at the 1994, 1996, 1998, and 2000-2002 biennial examinations were 95.7%, 94.3%, 92.0%, and 94.8%. Dipstick urinalysis was included at each follow-up visit. Among participants receiving an evaluation of urine protein level at baseline, 95.2% had at least 1 follow-up assessment of urine protein level, 87.9% had 2, 76.6% had 3, and 64.7% had 4.

**INDEPENDENT PREDICTORS OF INCIDENT PROTEINURIA**

We considered participants to have diabetes if they had a fasting glucose level of 126 mg/dL or more (≥7.0 mmol/L) or if they were taking medications for the treatment of diabetes. We defined hypercholesterolemia according to the National Cholesterol Education Program guidelines (desirable, total serum cholesterol level of < 200 mg/dL [< 5.18 mmol/L]; borderline-high, total serum cholesterol level of 200-239 mg/dL [5.18-6.19 mmol/L]; and high, total serum cholesterol level of ≥ 240 mg/dL [≥ 6.22 mmol/L]). We categorized blood pressure level according to the guidelines of the Seventh Joint National Committee for the Detection, Evaluation, and Treatment of High Blood Pressure (normal, SBP of < 120 and DBP of < 80 mm Hg; prehypertension, SBP of 120-139 mm Hg or DBP of 80-89 mm Hg; stage 1 hypertension, SBP of 140-159 or DBP of 90-99 mm Hg; and stage 2 hypertension, SBP of ≥ 160 or DBP of ≥ 100 mm Hg). To reduce measurement error, the mean of the values obtained in 1990 and 1992 was used for estimating baseline fasting glucose level, weight, height, total cholesterol level, and blood pressure. We classified participants as current smokers, ex-smokers, or nonsmokers. Assessments of these variables made at baseline were used in adjusted models.

**STANDARDIZED ANALYSIS**

The primary outcome was a positive finding for proteinuria using a urine dipstick test at any of the 4 follow-up visits. We used Cox proportional hazards regression to ascertain the independent contribution of potential risk factors stratified by sex. We added all potential predictors of proteinuria into the Cox models simultaneously to assess the independent relationship with incident proteinuria. In our primary analysis, we used standard diagnostic criteria for each risk factor. In dose-response analyses, we further divided risk factors (ie, BMI in 1-U increments, SBP in 10-mm-Hg increments, and fasting glucose in 10-mg/dL [0.6-mmol/L] increments). Age-adjusted incident proteinuria by BMI, total cholesterol level, SBP, and fasting glucose level were calculated to the age distribution of the 1995 South Korean national population. All analyses were stratified by sex. All analyses were conducted using SAS statistical software, version 8.0 (SAS Institute Inc, Cary, NC). A P value of less than .05 was considered statistically significant.

**RESULTS**

**POPULATION CHARACTERISTICS**

Baseline characteristics of the 157,377 persons are presented in Table 1. The mean (SD) age was 45.0 (6.7) years in men and 42.5 (6.2) years in women. Among men and women, 4.3% and 1.2%, respectively, had diabetes; 8.5% and 6.7%, respectively, had a total cholesterol level of 240 mg/dL or more (≥6.22 mmol/L); 27.5% and 10.2%, respectively, had hypertension; and 1.6% and 1.2%, respectively, reported treatment for hypertension. Cigarette smoking was highly prevalent in men (57.6%) but uncommon in women (0.4%).

**INDEPENDENT PREDICTORS OF INCIDENT PROTEINURIA**

During 10 years of follow-up, proteinuria developed in 3951 men (3.8%) and 1527 women (2.9%). Men and women with diabetes had relative risks (RRs) of incident proteinuria of 3.27 (95% confidence interval [CI], 2.98-3.58; P<.001) and 2.60 (95% CI, 1.98-3.43; P<.001), respec-
tively, compared with participants without diabetes (Table 2). In nondiabetic participants at baseline, the RR for incident proteinuria increased with increased fasting glucose level across ranges of glucose levels without an apparent threshold of increased risk (Table 3). Each 5-U increase in BMI was associated with an RR of incident proteinuria of 1.43 (95% CI, 1.35-1.50; P < .001) among men and 1.45 (95% CI, 1.35-1.55; P < .001) among women. The RR for each unit of increase in BMI across the range of BMIs was 1.08 (95% CI, 1.06-1.09) for men and 1.09 (95% CI, 1.07-1.12) for women.

Compared with participants with a cholesterol level of less than 200 mg/dL (< 5.18 mmol/L), men with cholesterol levels of 200 to 239 mg/dL (5.18-6.19 mmol/L) and 240 mg/dL or more (> 6.22 mmol/L) had RRs of proteinuria of 1.13 (95% CI, 1.05-1.21; P < .001) and 1.40 (95% CI, 1.27-1.54; P < .001), respectively. A similar trend was present for women, with corresponding RRs of 1.14 (95% CI, 1.01-1.38; P = .01) and 1.22 (95% CI, 1.00-1.37; P = .05), respectively. Men with stages 1 and 2 hypertension had RRs of development of proteinuria of 1.62 (95% CI, 1.47-1.79; P < .001) and 2.06 (95% CI, 1.81-2.34; P < .001), respectively, compared with normotensive men. The corresponding RRs for women were 1.37 (95% CI, 1.14-1.65; P < .001) and 2.10 (95% CI, 1.59-2.76; P < .001), respectively. Smoking did not predict incident proteinuria in men or women.

The relation of fasting blood glucose level, BMI, total cholesterol level, and SBP with incident proteinuria was direct and progressive (Figure) without an apparent threshold. Furthermore, increases in proteinuria incidence were present at levels below the standard clinical diagnostic criteria.

### COMMENT

In this cohort study of middle-aged Korean adults, there were direct, progressive dose-response relationships of fasting blood glucose levels, BMI, total cholesterol level, and blood pressure with incident proteinuria. For fasting serum glucose level and BMI, statistically significant associations with incident proteinuria were evident at low levels of exposure. This observation is most striking for serum glucose level, for which increased risk occurs at levels of serum glucose well below those classified as diabetes based on current diagnostic criteria.25-27

The presence of a threshold effect of serum glucose level on the progression of CKD has been debated in studies of persons with diabetes. Prospective observational studies have documented that diabetes and hypertension are major risk factors for progression of CKD and the incidence of end-stage renal disease.28-30 However, few studies have examined longitudinal associations of serum glucose level and blood pressure with the development of incident proteinuria in general populations and at levels that are below the diagnostic thresholds (ie, SBP of > 140 mm Hg or fasting serum glucose level of > 125 mg/dL [> 6.9 mmol/L]). Our data indicate that the incidence of proteinuria is not associated with conventional thresholds of serum glucose level or SBP that define diabetes or hypertension, but that it is associated with a progressive graded risk of proteinuria across levels of fasting serum glucose and blood pressure.31-33

Cross-sectional and longitudinal data from large epidemiological studies support our findings of a positive association between BMI and proteinuria as well as an association between body fat distribution (ie, central fat distribution) and proteinuria.22,34 Proposed mechanisms for the relation between body fat and the presence or development of proteinuria include hyperinsulinemia causing direct glomerular damage or mediation through hyperglycemic effects on glomerular hemodynamics increasing glomerular pressure.35,36

Our findings of an association between serum cholesterol level and incident proteinuria are supported by cross-sectional and longitudinal studies demonstrating associations between lipid abnormalities and progressive CKD. Secondary analyses of statin trials provide indirect support. Specifically, some recent trials have demonstrated that statin therapy reduces urinary protein...
excretion and slows progression of CKD.\textsuperscript{37-39} Whether proteinuria reduction with statin therapy is due to reduction of lipid levels or the reported pleotropic effects of statins is unknown.

The lack of association between smoking and proteinuria is somewhat surprising, given a preponderance of evidence implicating smoking as a major risk factor for the development of CVD outcomes.\textsuperscript{40-43} However, our findings are supported by a prospective epidemiological study in Japan.\textsuperscript{22} Results of prior cross-sectional studies of the association between smoking and albuminuria among persons in the general population are inconsistent.\textsuperscript{22,44,45}

Body mass index appears to be an independent risk factor for incident proteinuria in this relatively lean population, despite adjustment for SBP, diabetes, and hypercholesterolemia. A direct effect of BMI on proteinuria, mediated through other mechanisms such as glomerular hyperfiltration, is plausible.

Our results extend existing evidence of a common link between CVD risk factors and incident proteinuria and provide additional strong evidence in support of early identification and appropriate management of these risk factors.\textsuperscript{36-48} Our findings regarding incidence of proteinuria at low levels of fasting serum glucose, BMI, total cholesterol, and blood pressure suggest that attainment of lower goals for these clinical measures might have a substantial impact on the incidence of proteinuria.

Limitations of this analysis deserve mention. First, dipstick urinalysis has imperfect sensitivity and specificity, particularly in women and older persons, in whom the number of false-positive results can be high owing to menstruation or comorbid illness.\textsuperscript{49} Second, the body habits and dietary patterns of Korean adults differ from those of Western populations, potentially affecting the distribution of risk factors and the magnitude of risk relationships. Still, as for other chronic diseases, risk relationships tend to be similar even if absolute risks differ across populations.\textsuperscript{50} Notwithstanding these limitations, our study finding that CVD risk factors are prospectively associated with incident proteinuria is consistent with the

### Table 2. Risk Factors Associated With Incident Proteinuria*

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR (95% CI)</th>
<th>P Value</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 5-y increments</td>
<td>1.01 (0.97-1.13)</td>
<td>.12</td>
<td>1.01 (0.99-1.10)</td>
<td>.10</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>3.27 (2.98-3.58)</td>
<td>&lt;.001</td>
<td>2.60 (1.98-3.43)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI per 5-U increment</td>
<td>1.43 (1.35-1.50)</td>
<td>&lt;.001</td>
<td>1.45 (1.35-1.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>200-239</td>
<td>1.13 (1.05-1.21)</td>
<td>&lt;.001</td>
<td>1.14 (1.01-1.38)</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;240</td>
<td>1.40 (1.27-1.54)</td>
<td>&lt;.001</td>
<td>1.22 (1.00-1.37)</td>
<td>.052</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Prehypertension</td>
<td>1.17 (1.07-1.28)</td>
<td>&lt;.001</td>
<td>1.24 (1.00-1.26)</td>
<td>.04</td>
</tr>
<tr>
<td>Stage 1</td>
<td>1.62 (1.47-1.79)</td>
<td>&lt;.001</td>
<td>1.37 (1.14-1.65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2.06 (1.81-2.34)</td>
<td>&lt;.001</td>
<td>2.10 (1.59-2.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.00 (Reference)</td>
<td></td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0.97 (0.88-1.06)</td>
<td>.47</td>
<td>0.97 (0.46-2.03)</td>
<td>.97</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.03 (0.95-1.11)</td>
<td>.51</td>
<td>1.20 (0.57-2.53)</td>
<td>.63</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; RR, relative risk. 

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

### Table 3. Relative Risk of Incident Proteinuria by Fasting Blood Glucose Level Stratified by Sex After Excluding All Diabetics at Baseline*

<table>
<thead>
<tr>
<th>Fasting Blood Glucose Level, mg/dL</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>No. With Proteinuria</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>&lt;90</td>
<td>53405</td>
<td>1605</td>
</tr>
<tr>
<td>90-99</td>
<td>29086</td>
<td>1064</td>
</tr>
<tr>
<td>100-109</td>
<td>12236</td>
<td>466</td>
</tr>
<tr>
<td>110-119</td>
<td>3913</td>
<td>205</td>
</tr>
<tr>
<td>120-129</td>
<td>978</td>
<td>55</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; RR, relative risk. 

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

*Proportional hazards models for men and women are adjusted for body mass index, total cholesterol level, and systolic blood pressure.

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hypothesis that common pathways underlie the pathogenesis of CVD and proteinuria and early manifestation of kidney disease.

CONCLUSIONS

Results from the KMIC study document that fasting blood glucose level, BMI, cholesterol level, and blood pressure in men and women are independent predictors of incident proteinuria. Furthermore, risk increases in a progressive, dose-response manner at levels below currently accepted clinical risk factor thresholds for the prevention of CVD. Early detection and management of these modifiable risk factors may prevent CVD and proteinuria, a risk factor for kidney disease.

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