Proteinuria and Risk for Stroke and Coronary Heart Disease During 27 Years of Follow-up

The Honolulu Heart Program

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Background: Urinary protein excretion has been linked to coronary heart disease (CHD); the relationship to stroke is less clear. We assessed whether urine dipstick screening for protein predicted stroke and CHD in the Honolulu Heart Program cohort.

Methods: Prospective, observational study of 6252 Japanese American men in Honolulu aged 45 to 68 years. Proteinuria was detected by means of urine dipstick screening during the first and third examinations. Subjects were classified as having no proteinuria if results were negative at both examinations, transient proteinuria if results were positive at 1 examination, and persistent proteinuria if results were positive at both examinations. Relative risk was derived using those subjects with no proteinuria as the reference. Outcomes were assessed through 27 years.

Results: No proteinuria was found in 92.8% of subjects, transient proteinuria in 6.1%, and persistent proteinuria in 1.1%. The age-adjusted incident stroke rates were 3.7, 7.3, and 11.8 per 1000 person-years in subjects with no, transient, or persistent proteinuria, respectively (P<.001). Age-adjusted rates of incident CHD were 9.4, 15.8, and 35.2 events per 1000 person-years, respectively (P<.001). Using Cox proportional hazards models, adjusting for age, body mass index, physical activity, smoking status, cholesterol level, presence of hypertension or diabetes mellitus, and alcohol consumption, the relative risk for 27-year incident stroke was 1.66 (95% confidence interval, 1.21-2.30; P=.002) with transient proteinuria and 2.84 (95% confidence interval, 1.51-5.34; P=.001) with persistent proteinuria, and relative risk for 27-year incident CHD was 1.48 (95% confidence interval, 1.19-1.83; P<.001) with transient proteinuria and 3.72 (95% confidence interval, 2.62-5.27; P<.001) with persistent proteinuria.

Conclusion: Proteinuria detected at urine dipstick screening independently predicted increased risk for incident stroke and incident CHD over 27 years in this cohort.

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CHD and stroke. The study details are described elsewhere. In brief, participants, aged 45 to 68 years at the first examination in 1965 to 1968, were followed up by means of serial examinations and comprehensive surveillance of hospital records, death certificates, and autopsy reports. Follow-up has been nearly complete through 27 years. Study protocols were established in accord with guidelines approved by relevant institutional review committees. Each subject provided informed consent.

Baseline data, including history, findings at physical examination, and laboratory data, were collected during the first examination (1965-1968; n=8006) and the third examination (1971-1974; n=6860). Urine protein screening using simple dipstick was performed. We excluded subjects with prevalent stroke or CHD at these examinations and those for whom urine dipstick test results were unavailable from both examinations. After exclusions, data for 6252 men were included in the analysis.

For each subject, data obtained at examination 3 were used as covariates in our Cox proportional hazards models and included age, body mass index (calculated as weight in kilograms divided by the square of height in meters), alcohol consumption (ounces per month), presence of hypertension or diabetes mellitus, and cigarette smoking status. Hypertension was defined as systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher, or there was documented use of antihypertensive agents. Diabetes was defined as use of insulin or oral hypoglycemic medications, or if there was a documented history. Physical activity index, another covariate we controlled for in our Cox proportional hazards models, was recorded at examination 1 and was not measured at examination 3. It was based on 5 levels of activity (basal, sedentary, slight, moderate, and heavy) that would describe typical levels of exertion over 24 hours. For each activity level, the total hours spent at that level were multiplied by a weighting factor. The higher levels indicated a more active lifestyle.

Urine screening was performed at 2 separate examinations 6 years apart. Subjects were assigned to 1 of the following 3 groups for the analysis: those with no proteinuria, those with transient proteinuria (positive results at only 1 screening), and those with persistent proteinuria (positive results at both screenings). Information on preexisting renal disease or conditions associated with potentially reversible proteinuric states were unavailable.

Outcome events occurring after the third examination were identified through the period ending December 31, 1998 (27 years). Incident stroke occurred if a new neurologic deficit developed without prolonged loss of consciousness, when there was evidence of nuchal rigidity or bloody cerebrospinal fluid identified by an atraumatic lumbar puncture, and when there was absence of fever or pronounced leukocytosis. In addition, subarachnoid hemorrhage was excluded from our stroke diagnosis. Each diagnosis was reviewed and confirmed by a study neurologist and by the HHP Morbidity and Mortality Review Committee. The diagnostic criteria for stroke evolved to include computed tomographic results as the technology became clinically available in Hawaii. Other criteria included information obtained at surgery or autopsy. Transient ischemic attacks and other possible stroke scenarios, in which the deficit resolved in less than 2 weeks or could be attributed to other causes, were excluded because of diagnostic uncertainty.

Incident CHD was defined as an acute or temporally associated change on the electrocardiogram or in measured enzyme levels suggesting myocardial infarction, sudden death within an hour of the observation that could not be attributed to another cause and with typical features of angina, pathologic findings of acute infarct at autopsy or surgery, or compensated heart failure leading to hospitalization or death. Each event was confirmed by a study cardiologist and reviewed by the HHP Morbidity and Mortality Review Committee.

For all analyses, P<.05 was deemed statistically significant. Univariate analyses for comparisons of means of each risk factor within the proteinuria groups were performed using χ² analysis for categorical variables or analysis of variance for continuous variables. Age-adjusted incidence rates of stroke and CHD were calculated per 1000 person-years of follow-up. Kaplan-Meier 27-year disease-free survival curves were plotted for each proteinuria group within the cohort.

Multivariate analyses were performed using Cox proportional hazards models to calculate risk for incident stroke and CHD by proteinuria group, using participants with no proteinuria as the reference group. The models were adjusted for age, the presence of diabetes or hypertension, body mass index, alcohol consumption, total cholesterol level, physical activity index, and smoking status at baseline. All reported P values were based on 2-sided tests of significance. To address the significant effect of diabetes on these relationships, we performed separate analyses using stratified Cox models dichotomizing the cohort into 2 groups: those with diabetes at any examination and those without diabetes.

**RESULTS**

After exclusions, our study population included 6252 participants who were followed up through 27 years for the development of incident stroke and then the analysis was repeated for the development of incident CHD. Baseline characteristics by proteinuria group are given in Table 1. Participants with proteinuria were generally older, had greater body mass index, and were more likely to have diabetes or hypertension. Among those with proteinuria, smoking was more common in the group with transient proteinuria. We found no significant differences in the prevalence of alcohol consumption, total cholesterol level, or physical activity between the groups.

**PROTEINURIA**

Figure 1 shows the percent prevalence of transient and persistent proteinuria by 5-year age group. Although there was a notable decrease in the percentage of participants in the oldest 5-year age group with persistent proteinuria, the overall trend observed was a gradual increase in the percentage of subjects with either transient or persistent proteinuria as participant age increased (P<.001).

**OUTCOMES**

In our outcomes analysis, we present both the absolute number of events and the age-adjusted events per 1000 person-years for each group (Table 2). Our age-adjusted incident stroke rate was 3.7, 7.3, and 11.8 events per 1000 person-years for subjects with no proteinuria, transient proteinuria, and persistent proteinuria, respectively. For incident CHD, the event rate was 9.4, 15.8, and 35.2 per 1000 person-years, respectively.
Because the HHP cohort was prospectively observed for these outcomes, we were also able to generate the participants’ disease-free Kaplan-Meier survival curves. These curves illustrate that increasing presence of urinary protein at dipstick screening correlates with decreased disease-free survival for both incident stroke (Figure 2A) and CHD (Figure 2B).

The independent association of either transient or persistent proteinuria to our incident outcomes was assessed by our Cox proportional hazards model. After adjusting for confounders, the relative risk (RR) for 27-year incident stroke and CHD was greatest for the group with persistent proteinuria. While subjects with transient proteinuria were at slightly less risk, they were still more likely to have either outcome than were those with no proteinuria (Figure 3).

For subjects without diabetes, after adjusting for age, body mass index, physical activity, smoking status, cholesterol level, hypertension, and alcohol consumption, the RR for incident stroke was 1.98 (95% CI, 1.31-3.00) with transient proteinuria and 2.07 (95% CI, 0.85-5.05) with persistent proteinuria. For CHD, the RR was 1.51 (95% CI, 1.12-2.03) with transient proteinuria and 3.20 (95% CI, 2.02-5.08) with persistent proteinuria. Again, we used subjects with no proteinuria as our reference.

For subjects with diabetes, adjusting for the same confounders, we found that the RR of incident stroke was 1.40 (95% CI, 0.82-2.37) with transient proteinuria and 5.42 (95% CI, 2.18-13.48) with persistent proteinuria. For CHD, the RR was 1.52 (95% CI, 1.10-2.10) with transient proteinuria and 5.14 (95% CI, 2.86-9.23) with persistent proteinuria.

**Table 1. Baseline Characteristics and Percentage of Prevalence Among Participants Within Each Assigned Proteinuria Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Transient</th>
<th>Transient</th>
<th>Persistent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>59.9 (0.1)</td>
<td>61.1 (0.3)</td>
<td>61.4 (0.7)</td>
<td>.03</td>
</tr>
<tr>
<td>Current smoker,‡ % of participants within each group assignment†</td>
<td>34.2</td>
<td>44.1</td>
<td>41.2</td>
<td>.003</td>
</tr>
<tr>
<td>Alcohol, oz/mo†</td>
<td>14.0 (0.3)</td>
<td>14.3 (1.3)</td>
<td>13.6 (3.1)</td>
<td>.09</td>
</tr>
<tr>
<td>BMI†</td>
<td>23.58 (0.04)</td>
<td>24.17 (0.16)</td>
<td>24.63 (0.37)</td>
<td>.005</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL†</td>
<td>215.5 (0.5)</td>
<td>218.0 (1.9)</td>
<td>218.2 (4.4)</td>
<td>.55</td>
</tr>
<tr>
<td>Diabetes mellitus, % of cohort‡</td>
<td>14.3</td>
<td>23.3</td>
<td>29.0</td>
<td>.001</td>
</tr>
<tr>
<td>Hypertension, % of cohort‡</td>
<td>50.6</td>
<td>62.4</td>
<td>74.9</td>
<td>.001</td>
</tr>
<tr>
<td>Physical activity index‡</td>
<td>32.9 (0.1)</td>
<td>32.7 (0.2)</td>
<td>32.7 (0.6)</td>
<td>.63</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

*Calculations were performed using χ² for categorical variables and analysis of variance for continuous variables. All continuous variables are reported as mean (SE).

†Baseline characteristics from examination 3.

‡Baseline characteristic from examination 1.

**Table 2. Raw and Age-Adjusted Incidence Rates per 1000 Person-Years of Incident Stroke and Incident Coronary Heart Disease (CHD) by Proteinuria Group**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No</th>
<th>Transient</th>
<th>Persistent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>5802</td>
<td>381</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Incident stroke events</td>
<td>391</td>
<td>49</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted incidence rate of stroke per 1000 person-years</td>
<td>3.7</td>
<td>7.3</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Incident CHD events</td>
<td>1017</td>
<td>101</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted incidence rate of CHD per 1000 person-years</td>
<td>9.4</td>
<td>15.8</td>
<td>35.2</td>
<td></td>
</tr>
</tbody>
</table>

*For all of the outcomes, P<.001.
known major risk factors, including diabetes, and extends the previously reported relationship to CHD through almost 3 decades. These data reinforce the concept that proteinuria may be considered a major predictor for both outcomes.

There are some features in our report that are not found in previously published studies.6-23 First, we present outcomes on the relationship between proteinuria and stroke in a community-dwelling population in Hawaii. While our outcomes are consistent with data from Miettinen et al,27 who reported an incident relationship between proteinuria and stroke among a cohort in Finland, we report results stratified for the presence or absence of diabetes, further our findings extend this relationship through an additional 20 years of follow-up and in a cohort 2.5-fold larger.

The prevalence of persistent proteinuria in our cohort was 1.1%, which nicely correlates with the recent estimates of approximately 1% prevalence among the general US population.7 By evaluating for the presence of proteinuria with 2 different examinations, we were able to generate outcomes data in 2 different groups of participants, one with clearly prevalent proteinuria (persistent) and the other with either intermittent or incident proteinuria (transient). Among those with transient proteinuria, most were likely to have developed incident proteinuria in the interval between examinations. It is possible that there was an error in the screening, this is unlikely since only 7 members of the entire group initially tested positive then subsequently tested negative.

We determined the age-adjusted event rates per 1000 person-years for both outcomes among participants in each proteinuria group and observed an increased occurrence of incident stroke and CHD with the increased presence of proteinuria at dipstick screening (Table 2). This observed stepwise increase in events across each outcome group was statistically significant (P < .001) and a novel finding of our study. The stepwise relationship persisted after adjusting for the other confounders in our multivariate analyses.

The most unique aspect of our study is the method used to assess for proteinuria, that is, the standard urine dipstick test. While this may be considered a less sophisti-
ticated technique of identifying proteinuria, its ease of use and low cost seems to make it an ideal screening tool. Further, one potential implication of this article suggests that urine dipstick screening may facilitate early identification of individuals at highest risk for stroke or CHD. This early identification may allow early intervention and possibly improve outcomes.

Whereas the exact mechanism by which urinary protein excretion is associated with increased risk for stroke and CHD is unclear, it is likely multifactorial. One possible mechanism may be excessive protein reabsorption in the proximal tubule of the kidney, eliciting an inflammatory response. This inflammation may promote local and possibly systemic endothelial dysfunction. Alternatively, the presence of proteinuria may represent a surrogate marker of diffuse systemic vascular disease and may reflect the increased transvascular leak of a variety of proteins, including lipoproteins. While we recognize that significant work has been done to explain these complex interactions, a more thorough understanding is needed.

Our study has several limitations. This is an observational study; thus, cause and effect cannot be confirmed. Further, the HHP cohort constitutes a unique population of Japanese American men in Hawaii, and this may limit the generalization of our findings to other populations. In addition, the overall number of participants with proteinuria was small. This was particularly true for the number of participants with persistent proteinuria in the oldest age group.

Furthermore, we do not have data on the presence of preexisting kidney disease or long-term kidney-specific outcomes for the participants. Also, we were unable to observe the effects of various medications on the cohort because these details were not collected.

Using a simple urine dipstick screening method may lead to sampling errors. However, the accuracy of dipstick screening for proteinuria, reported by the Canadian Task Force on Preventive Health Care, is 95% to 99%. Nevertheless, there are factors that can lead to false-positive results, such as alkaline urine, gross blood in the urine, accidental introduction of detergents to the urine collection, and recent administration of intravenous contrast medium. Likewise, states that can cause functional proteinuria include fever, exercise, and postural or orthostatic proteinuria. It is unlikely that these were controlled for during the urine screening, thereby potentially resulting in misclassification. This effect would likely be minimized because subjects were grouped based on results from 2 separate urine screening tests performed 6 years apart.

We found that proteinuria independently predicts incident stroke and CHD among the participants of the HHP. Our report adds to previous work, with outcomes from 27 years of follow-up, and suggests that urine dipstick screening may be sufficient to identify individuals at increased risk for stroke or CHD. Future work should be directed at the mechanisms behind these relationships and at exploring our observations of the stepwise increased risk across our study groups.

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REFERENCES

and non-diabetic control subjects surviving the first 5 years after assessment. Diabetologia. 1993;36:1030-1036.