Pre-hypertension as a significant predictor of chronic kidney disease in a general population: the Ohasama Study

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Abstract
Background. Hypertension is associated with an increased risk of development of chronic kidney disease (CKD). However, it is unclear whether pre-hypertension is related to the incidence of CKD.

Methods. The incidence of CKD defined as positive proteinuria or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² was examined in 2150 inhabitants without pre-existing CKD from the general Japanese population. The association of blood pressure and CKD incidence was examined using a Cox regression model adjusted for age, sex, habitual smoking and drinking, obesity, history of cardiovascular disease, diabetes mellitus or hypercholesterolemia, eGFR at baseline, number of follow-up examinations and year of baseline examination. Participants were categorized according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

Results. Participants were categorized into normotension (n = 586, 27.3%), pre-hypertension (n = 815, 37.9%), Stage 1 hypertension (n = 386, 18.0%) and Stage 2 hypertension (n = 363, 16.9%). During a mean follow-up of 6.5 years (14 023 person-years), 461 incidences of CKD were recorded. Compared to normotension, adjusted hazard ratios of CKD were significantly higher for pre-hypertension (1.49, P < 0.003), Stage 1 (1.83, P < 0.001) and Stage 2 (2.55, P < 0.001) hypertension. The population-attributable fraction of pre-hypertension (12.1%) was considered to be compatible to that of Stage 1 (8.6%) and Stage 2 (14.9%) hypertension.

Conclusion. This was the first study to demonstrate that pre-hypertension was significantly associated with an increased risk of CKD and was one of the considerable causes of CKD in the general population.

Keywords: chronic kidney disease; epidemiology; population-attributable fraction; pre-hypertension; risk factors

Introduction

Pre-hypertension, defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) [1], is reported to be associated with a risk for developing hypertension [2] and is related to the morbidity and mortality of cardiovascular disease (CVD) [2, 3]. Therefore, identification of individuals with pre-hypertension is an important strategy to inhibit progression to hypertension and thereby reduce the risk of CVD in the general population.

The high prevalence of chronic kidney disease (CKD) is now considered a major public health issue. In fact, the number of patients with end-stage renal disease (ESRD) on chronic hemodialysis in 2008 exceeded 283 421 in Japan [4]. Both early detection and appropriate intervention during the initial stages of CKD are necessary for prevention of a further increase in the number of patients with ESRD. Hypertension is a critical risk factor for progression of CKD [3, 5, 6] and a predictor of development to ESRD [7]. On the other hand, in previous studies, it has not been definitely shown that pre-hypertension based on the JNC7 criteria is significantly associated with progression to CKD [8–10]; therefore, its relationship remains controversial.

In the present study, the risk of CKD was investigated among people with pre-hypertension, and the impact of the burden of pre-hypertension in the general population was examined.
Materials and methods

Design

The present study was based on longitudinal observation of individuals who had been participating in a survey on CVD in Ohasama, Iwate Prefecture, Japan. This project was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. All of the participants provided written informed consent. The socioeconomic and demographic characteristics of this region and the details of this project have been previously described [11].

Study cohort

In Japan, annual health check-ups are available for farmers, the self-employed, pensioners and dependents aged at least 40 years. Ohasama, a rural community, in 1992 had a total population of 7496, and 3076 residents were eligible for annual health check-ups. Among them, subjects who did not undergo the examinations at all from 1993 to 2007 (n = 549), those who did not provide an informed consent (n = 55) and those diagnosed with CKD including each of positive proteinuria (n = 91) and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (n = 231) at baseline were excluded. Thus, the number of subjects who were included in the present statistical analysis totaled 2150.

Measurement of eGFR and proteinuria

Serum creatinine (Scr) was measured using the Jaffé method during annual check-ups before 2002 and by the enzymatic method subsequently. Renal function was estimated by calculated glomerular filtration rate (GFR) using a modified Japanese equation based on inulin clearance as follows: eGFR (mL/min/1.73 m²) = 194 × (Scr in enzymatic method)−1.094 × age−0.283 × (× 0.739, if female) [12]. The following equation was used to convert the level of Scr from the Jaffé method to that for the enzymatic method (Scr in enzymatic method = Scr in Jaffé method × 0.2) [13]. Diagnosis of proteinuria was made using a urine dipstick test (Urohemabonix 5G08C; Bayer Medical, Tokyo, Japan). Positive proteinuria was considered to be present for a dipstick result of ≥ 1 + , corresponding to a urinary protein level > 30 mg/dL [14]. CKD was defined as positive proteinuria or eGFR < 60 mL/min/1.73 m².

Blood pressure measurement

Blood pressure (BP) was measured twice by nurses at local medical centers using a semi-automatic BP-measuring device (USM-700F; UEDA Electronic Works, Tokyo, Japan) based on the microphone method with subjects in a seated position after resting for at least 2 min. The average of the two readings was used in this analysis. The devices have been validated previously [15] and meet the criteria of the Association for the Advancement of Medical Instrumentation [16].

Diagnostic criteria for hypertension and BP category

Participants were categorized according to the JNC7 [1] as having normotension (systolic BP < 120 mmHg and diastolic BP < 80 mmHg), pre-hypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg), Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg) and Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg). Treated participants were categorized as having Stage 2 hypertension.

Data collection and diagnostic criteria on other variables

Information on smoking status, habitual drinking, use of anti-hypertensive medications at baseline, as well as a history of CVD, diabetes mellitus or hypercholesterolemia were verified on the basis of information recorded in medical charts at the Ohasama Hospital and a questionnaire administered during annual health check-ups as we described previously [17]. The history of CVD was derived from a disease of the circulatory system (ICD-10: I00-I99) or transient ischemia attack. Subjects treated with lipid-lowering drugs or displaying serum cholesterol levels ≥ 220 mg/dl were considered to have hypercholesterolemia. Subjects with fasting serum glucose levels ≥ 126 mg/dL or non-fasting glucose levels ≥ 200 mg/dL or who used insulin or oral anti-hyperglycemic agents were defined as having diabetes mellitus. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). The presence of obesity was diagnosed with BMI levels ≥ 25 kg/m².

Follow-up and outcomes

Primary outcomes were defined as the onset of CKD at the time of the annual check-up from 2002 to 2010. If a participant experienced more than one CKD event during follow-up, only the first outcome for the individual contributed to the outcome analysis. The date of onset of CKD was defined as the midpoint between the last date when the subjects did not have CKD and the first date when the subject was diagnosed with CKD. The follow-up period was defined as the number of days from the date of observation to the date of CKD diagnosis or to the date of the final check-up. Similarly, an eGFR < 60 mL/min/1.73 m² or an isolated positive proteinuria were analyzed as individual primary outcomes. Secondary outcomes were defined as a composite of CKD or death from all causes.

Statistical analysis

For statistical analysis, SAS software, version 9.1 (SAS Institute, Cary, NC) was used. Statistically significant differences were compared by means of one-way analysis of variance. The association between baseline BP and the incidence of CKD, eGFR < 60 mL/min/1.73 m² and positive proteinuria was examined using the Cox proportional hazard regression model adjusted for age, sex, habitual smoking and drinking, obesity, CVD, diabetes mellitus, hypercholesterolemia, anti-hypertensive treatment, eGFR at baseline, the number of follow-up examinations and year of baseline examination. In subgroup analysis, participants were stratified according to age (≥ 60, < 60 years), sex, number of follow-up examinations (≥ 3, < 3) and length of follow-up period (≥ 6, < 6 years).

The incidence rates of CKD were examined for participants among BP groups using Kaplan–Meier survival function estimates and the log-rank test. To evaluate the impact of pre-hypertension and hypertension on the onset of CKD, the adjusted population attributable fraction (adjusted PAF) was calculated as Pe × [adjusted hazard ratio (HR) − 1], in which Pe is the proportion of exposed subjects in each BP categories and adjusted HR is the multiple-adjusted HR for CKD in reference to normotension. The PAF is an index of how much of the scale of the disease burden in a population could be eliminated if the effects of certain causal factors were eliminated from the population [18, 19].

Results

Baseline subject characteristics

The 2150 study participants consisted of 1364 (63.4 %) women, 815 (37.9 %) patients with pre-hypertension, 386 (18.0 %) patients with Stage 1 hypertension and 363 (16.9 %) with Stage 2 hypertension which included 274 (12.7 %) patients who were treated with anti-hypertensive drugs. The overall mean value ± SD was 60.3 ± 9.6 years for age. Characteristics of the study population across BP groups are shown in Table 1. After conversion of the level of Scr from the Jaffe method to that for the enzymatic method, baseline Scr was 0.65 ± 0.12 mg/dL and eGFR was 82.3 ± 14.7 mL/min/1.73 m².

Follow-up and outcomes

The mean duration of follow-up was 6.5 ± 4.7 years (maximum 14.9 years). The numbers of follow-up visits were 1, 2, 3, 4 or 5 + in 480, 526, 206, 259 and 679 participants, respectively. Of the 2150 participants, the number of patients with onset of CKD was 461 subjects, which included solely an eGFR < 60 mL/min/1.73 m² in 360 (78.1 %) subjects, isolated positive proteinuria in 149 (32.3 %) subjects and both criteria in 48 (10.4 %) subjects. Additionally, a total of 290 deaths during the follow-up period were recorded and consisted of 54 (18.6 %), 96 (33.1 %) and 140 (48.3 %) subjects with...
normotension, pre-hypertension and hypertension, respectively. Kaplan–Meier curves for the cumulative incident of CKD are shown in Figure 1. There was a significant difference in the cumulative incidence of CKD between normal, pre-hypertension and hypertension categories (log-rank test, P < 0.001).

Risk factors associated with CKD

Independent association was investigated between the incidence of CKD and confounding factors in a multivariate model containing systolic and diastolic BP (Table 2). Significant determinants for the incidence of CKD were age, eGFR, systolic BP and diastolic BP. Associations between the incidence of eGFR < 60 mL/min/1.73 m² and confounding factors were similar to associations between confounding factors and the incidence of CKD (Supplemental Table S1). Significant determinants for the incidence of eGFR < 60 mL/min/1.73 m² were age, eGFR, smoking, systolic BP and diastolic BP.

Only systolic BP was a significant determinant of the incidence of proteinuria (HR 1.12 per 10 mmHg increase in systolic BP, P = 0.04) (Supplemental Table S2). On the other hand, in the model, if diastolic BP was added instead of systolic BP, age (HR 1.28 per 10 years of age, P = 0.03) and the use of anti-hypertensive medication (HR 1.52, P = 0.04) were significantly related to the incidence of proteinuria (Supplemental Table S2).

Adjusted HR and PAF of CKD for pre-hypertension and hypertension

Adjusted HR and adjusted PAF for CKD incidence in pre-hypertension and hypertension compared to normotension are demonstrated in Figure 2A. The HR of a composite end point of CKD or death from all causes in pre-hypertension and hypertension were evaluated and similar results were revealed (Figure 2B).

Discussion

The present study demonstrated that the risk for CKD in pre-hypertension was significantly higher compared to normotension in the general population. The PAF for CKD in pre-hypertension was comparable to that of Stage 1 and Stage 2 hypertension.

Table 1. Clinical characteristics in the three BP groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal (N = 586)</th>
<th>Pre-HT (N = 815)</th>
<th>HT-1 (N = 386)</th>
<th>HT-2 (N = 363)</th>
<th>P_VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.8 ± 10.5</td>
<td>59.8 ± 9.4c</td>
<td>62.4 ± 8.6c,d</td>
<td>64.8 ± 6.9c,d,e</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female, %</td>
<td>75.8</td>
<td>61.2c</td>
<td>51.3c,d</td>
<td>61.4c,d,e</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>8.2</td>
<td>11.4</td>
<td>12.2</td>
<td>9.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Current drinker, %</td>
<td>11.3</td>
<td>16.3</td>
<td>20.0e</td>
<td>21.5c</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.5 ± 3.0</td>
<td>23.5 ± 3.1c</td>
<td>24.1 ± 3.1c,d</td>
<td>24.2 ± 3.2c,d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of CVD, %</td>
<td>0.6</td>
<td>1.6</td>
<td>6.0</td>
<td>8.0c,d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>4.8</td>
<td>6.6</td>
<td>31.3c</td>
<td>38.6c,d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertensive treatment, %</td>
<td>19.6</td>
<td>25.9</td>
<td>0</td>
<td>75.5c,d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.63 ± 0.11</td>
<td>0.65 ± 0.13c</td>
<td>0.67 ± 0.12c,d</td>
<td>0.66 ± 0.12c</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>82.6 ± 14.6</td>
<td>83.6 ± 22.6</td>
<td>81.7 ± 13.7</td>
<td>79.4 ± 14.0c,d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No. of follow-up exams</td>
<td>3.6 ± 2.2</td>
<td>3.5 ± 2.1</td>
<td>2.9 ± 1.9c,d</td>
<td>3.3 ± 2.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Follow-up period, years</td>
<td>7.2 ± 5.0</td>
<td>6.8 ± 4.7</td>
<td>5.5 ± 4.3c,d</td>
<td>5.7 ± 4.6c,d</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>109.4 ± 7.6</td>
<td>129.3 ± 5.9c</td>
<td>146.2 ± 5.5c,d</td>
<td>143.1 ± 19.6c,d,</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>63.3 ± 7.1</td>
<td>73.1 ± 7.1c</td>
<td>81.4 ± 9.1c,d</td>
<td>78.3 ± 12.6c,d</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are expressed as percentage or mean ± SD. HT, hypertension; Normal, normotension; Pre-HT, pre-hypertension; Scr, serum creatinine.

Analysis of variance and χ² tests were used to compare continuous and categorical variables across BP groups, respectively.

bp < 0.05 for comparison used Scheffe’s multiple comparison test between each BP groups and normotension.

dP < 0.05 for comparison between each BP groups and pre-hypertension.

eP < 0.05 for comparison between each BP groups and Stage 1 hypertension.

Fig. 1. Kaplan–Meier curves for the cumulative incident of CKD for normotension, pre-hypertension (Pre-HT) and Stage 1 hypertension (HT-1) and Stage 2 hypertension (HT-2).
was no strong statistical significance [20, 21]. Independent significance was shown only in a younger population (mean age 37 ± 13 years) [22]. Concerning prospective studies of pre-hypertension and CKD in the general population, there have only been a few studies [8–10], all of which have failed to clearly demonstrate the prognostic significance of pre-hypertension for CKD. A study of 17 375 healthy volunteers from the general Viennese population showed an increased risk for CKD in pre-hypertension, but this was not statistically significant (P = 0.35) [8]. In a 12-year follow-up study of 8093 men, a systolic BP of 120–129 mmHg did not predict CKD [9]. In a prospective study of 23 534 subjects, normal or high-normal BP was also not significantly associated with the risk of CKD (P ≥ 0.07) [10]. Thus, the present study is the first report to demonstrate a significant association between individuals with pre-hypertension and the development of CKD in a general population. One of the reasons for the differences in the results of the present study compared to past studies is that participants in the present study were mainly elderly (mean age 60 years in this study versus 41–51 years in previous studies [8–10]). Elderly people are more susceptible to various stresses such as dehydration, chronic inflammation and malnutrition; therefore, there is a possibility that levels of eGFR in elderly participants might easily deteriorate. Secondly, the definition of CKD used in the present study was either positive proteinuria or eGFR < 60 mL/min/1.73 m², whereas decreased eGFR alone was used as the definition of CKD in previous studies [8, 9]. Thirdly, in statistical analysis, a Cox proportional hazard regression was used to examine the association between pre-hypertension and the risk of CKD. In previous studies, multivariate logistic regressions were performed [8, 9], but the censored subjects were not fully considered. These factors could have led to the novel significant association in the present study.

In the present study, participants were mainly elderly subjects. In the elderly, CKD is associated with clinical and subclinical vascular pathology, atherosclerosis [23, 24] and age-related decline in renal function (which may be a consequence of atherosclerosis). In morphological analysis, as a result of renal biopsy, pre-hypertension was associated independently with renal arteriosclerosis and arteriolar hyalinosis. The association was present even after adjustment for traditional cardiovascular risk factors such as total cholesterol, glucose intolerance, BMI, habitual smoking and alcohol intake in Japanese population-based autopsy samples [25]. In a similar study for IgA
nephropathy based on renal biopsy, pre-hypertension was significantly related to the severity of mesangial proliferation and arteriolar sclerosis, including intimal thickening and hyalinosis [26]. Prolonged systemic high BP might induce pathological changes such as atherosclerosis, which can cause a disturbance in renal perfusion and renal ischemia, resulting in a subsequent decline in renal function [27, 28].

The prevalence of subjects with pre-hypertension was 37.9% in the present study, comparable to results of the Japanese National Health and Nutrition Examination Survey in 2006 (39.7%) [29]. In the present study population, due to the high prevalence of pre-hypertension compared to that of Stage 1 (18.0%) and Stage 2 (16.9%) hypertension, the PAF for CKD in pre-hypertension was considerably high (12.1%) and comparable to that of Stage 1 (8.6%) and Stage 2 (14.9%) hypertension. Therefore, it is preferable to consider earlier interventions for pre-hypertension in order to prevent the progression of CKD among the general population. In practice, it is supposed that lifestyle intervention is the mainstay of treatment for pre-hypertension for the general population. Lifestyle modifications such as weight reduction for maintaining a normal body weight, improving dietary habits, reducing sodium intake, increasing physical activity and restricting alcohol consumption have all been shown both to lower BP effectively and have a beneficial effect on cardiovascular risks [30–32]. Such lifestyle changes are also recommended for patients with pre-hypertension. Essentially, the definition of the pre-hypertension according to JNC7 was intended to emphasize the importance of identification of individuals who could lower their BP in order to prevent progression to hypertension and cardiovascular events through adoption of a healthier lifestyle [1]. Population strategies such as a public health and social and policy reforms, not high-risk strategies limited to hypertension, might be necessary in order to attain a better BP target.

In line with previous studies [33, 34], the present study confirmed a weak, but significant, relationship between systolic BP and the development of proteinuria. In relation to diastolic BP, it remains controversial whether diastolic BP is an independent predictor of CKD [9, 35, 36]. In the present study, however, when diastolic BP was added into the model for prediction of CKD instead of systolic BP, the results were not statistically different from when systolic BP was used, excluding the onset of proteinuria.

In patients with hypertensive CKD, it was recently reported that intensive BP control had no favorable effect on the progression of decreased renal function [37]. Additionally, it was suggested that even strict control of BP is ineffective for the treatment of full-blown hypertension. Therefore, early intervention for pre-hypertension is essential to prevent declines in renal function in the general population.

The present study has some limitations. Firstly, the subjects in the present study were participants of an annual health check-up. Thus, the present population had a tendency to be health conscious, and, as a result, there is a possibility that a selection bias exists. However, the prevalence of pre-hypertension in the present study is at least similar to that of Japan as a whole. Secondly, the diagnosis of CKD in the present study depended on the value of creatinine or positive proteinuria on only one occasion. In 2002, the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) provided guidelines that include a clear definition and classification for CKD. It defined CKD as the presence of kidney damage or GFR of < 60 mL/min/1.73 m² for ≥ 3 months [38]. In previous epidemiological studies [6, 8, 23, 39], diagnosis of CKD had been determined in the same manner as in the present study. Thirdly, the analysis focused exclusively on Japanese residents and therefore might not be representative of non-Asian or non-Japanese subjects. There are several reports that have referred to a comparison of the epidemiology of CKD between Japanese and other ethnicities [40, 41], and its interpretation remains controversial. Thus, further research in other ethnic and cultural groups is needed to confirm the generalizability of the present findings. Finally, serum creatinine was measured in some cases using the Jaffe method and in those cases, the values were corrected in order to obtain an equivalent value for the enzymatic method using a modified equation, which may have altered the results of the present study.

In conclusion, pre-hypertension was significantly associated with an increased risk of CKD in a general Japanese population. The PAF for CKD in pre-hypertension was found to be comparable to that in Stages 1 and 2 hypertension. These results suggest that a public health strategy solely based on hypertension might be inappropriate, and that it is valuable to pay more attention to pre-hypertension in order to improve primary prevention of CKD.

**Supplementary data**

Supplementary data is available online at http://ndt.oxfordjournals.org.

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**Conflict of interest statement.** None declared.

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Pre-hypertension predicts the onset of CKD


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