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Authors: Nobuko Sera, Ayumi Hida, Misa Imaizumi, Eiji Nakashima, and Masazumi Akahoshi

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The Association Between Chronic Kidney Disease and Cardiovascular Disease Risk Factors in Atomic Bomb Survivors

Nobuko Sera,1 Ayumi Hida,2 Misa Imaizumi,3 Eiji Nakashima and Masazumi Akahoshi

Departments of 1Nagasaki Clinical Studies and 2Statistics, Radiation Effects Research Foundation, Nagasaki, Japan

INTRODUCTION

High-dose radiation therapy to the chest or neck has been shown to induce ischemic heart disease (IHD) (1, 2) and stroke (3, 4), but the effect of low-dose radiation on heart disease is controversial (5, 6). Atomic bomb (A-bomb) radiation increases both cardiovascular disease (CVD) mortality (7) and the incidence of myocardial infarction (8). It is also associated with aortic calcification (9) and retinal arteriosclerosis (10), suggesting that general atherosclerosis is involved in the connection between A-bomb radiation and CVD.

Atomic bomb radiation is associated with systolic and diastolic blood pressure trends of the younger exposed subjects (7) and cholesterol trends of all exposed subjects shifted upward in the growth-curve analysis (11). Also, it has been reported that A-bomb radiation was associated with increased risk of hypertension in a longitudinal follow-up study from 1958–1998 (12) and prevalence of dyslipidemia in a cross-sectional study (13). In addition, it is associated with an increase in many inflammatory markers, including C-reactive protein (CRP), interleukin-6, and interferon-γ, as well as the erythrocyte sedimentation rate (14, 15) and may be associated with diabetes mellitus (DM) (11). Thus, A-bomb survivors show an increase in metabolic CVD risk factors and inflammatory markers in much the same way as people with metabolic syndrome (MetS), suggesting the possibility that MetS plays a role in the development of CVD in A-bomb survivors. Indeed, fatty liver, a surrogate marker for MetS, is associated with A-bomb radiation dose (13) and CVD risk factors (16), and it predicts IHD (17).

Chronic kidney disease (CKD) as a clinical entity has started to draw attention only recently, with its categorization advocated by the U.S. National Kidney Foundation in 2002 (18); it is a risk factor for CVD (19, 20). The MetS and the increase of MetS components (obesity, high blood pressure, dyslipidemia and impaired glucose tolerance) predicted the development of CKD in a longitudinal follow-up study (21), and the cumulative incidence of CKD was significantly higher in subjects with MetS (22). The aforementioned findings in A-bomb survivors suggest that CKD may also have a role in the development of CVD.
Therefore, we examined here whether CKD is associated with MetS with its individual components, and with radiation dose in A-bomb survivors.

**METHODS**

**Participants**

The Adult Health Study (AHS) was established in 1958 by the Atomic Bomb Casualty Commission, now the Radiation Effect Research Foundation (RERF), to study the late effects of radiation in Hiroshima and Nagasaki A-bomb survivors. The AHS conducts biennial health examinations whose clinical information complements death and tumor registry data. A detailed description of the program has been published elsewhere (27).

From 2004 through 2007, 1,366 people (521 men and 845 women) in the Nagasaki AHS cohort underwent clinical examinations, and hematological, biochemical, electrocardiogram and pulse wave velocity (PWV) measurements. They were excluded from the study if they had not undergone waist circumferences or PWV measurements or if they were not taking medication for hyperlipidemia but had postprandial hypertriglyceridemia (because we could not determine whether they had hyperlipidemia (HLP)).

Therefore, we examined here whether CKD is associated with MetS with its individual components, and with radiation dose in A-bomb survivors.

**Radiation Dose**

As the renal dose for individual subjects is not available, for our statistical analysis we used a shielded total kerma dose based on Dosimetry System 2002 (DS02) (25) with adjustment of the γ and neutron doses for 35% dose error, truncating them at 4 Gy, to reduce radiation effect estimation bias (26). We thought shielded total kerma dose would be appropriate for analysis of CKD, which seems to be more of a secondary condition caused by the systemic vascular pathology that is attributable to DM and hypertension, as evidenced by the breakdown of patients who started undergoing dialysis for end-stage renal disease in Japan. As this tendency is seemingly more pronounced in CKD, we think radiation effects on the overall vascular system play a more important role in CKD, and thus used a shielded total kerma dose.

Out of the 1,040 potential participants, we analyzed the relationship between CKD and radiation dose for 746 participants whose A-bomb radiation dose was estimated.
Diagnostic Criteria

1. **CKD and renal dysfunction level.** We calculated estimated glomerular filtration rate (eGFR) using an equation adjusted for the Japanese: eGFR (ml/min/1.73 m²) = 194 × age⁻⁰.⁰²⁰ × creatinine⁻¹.⁰⁰⁴ (for women, the eGFR was multiplied by 0.739) (27). Subjects were grouped by renal function according to their eGFR as follows: ≥90 ml/min/1.73 m² as normal, 60–89 ml/min/1.73 m² as mildly dysfunctional, 30–59 ml/min/1.73 m² as moderately dysfunctional, and <30 ml/min/1.73 m² as severely dysfunctional.

2. **Hypertension.** Subjects were diagnosed as hypertensive if they had a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or were taking anti-hypertensive medication.

3. **Diabetes mellitus.** Subjects were diagnosed as having DM if they had a fasting blood glucose ≥126 mg/dl, a postprandial glucose ≥200 mg/dl, HbA1c ≥6.5%, a blood glucose ≥200 mg/dl at 2 h in a 75-g oral glucose tolerance test, or if they were under treatment for DM, or had a history of DM.

4. **Hyperlipidemia.** We diagnosed subjects as having hyperlipidemia if they had a total cholesterol level ≥220 mg/dl, an LDL cholesterol level ≥140 mg/dl, a fasting triglyceride level ≥150 mg/dl, or if they were taking a lipid-lowering medication. A total of 106 subjects were not taking medication for hyperlipidemia, but had postprandial hypertriglyceridemia. These subjects were excluded in this study because we could not determine whether or not they had hyperlipidemia (Fig. 1).

5. **MetS.** We used the modified criteria on the MetS guidelines in Japan (28) and diagnosed MetS when waist circumference was ≥85 cm in men or ≥90 cm in women and subjects showed 2 of the following 3 features: (1) serum triglyceride ≥150 mg/dl; HDL cholesterol ≤40 mg/dl, or the subject was being treated for hyperlipidemia; (2) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or subject was being treated for hypertension; (3) fasting blood glucose ≥100 mg/dl or subject was being treated for DM.

The definition of hypertension, DM and hyperlipidemia were restricted to current medication use but not to past medication use.

**Statistical Analysis**

All statistical analyses were performed with the Statistical Analysis System package for personal computers (SAS, Cary, NC). Baseline covariate values were compared between the normal subjects and the subjects with renal dysfunction using general linear model (GLM) analysis adjusted for age, gender, and smoking and drinking habits. Several factors (SBP, HDL cholesterol, triglyceride, HbA1c, Hs-CRP), which tend to be right-skewed, log transformation for statistical testing was used (Table 1). Ordinal logistic regression analysis was performed with the Statistical Analysis System package for personal computers (SAS, Cary, NC).
TABLE 2
Prevalence and Odds Ratio (95% Confidence Interval) of Cardiovascular Disease (CVD) Risk Factors by Renal Dysfunction

<table>
<thead>
<tr>
<th>CVD risk factor</th>
<th>Renal dysfunction</th>
<th>Odds ratio (95% confidence interval )</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n = 121)</td>
<td>Mild (n = 686)</td>
<td>Moderate (n = 217)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (60.3)</td>
<td>419 (61.1)</td>
<td>153 (70.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>0.96 (0.63–1.46)</td>
<td>1.39 (0.83–2.32)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>26 (21.5)</td>
<td>101 (14.7)</td>
<td>48 (22.1)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.64 (0.39–1.06)</td>
<td>1.08 (0.60–1.94)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>57 (47.1)</td>
<td>379 (55.2)</td>
<td>128 (59.0)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.75 (1.16–2.66)*</td>
<td>2.34 (1.42–3.88)*</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>16 (13.2)</td>
<td>140 (20.4)</td>
<td>60 (27.6)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.85 (1.04–3.29)*</td>
<td>2.76 (1.44–5.26)*</td>
</tr>
</tbody>
</table>

Note. P for trend was analyzed with ordinal logistic regression model adjusted for age, gender, and smoking and drinking habits. *P < 0.05 vs. normal group (n = 121) adjusted for age, gender, and smoking and drinking habits.

RESULTS

Table 1 shows the distribution of risk factors in the 4 renal dysfunction groups and in the anthropometric indexes and variables relating to renal dysfunction. Almost all the CVD risk factors relating to blood pressure, lipid metabolism, and glucose metabolism deteriorated with renal dysfunction but medication history was not taken into account, which could have led to some measurement error. The Hb level was low in the severe renal dysfunction group, while the adiponectin level was high. HOMA-IR was significantly high in the severe renal dysfunction group. Additionally, ba-PWV increased with renal dysfunction, while ba-PWV significantly decreased with renal dysfunction when age, gender, and smoking and drinking habits were incorporated into the analysis (data not shown).

TABLE 3
Odds Ratio (95% Confidence Interval) of Cardiovascular Disease (CVD) Risk Factors for Chronic Kidney Disease

<table>
<thead>
<tr>
<th>CVD risk factor</th>
<th>Odds ratio (95% CI )</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.57 (1.12–2.20)</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.79 (1.23–2.61)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.55 (1.12–2.14)</td>
<td>0.008</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>1.86 (1.32–2.63)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note. P, compared with combined normal and mild renal dysfunction groups (n = 807) adjusted for age, gender, and smoking and drinking habits.

TABLE 4
Mean Radiation Doses for Three Levels of Renal Dysfunction

<table>
<thead>
<tr>
<th>Renal dysfunction</th>
<th>n</th>
<th>mGy (mean ± SD)</th>
<th>P</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-mild</td>
<td>584</td>
<td>503.2 ± 720.7</td>
<td>0.279</td>
<td>0.278</td>
</tr>
<tr>
<td>Moderate</td>
<td>149</td>
<td>572.8 ± 769.6</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>13</td>
<td>1199.3 ± 1034.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P; v.s. combined normal and mild renal dysfunction groups (n = 584) adjusted for age, gender, and smoking and drinking habits.
P*; v.s. combined normal and mild renal dysfunction groups adjusted for age, gender, and smoking and drinking habits, hypertension, diabetes mellitus, hyperlipidemia and metabolic syndrome.
groups used as the reference, show that all 4 conditions were significantly associated with CKD (Table 3).

Compared with combined normal and mild renal dysfunction groups, the severe renal dysfunction group had received a significantly higher dose of A-bomb radiation (Table 4), and radiation dose was significantly associated with both CKD and severe renal dysfunction with or without adjustment for age, gender, and smoking and drinking habits, hypertension, DM, hyperlipidemia and MetS. Our findings suggest that CKD is involved in the mechanism(s) linking radiation exposure with CVD risk factors. When we assessed the association of hypertension, DM, hyperlipidemia and MetS with renal dysfunction, odds ratios representing these associations increased along with the deterioration of renal functions from mild to severe dysfunctions, although significance was not observed for DM. However, when we compared the clinical setting of CKD, including moderate and severe, to the reference group including normal and mild, hypertension, DM, hyperlipidemia and MetS were significantly associated with CKD, which was the same as that reported for non A-bomb survivors (21).

PWV, a marker of aortic wall stiffness, predicts cardiovascular events (29), and vascular function and arterial compliance are impaired in patients with CKD (30). Thus, PWV is associated inversely with GFR in patients with non-dialysis-dependent renal insufficiency (31, 32). Also, in hypertensive patients, GFR >60 ml/min/1.73 m² correlates inversely with aortic PWV (33). In the present study, ba-PWV was inversely associated with eGFR and it increased with renal dysfunction when no adjustment was made. Our finding that both PWV and eGFR were closely related to age, and that the association between ba-PWV and renal dysfunction disappeared when age was incorporated into the analysis (data not shown) was in agreement with a previous study (34).

**DISCUSSION**

In this study, we found radiation dose to be significantly associated with CKD (moderate/severe renal dysfunction) and with severe renal dysfunction in A-bomb survivors, with or without adjustment for age, gender, and smoking and drinking habits, hypertension, DM, hyperlipidemia and MetS. Our findings suggest that CKD is involved in the mechanism(s) linking radiation exposure with CVD risk factors.

PWV, a marker of aortic wall stiffness, predicts cardiovascular events (29), and vascular function and arterial compliance are impaired in patients with CKD (30). Thus, PWV is associated inversely with GFR in patients with non-dialysis-dependent renal insufficiency (31, 32). Also, in hypertensive patients, GFR >60 ml/min/1.73 m² correlates inversely with aortic PWV (33). In the present study, ba-PWV was inversely associated with eGFR and it increased with renal dysfunction when no adjustment was made. Our finding that both PWV and eGFR were closely related to age, and that the association between ba-PWV and renal dysfunction disappeared when age was incorporated into the analysis (data not shown) was in agreement with a previous study (34).

Serum adiponectin levels reportedly decrease in patients with hypertension (35), DM (36), dyslipidemia (37, 38), or MetS (39), which is in agreement with the results of the present study. On the other hand, we also found that elevated serum adiponectin levels are seen in patients with moderate renal dysfunction (17, 40). Further studies are necessary to explain the association we found between elevated serum adiponectin level and severe renal dysfunction.

The prevalence of systemic CVD risk factors such as hypertension, DM and hyperlipidemia, as well as the level of inflammatory markers, increases with radiation dose in A-bomb survivors (7, 11, 14, 15). The clustering of systemic CVD risk factors suggests the possibility that MetS plays a role. In line with this, we previously reported that fatty liver, a surrogate marker of MetS, clusters with CVD risk factors (16), predicts IHD (17), and is associated with A-bomb radiation dose (13). Since aortic calcification and retinal arteriosclerosis also increase with radiation dose (9), it is reasonable to think that a general rather than a regional atherosclerotic process is involved in the development of CVD in A-bomb survivors. Thus, we think that the mechanism(s) that induces MetS is stimulated, leading to the clustered systemic CVD risk factors, general atherosclerosis, and CVD, although that mechanism(s) has yet to be clarified.

High-dose radiation therapy induces renal injury, leading to renovascular hypertension (41), and high levels of A-bomb radiation induce ureter and renal calculi in men (12), but the effect of low-to-moderate dose radiation on the kidney has not been elucidated. In the present study, low-dose radiation was significantly associated with CKD and severe renal dysfunction independently of hypertension, DM, hyperlipidemia and MetS, suggesting that A-bomb radiation affects the kidney directly. Prospective studies are needed to clarify how the association between low-dose radiation and CVD may be mediated by CKD.

**ACKNOWLEDGMENTS**

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<table>
<thead>
<tr>
<th>Renal dysfunction</th>
<th>n</th>
<th>Not adjusted OR/Gy (95%CI)</th>
<th>P</th>
<th>Adjusted* OR/Gy (95%CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal–mild</td>
<td>584</td>
<td>1</td>
<td>1</td>
<td>1.09 (1.01–1.16)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Moderate</td>
<td>149</td>
<td>1.13 (0.90–1.44)</td>
<td>0.295</td>
<td>1.15 (0.89–1.48)</td>
<td>0.293</td>
</tr>
<tr>
<td>Severe</td>
<td>13</td>
<td>2.25 (1.36–3.78)</td>
<td>0.002</td>
<td>3.19 (1.63–6.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD (moderate + severe)</td>
<td>162</td>
<td>1.26 (1.01–1.57)</td>
<td>0.040*</td>
<td>1.29 (1.01–1.63)</td>
<td>0.038*</td>
</tr>
</tbody>
</table>

*Notes. Reference was the combined normal and mild renal dysfunction group. CKD; chronic kidney disease.

*Adjusted for age, gender, and smoking and drinking habits, hypertension, diabetes mellitus, hyperlipidemia and metabolic syndrome.

*Analyzed with ordinal logistic regression model.
based on RERF Research Protocol RP 2–75. The views of the authors do not necessarily reflect those of the two governments.

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