Increased Risk of Chronic Kidney Disease in Elderly with Metabolic Syndrome and High Levels of C-Reactive Protein: Kahrizak Elderly Study

Hossein Fakhrzadeh a Maryam Ghaderpanahi a Farshad Sharifi a, b Zohre Badamchizade a Mojde Mirarefin a Bagher Larijani a

a Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, and b University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Key Words
Chronic kidney disease · C-reactive protein · CKD, elderly population · Metabolic syndrome

Introduction

Metabolic syndrome (MS) is characterized by clustering of abdominal obesity, elevated blood pressure, low levels of high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, and impaired fasting glucose [1]. In Western societies it is estimated to affect nearly 20% of the adult population and approximately 40% of those over 60 years of age [2]. The prevalence of MS in Iranian adults is estimated at 27% [3]. Cross-sectional [4–9] as well as longitudinal [10–14] studies have shown a relationship between MS and chronic kidney disease (CKD). CKD is a serious harbinger of end-stage renal disease and is associated with an increased risk of cardiovascular disease and premature death [15–17]. Recognition and prevention of risk factors for CKD can be the most suitable alternative for prevention of these adverse outcomes.

A previous study in Iran has shown that the threat of MS for developing CKD is highly affected by the presence of diabetes and hypertension [10] whereas in other studies after adjustment for diabetes and hypertension, MS independently contributed to development of CKD [5, 9, 12, 13].

On the other hand, there is a relation between inflammation as measured by C-reactive protein (CRP) and MS [18]. Inflammation has also been implicated in the pathogenesis of MS [19, 20]. In one study, high CRP was associ-
ated with an increased prevalence of CKD and the odds of CKD increased in the presence of high CRP and MS [7]. To our knowledge there has been only one study in Iranian adults discussing the relation of MS and CKD [10]. We aimed to investigate the relation of MS with CRP and the risk of developing CKD in the elderly residents of Kahrizak Charity Foundation Nursing Home.

**Materials and Methods**

**Study Population**

The Kahrizak Elderly Study (KES) is a prospective survey of health status conducted in elderly residents of Kahrizak Charity Foundation in Tehran, Iran, since 2006 until now and in continuance. The cross-sectional analysis reported in this article was restricted to persons aged 60 years and older who fulfilled the information necessary for this study. 152 subjects participated in the study of which 122 individuals completed the survey. The study was approved by the Research Ethics Committee of the Tehran University of Medical Sciences and conforms to the Declaration of Helsinki. Informed consent was obtained from all subjects before data collection.

**Definitions**

Hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or current use of antihypertensive drugs. Diabetes was defined as a self-reported history of a prior diagnosis of diabetes or fasting serum glucose ≥126 mg/dl. MS was defined according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) criteria as the presence of three or more of the following risk factors: waist circumference ≥102 cm in men or ≥88 cm in women; serum triglyceride ≥150 mg/dl; HDL-C <40 mg/dl in men or <50 mg/dl in women; blood pressure ≥130/85 mm Hg and/or use of antihypertensive medications, or serum glucose level ≥110 mg/dl and/or use of insulin or hypoglycemic medication [1]. Glomerular filtration rate (GFR) was estimated from the simplified equation developed using Modification of Diet in Renal Disease (MDRD) data [21]. CKD was defined as a reduced estimated GFR (<60 ml/min/1.73 m²) according to the US National Kidney Foundation guidelines. In agreement with American Heart Association/Centers for Disease Control (AHA/CDC) consensus, CRP ≥3 mg/dl was regarded high [22].

**Data Collection**

Information based on demographic characteristics including age, sex, education and smoking status was collected by a trained nurse using a standard questionnaire. History of taking antihypertensive and/or hypoglycemic drugs including insulin therapy was obtained from their medical records. Anthropometric measurements were performed using standard protocols and technique. Weight and height were measured in light clothing without shoes. Waist circumference was measured at the umbilical level to the nearest centimeter with minimal respiration. Blood pressure measurements were performed according to guidelines of JNC IIV with the participant in a recumbent position after 5 min of rest and the average of three measurements were recorded. Participants were recommended to avoid alcohol, cigarette smoking, caffeinated beverages, and exercise for at least 30 min before their blood pressure measurement. Twelve-hour overnight fasting blood samples were collected to determine serum lipids, glucose, creatinine and CRP levels and were stored at –70°C until performing laboratory assays. Serum creatinine (Jaffe reaction), glucose, HDL-C and triglyceride were measured using an enzymatic-calorimetric assay (Hitachi 902-Boehringer Mannheim, 2000). Serum high-sensitivity CRP levels were measured using an enzymatic immunoturbidimetric assay.

**Statistical Analyses**

Continuous variables were expressed as mean ± SD and were compared using t test. Categorical variables were compared using the χ² test. The prevalence of CKD was calculated by the number of MS components present. Because only a few numbers of participants had all of the 5 components of MS, subjects with 4 or 5 components were considered together as a single group for analysis. Independent contribution to CKD was assessed by logistic regression analysis. Odds ratios (ORs) for MS as a whole, also individual components of MS and high-sensitivity CRP, were determined after adjustment for age, gender, body mass index (BMI), education level and smoking status. Because hypertension and diabetes are the most important identified risk factors for CKD, the association of CKD with MS after excluding subjects with hypertension and diabetes was separately examined.

To find the interrelationship between CRP levels and MS, subjects were divided into four groups: group 1, low CRP/without MS; group 2, high CRP/without MS; group 3, low CRP/with MS, and group 4, high CRP/with MS. ORs for groups 2, 3, and 4 were identified relative to that of group 1. To assess interaction between high CRP and the presence or absence of MS, a multiple logistic regression model was used. All data analyses were conducted using SPSS 15 software for Windows. p values ≤0.05 were considered statistically significant.

**Results**

The prevalence of individual MS components in the study population was 82.9% for high blood pressure, 82.9% for hypertriglyceridemia, 70.7% for abdominal obesity, 36.6% for high fasting glucose levels and 90.2% for low HDL-C levels. MS was diagnosed in 33.3% subjects.

37.7% of participants had high CRP levels. MS and abdominal obesity were significantly more prevalent in women than in men (fig. 1). On the other hand, all individual components of MS were more prevalent in women except for high fasting glucose but they did not have statistical significance.

Demographic and biochemical characteristics of participants categorized according to MS status are shown in table 1. Subjects with the syndrome relative to those without MS were more obese. There was no significant differ-
ence in CRP and high CRP levels between subjects with and without MS.

Five participants (4 women and 1 man) had proteinuria. Four of them had severe (3+) and 1 had mild (1+) proteinuria. Only 3 had kidney-related diseases. Of those with severe proteinuria, 1 had pyelonephritis, the second one had concomitant hypertension and diabetes, and in the third one no specific cause was detected. The subject with mild proteinuria had only hypertension.

Overall, 62.2% had CKD defined as an estimated GFR ≤ 60 ml/min/1.73 m². CKD was present in 82.9% of subjects with MS and in 59.3 of those without the syndrome (p < 0.006). There was a positive association between the increased number of MS components and the prevalence of CKD (fig. 2).

After being categorized according to CRP level, the prevalence of CKD in the low CRP/without MS, high CRP/without MS, low CRP/with MS, and high CRP/with MS was 54.7, 67.9, 82.6, and 83.3%, respectively (fig. 3). Nevertheless, there is no significant difference between the low CRP/without MS and high CRP/without MS groups as well as low CRP/with MS and high CRP/with MS groups.

In a multivariate model, among MS components, only high blood pressure and hypertriglyceridemia were independently associated with an increased prevalence of CKD (OR 4.01, 95% CI 1.55–10.37 and OR 3.27, 95% CI 1.25–8.53, respectively). After multiple adjustments, MS was a significant determinant of CKD (OR 5.81, 95% CI 1.72–19.58) (table 2).

Compared with the low CRP/without MS, the multivariate-adjusted ORs for CKD of the high CRP/without MS and low CRP/with MS were 1.09 (95% CI 0.95–1.25) and 1.18 (95% CI 0.56–2.46), respectively. Subjects with high CRP and MS had a 1.71-fold increased risk of CKD (95% CI 1.02–2.84) (table 3).

Sensitivity Analysis

After excluding subjects with diabetes, MS was significantly associated with an increased odds of CKD (OR 16.14, 95% CI 1.87–138.91) in the multivariate-adjusted models. However, after excluding participants with hypertension, MS did not show a significant association with increased odds of CKD (OR 8.05, 95% CI 0.71–90.73).

Discussion

We found a strong, positive relationship between MS and risk of CKD in elderly population of this study which is compatible with findings of other investigators [4–14]. In addition, there was an escalating dose-response relationship between the number of MS components and risk of CKD. To our knowledge, this is the first study to report a strong relationship between the MS and CKD risk in elderly Iranian people. Since MS is considered as a rela-
respectively common disorder in the Iranian population [3], these findings will potentially have important clinical and public health implications.

The relatively high prevalence of CKD (67.2%) in our study population could be attributable to their old age. In the present study, the risk of MS for developing CKD was highly affected by the presence of hypertension but independent of diabetes. This finding differs with other studies which reported the relation between MS and CKD to be independent of hypertension and diabetes [5, 9, 12–

### Table 1. Demographic and biochemical characteristics of study subjects with and without MS

<table>
<thead>
<tr>
<th></th>
<th>Without MS (n = 81)</th>
<th>With MS (n = 41)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>73.2 ± 10.65</td>
<td>74.4 ± 8.76</td>
<td>0.53</td>
</tr>
<tr>
<td>Men, %</td>
<td>51.9</td>
<td>31.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High school education, %</td>
<td>14.8</td>
<td>4.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>18.5</td>
<td>7.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125.3 ± 23.34</td>
<td>142.6 ± 25.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>74.35 ± 15.48</td>
<td>79.39 ± 14.62</td>
<td>0.08</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.68 ± 5.13</td>
<td>27.03 ± 6.54</td>
<td>0.3</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>88.43 ± 12.15</td>
<td>97.98 ± 12.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dl</td>
<td>88.79 ± 10.84</td>
<td>112.26 ± 0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>46.53 ± 12.69</td>
<td>38.12 ± 8.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>123.5 ± 67.05</td>
<td>198.26 ± 67.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.20 ± 0.34</td>
<td>1.32 ± 0.43</td>
<td>0.1</td>
</tr>
<tr>
<td>Estimated GFR, ml/min/1.73 m²</td>
<td>56.14 ± 19.29</td>
<td>47.96 ± 17.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic kidney disease, %</td>
<td>59.3</td>
<td>82.9</td>
<td>0.006</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>3.54 ± 4.19</td>
<td>4.44 ± 5.19</td>
<td>0.3</td>
</tr>
<tr>
<td>High CRP, %</td>
<td>34.6</td>
<td>43.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± SD and/or percentage. Chronic kidney disease is defined as an estimated GFR <60 ml/min/1.73 m². High CRP is defined as a CRP ≥3 mg/dl. HDL = High-density lipoprotein; GFR = glomerular filtration rate.
13]. Notwithstanding, in a longitudinal study after excluding participants with hypertension, MS did not show a significant association with CKD in the non-diabetic Iranian adult population [10]. While diabetes and hypertension are the most common causes of CKD [15, 23], it is suggested that hypertension is the more important threat for CKD in the elderly Iranians.

The relation between high blood pressure and CKD could be attributable to overt role hypertension in developing renal insufficiency. We also found hypertriglyceridemia to be independently and significantly associated with an increased risk of CKD. This is in concordance with findings of the Atherosclerosis Risk in Communities Study which showed that serum triglyceride and HDL-C levels predicted the development of renal failure in patients with normal renal function at baseline [24]. A meta-analysis of clinical trials has shown that lipid lowering preserves GFR and decreases proteinuria in patients with CKD [25] but effectiveness of lipid-lowering treatments in preventing the onset of renal failure in patients with normal renal function is still an issue of debate. Tozawa et al. [26] also showed that hypertriglyceridemia predicted progressive loss in renal function in women. Another study by Samuelsson et al. [27] reported a strong correlation between a declining GFR and increased plasma concentrations of triglyceride-rich apoB-containing lipoproteins. Although the mechanisms that lipids contribute to renal deterioration has not been clearly recognized, involvement of several cytokines has been reported in this process. Whilst being exposed to lipids, mesangial cells enhance the secretion of interleukin-6, platelet-derived growth factor, transforming growth factor-β, and tumor necrosis factor-α [28]. Lipoproteins also stimulate the production of fibronectin and monocyte chemoattractant protein-1 expression in mesangial cells [29]. Therefore, hypertriglyceridemia is likely a risk factor of CKD by these mechanisms.

### Table 2. ORs of CKD are associated with individual components of the MS and CRP

<table>
<thead>
<tr>
<th>Component</th>
<th>Unadjusted OR (95% CI)</th>
<th>p value</th>
<th>Age and gender adjusted OR (95% CI)</th>
<th>p value</th>
<th>Multivariate adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure ≥130/85 mm Hg b</td>
<td>3.04 (1.32–7.00)</td>
<td>0.009</td>
<td>2.69 (1.14–6.37)</td>
<td>0.02</td>
<td>4.01 (1.55–10.37)</td>
<td>0.004</td>
</tr>
<tr>
<td>High fasting glucose ≥110 mg/dl</td>
<td>0.88 (0.32–2.43)</td>
<td>0.81</td>
<td>0.96 (0.34–2.74)</td>
<td>0.95</td>
<td>1.20 (0.37–3.89)</td>
<td>0.75</td>
</tr>
<tr>
<td>Waist circumference &gt;102 cm in men or &gt;88 cm in women</td>
<td>1.65 (0.73–3.70)</td>
<td>0.22</td>
<td>1.38 (0.58–3.27)</td>
<td>0.46</td>
<td>1.40 (0.43–4.10)</td>
<td>0.57</td>
</tr>
<tr>
<td>Serum triglyceride ≥150 mg/dl</td>
<td>2.39 (1.05–5.42)</td>
<td>0.03</td>
<td>2.38 (1.01–5.57)</td>
<td>0.45</td>
<td>3.27 (1.25–8.53)</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL cholesterol &lt;40 mg/dl in men or &lt;50 mg/dl in women</td>
<td>1.09 (0.50–2.37)</td>
<td>0.81</td>
<td>1.04 (0.43–2.35)</td>
<td>0.91</td>
<td>0.96 (0.39–2.35)</td>
<td>0.93</td>
</tr>
<tr>
<td>Metabolic syndrome d</td>
<td>3.33 (1.32–8.43)</td>
<td>0.01</td>
<td>3.10 (1.19–8.07)</td>
<td>0.02</td>
<td>5.81 (1.72–19.58)</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum CRP ≥3 mg/dl</td>
<td>1.65 (0.73–3.70)</td>
<td>0.22</td>
<td>2.15 (0.90–5.11)</td>
<td>0.08</td>
<td>2.23 (0.85–5.85)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**OR = Odds ratio; CI = confidence interval; HDL = high-density lipoprotein; CRP = C-reactive protein.**

**a Adjusted for age, gender, BMI, smoking status, and high school education.**

**b Systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥85 mm Hg and/or using antihypertensive drugs.**

**c Fasting glucose ≥110 mg/dl or use of insulin or hypoglycemic drugs.**

**d Compared with those with <3 components.**

### Table 3. ORs of CKD according to CRP levels and MS

<table>
<thead>
<tr>
<th>CRP/MS Status</th>
<th>Unadjusted OR (95% CI)</th>
<th>p value</th>
<th>Age and gender adjusted OR (95% CI)</th>
<th>p value</th>
<th>Multivariate adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CRP/without MS</td>
<td>reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High CRP/without MS</td>
<td>1.07 (0.95–1.20)</td>
<td>0.25</td>
<td>1.08 (0.95–1.22)</td>
<td>0.22</td>
<td>1.09 (0.95–1.25)</td>
<td>0.19</td>
</tr>
<tr>
<td>Low CRP/with MS</td>
<td>0.97 (0.52–1.80)</td>
<td>0.93</td>
<td>0.98 (0.51–1.88)</td>
<td>0.95</td>
<td>1.18 (0.56–2.46)</td>
<td>0.65</td>
</tr>
<tr>
<td>High CRP/with MS</td>
<td>1.16 (0.97–1.40)</td>
<td>0.09</td>
<td>1.20 (0.99–1.46)</td>
<td>0.006</td>
<td>1.71 (1.02–2.84)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**a Adjusted for age, gender, BMI, smoking status, and high school education.**
Some studies proposed that measurement of CRP adds substantial prognostic information to MS [30, 31]. Lee et al. [7] found in Chinese adults that CRP was associated with an increased prevalence of CKD independent of having MS. On the other hand, results from the Third National Health and Nutrition Examination Survey (NHANES III) showed a cross-sectional association between CRP level and MS in patients with varying levels of kidney function. The authors suggested future studies to determine in patients with CKD whether there is on the incidence of atherosclerotic events and whether interventions targeted toward MS might modulate inflammation [32]. In our study, although 37.7% of subjects had high CRP levels, the odds for CKD increased independently only in subgroup having both high CRP and MS (table 3). This suggests that a synergistic effect of MS and inflammation on deterioration of renal function in elderly subjects of our study. Also in the study by Lee et al. [7], the odds for CKD increased in the combined setting of elevated CRP and MS even after excluding those with diabetes and hypertension. However, they found the CRP effect on development of renal impairment to be independent of MS. It should be mentioned that there was no difference in the prevalence of high CRP between those with and without MS in our study, while in the Chinese population CRP levels were significantly higher in those with MS than those without it [7]. This fact may play a role in the different results of our study relative to those of Lee et al. [7]. Also, we were not able to investigate the effect of taking statin drugs on CRP levels and CKD because the number of statin users was small. Just to mention, 11 out of total 122 participants (9%) were taking statins during the clinical trial period, of whom 9 had high CRP levels and 9 also had CKD.

A shortcoming of our study would be the relatively limited sample size. Also the cross-sectional study design makes it difficult to infer causality between MS and risk of CKD. In addition, although the abbreviated MDRD study equation used to define CKD has been used widely in large population-based studies and in clinical practice, it has not yet been validated for the Iranian elderly population. The mean GFR in our subjects was 55.39 ml/min/1.73 m², which is much lower than the estimated GFR reported by other studies of the US general population [4, 13]. This finding may be due to the older age of our subjects. On the other hand, using a single serum creatinine value to estimate kidney function may lead to the misclassification of CKD. The random measurement error, due to day-to-day variation in serum creatinine levels in persons, is likely to bias the association towards zero.

In conclusion, we found MS to be an independent risk factor for CKD in the elderly population and it was highly affected by the presence of hypertension but independent of diabetes.

**Recommendations**

Despite a lack of independent association between high CRP levels and CKD, elevated CRP levels combined with MS increased the odds for CKD significantly. This suggests a positive interrelationship between these two factors and CKD, and warrants future prospective and interventional studies to test the impact of preventing and treating MS on the risk of CKD. Also because of the observed association between high blood pressure and hypertriglyceridemia with increased risk of CKD, planning clinical trials which aim at verifying whether treatment of MS components may effectively prevent CKD should be considered a research priority.

**Acknowledgements**

This study was supported by grants from EMRC (Endocrinology and Metabolism Research Center) affiliated with Tehran University of Medical Sciences. We thank all study participants. We also thank Neda Nazari who greatly assisted in the supervision of this study in the Kahrizak Charity Foundation, and all who helped us with conducting the study.

**References**


