Serum potassium level is associated with metabolic syndrome: A population-based study

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**SUMMARY**

**Background & aims:** Evidence has suggested that low serum potassium concentration or low dietary potassium intake can result in many metabolic disorders. Our objective was to evaluate the association between serum potassium level and risk of prevalent metabolic syndrome.

**Methods:** We conducted a cross-sectional study in 10,341 participants aged 40 years or older. Metabolic syndrome was defined according to guidelines from the National Cholesterol Education Program with modification.

**Results:** The prevalence rate of metabolic syndrome was 51.7% in participants with hypokalemia and 37.7% in those with normokalemia. With the reduction of serum potassium quartiles, participants tended to have higher level of triglycerides and uric acid, lower level of high-density lipoprotein cholesterol (HDL-C), larger waist circumference and more severe insulin resistance. Serum potassium level significantly decreased with the increasing number of metabolic syndrome components. Compared with subjects in the highest quartile of serum potassium level, multivariate adjusted odds ratios for prevalent metabolic syndrome in the lowest quartile was 1.48 (95% confidence interval, 1.16–1.87).

**Conclusions:** Low serum potassium level significantly associated with prevalence of metabolic syndrome in middle-aged and elderly Chinese.

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1. Introduction

Metabolic syndrome is highly prevalent in Chinese adults\textsuperscript{1} which can lead to increased risk for all causes mortality.\textsuperscript{2} Metabolic syndrome consists of abdominal obesity, dyslipidemia, hypertension, insulin resistance and hyperglycemia.\textsuperscript{3} Additionally, nonalcoholic fatty liver disease (NAFLD) has been regarded as a hepatic manifestation of metabolic syndrome.\textsuperscript{4}

A low serum potassium concentration may be the most usual electrolytic disorder encountered in clinical practice.\textsuperscript{5} Relatively small change in the concentration of extracellular potassium could greatly affect the extracellular homeostasis and result in many metabolic disorders. Adults with lower serum potassium level and lower dietary potassium intake are at higher risk for incident diabetes.\textsuperscript{6} Recently, C. Meisinger et al. found that serum potassium levels were inversely associated with prevalent prediabetes.\textsuperscript{7} In addition, patients with central obesity have lower plasma potassium level compared with non-obese patients during diuretic therapy.\textsuperscript{8} Higher prevalence of NAFLD and more serious insulin resistance are found in primary aldosteronism patients with potassium depletion than those with normokalemia.\textsuperscript{9} Aside from the association of serum potassium level with glucose and lipids metabolism, the relationship of potassium with metabolic syndrome is also of interest. Aldosterone over production and
concurrent hypokalemia can impair the insulin action, which seem to be the major contributors to the high prevalence of metabolic syndrome in patients with primary aldosteronism.\textsuperscript{40} Reungjui et al.\textsuperscript{11} proposed that potassium depletion might have a pivotal role in the exacerbation and worsening of the metabolic syndrome in response to thiazides. They also claimed that controlling serum potassium level to a normal range could reduce the risk of metabolic syndrome.

Further clarify the relationship between serum potassium level and metabolic syndrome would be conducive to the prevention and treatment of the disease. However, to our knowledge, studies that investigated the association in a general population were not available. Therefore, we analyzed data from a Chinese population to explore the possible association between serum potassium level and risk of prevalent metabolic syndrome.

2. Subjects and methods

2.1. Study population and design

We performed a population-based cross-sectional study in a community of Jiading District, Shanghai, China from March to August, 2010.\textsuperscript{15} During the recruiting phase, a total of 10,569 residents who aged 40 years and older were invited to participate by examination notice and home visits. Totally, there were 10,375 subjects signed the consent form and agreed to take part in the survey, with a participation rate of 98.2%. Subjects who missed information on metabolic syndrome status (n = 29) were excluded from analysis. Subjects were also excluded if their serum potassium level greater than 5.5 mmol/L (n = 5).\textsuperscript{15} Eventually, a total of 10,341 eligible individuals were included in the data analyses. The study protocol was approved by the Institutional Review Board of the Ruijin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine and was in accordance with the principles of the Helsinki Declaration II. Written informed consent was obtained from each participant before data collection.

2.2. Clinical and biochemical measurements

We collected information on lifestyle factors, medical history, sociodemographic characteristics and family history by using a standard questionnaire. Smoking or drinking habit was classified as ‘never’, ‘current’ (smoking or drinking regularly in the past 6 months) or ‘ever’ (cessation of smoking or drinking more than 6 months).\textsuperscript{13} A short form of the International Physical Activity Questionnaire (IPAQ) was used to estimate physical activity at leisure time by adding questions on frequency and duration of moderate or vigorous activities and walking.\textsuperscript{14} Separate metabolic equivalent hours per week (MET-h/week) were calculated for evaluation of total physical activity.

All participants completed anthropometric measurements with the assistance of trained staff by using standard protocols. Three times consecutively blood pressure measurements by the same observer with 5 min interval were obtained by an automated electronic device (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China). The average of three measurements of blood pressure was used for analysis. Body height and body weight were recorded to the nearest 0.1 cm and 0.1 kg while participants were wearing light indoor clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Obesity was defined as BMI equal or greater than 28 and overweight was defined as BMI equal or greater than 24. Waist circumference (WC) was measured at the umbilical level with participant in standing position, at the end of gentle expiration.

Venous blood samples were collected for laboratory tests after an overnight fasting of at least 10 h. Measurement of serum potassium, fasting serum insulin, fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and creatinine was done using an autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). Hemoglobin A1c (HbA1c) was assessed by high-performance liquid chromatography (Bio-Rad, Hercules, CA). The abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for Chinese population was used to calculate estimated glomerular filtration rate (eGFR) expressed in ml/min per 1.73 m²: eGFR = 186 × [serum creatinine × 0.011]⁻¹.¹⁵⁴ × [age]⁻⁰.²⁰³ × [0.742 if female] × 1.233, where serum creatinine was expressed as μmol/L and 1.233 was the adjusting coefficient for Chinese population.\textsuperscript{15} The insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) was calculated as fasting insulin (μIU/ml) × fasting glucose (mmol/L)/22.5.\textsuperscript{16} Insulin resistance was defined as HOMA-IR index in the top quartile (more than 2.5 in the present study).\textsuperscript{17} Diabetes was diagnosed according to the 1999 World Health Organization diagnostic criteria. Prevalence of diabetes was calculated on both questionnaire and baseline blood sample test while anti-diabetic medications use was collected by questionnaire.

2.3. Definition of metabolic syndrome

According to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) criteria,\textsuperscript{2} metabolic syndrome was defined as the presence of three or more of the following abnormal factors: 1. Central obesity: WC greater than 102 cm in men and 88 cm in women, respectively; 2. Hypertriglyceridemia: serum triacylglycerol concentration of 1.69 mmol/L or greater; 3. Low HDL-C level: HDL-C concentration of less than 1.03 mmol/L in men or less than 1.29 mmol/L in women; 4. Hyperglycemia: fasting glucose concentration greater than 6.1 mmol/L or previous diagnosis of diabetes; 5. Elevated blood pressure: blood pressure of 130/85 mm Hg or greater. However, previous studies suggested that the ATP III criteria for WC might not be appropriate for Asian populations. Therefore, analyses of the prevalence of the metabolic syndrome in this study were done based on a more accurate cutoff for WC, which was equal to or greater than 90 cm for men and 80 cm for women.\textsuperscript{1}

2.4. Statistical analysis

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA). Continuous variables were presented as means ± standard deviation (SD) except for skewed variables, which were presented as medians (interquartile ranges). Categorical variables were expressed as numbers (proportions). FPG, TG, HbA1c, HOMA-IR, eGFR and MET-h/week were logarithmically transformed before analysis due to a non-normal distribution. The study population was divided into quartiles on the basis of serum potassium distribution: quartile 1 (2.54–3.85 mmol/L), quartile 2 (3.86–4.11 mmol/L), quartile 3 (4.12–4.39 mmol/L) and quartile 4 (4.40–5.50 mmol/L). Linear regression analysis was used to test for trend across serum potassium quartiles. Differences among groups were tested by one-way ANOVA and post hoc comparisons were performed by using Bonferroni correction. Comparisons between categorical variables were performed with the χ² test. Hypokalemia was defined as serum potassium less or equal than 3.5 mmol/L.

We analyzed the impact of serum potassium level on the prevalence rates of metabolic syndrome and its related components. The unadjusted and multivariate adjusted logistic regression analysis was used to assess the risk of prevalent metabolic syndrome for each quartile of serum potassium compared with the

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reference group (quartile 4 in the study). Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were calculated. Model 1 was unadjusted. Model 2 was adjusted for age, sex, BMI, current smoking and drinking status, physical activity, and use of anti-diabetic medications, hypolipidemic and anti-hypertension medication. Model 3 was further adjusted for FPG, HbA1C, TG, TC, LDL-C, HDL-C, systolic blood pressure (SBP), diastolic blood pressure (DBP), eGFR, and HOMA-IR. In the adjustment, variables not normally distributed were logarithmically transformed before entering into the logistic regression models. Smoking and drinking status (never/former/current) and use of anti-hypertension medication (yes/no) were considered as categorical variables. In logistic regression analysis, test for linear trend across decreasing serum potassium quartiles was treating the quartiles as a continuous variable. We used one-way ANOVA test to evaluate the difference of serum potassium level within strata of prevalent individual metabolic syndrome component (yes/no) after adjusted for age and sex. Relationship between metabolic syndrome and serum potassium level was also explored in subgroup analysis and conducted within strata of sex (men/women), age (>58/<58 years), BMI (normal/overweight/obesity), diuretic medications use (yes/no) and diabetes (yes/no). Median age of the participants was 58 years in the present study. Tests for interaction were performed by including the interaction terms (strata factor multiplied by quartiles of serum potassium level) in the models.

The statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of the study population

Among the 10,341 enrolled individuals, 3981 were diagnosed with metabolic syndrome and the prevalence rate was 38.5% in this population. The prevalence of metabolic syndrome in hypokalemia group and normokalemia group were 51.7% and 37.7%, respectively (p < 0.0001). The demographic and biochemical characteristics of the study population in relation to serum potassium quartiles were provided in Table 1. The mean level of age, WC, SBP, TG, uric acid, oral glucose tolerance test (OGTT) 2 h plasma glucose, fasting insulin, HOMA-IR were highest in quartile 1 of serum potassium, whereas TC, HDL-C, LDL-C, proportions of current smokers and drinkers, were lowest in the same quartile (all p for trend < 0.05). However, no statistically significant difference was found among potassium quartiles for BMI and DBP.

3.2. Associations of serum potassium level with metabolic syndrome and its components

The prevalence rates of metabolic syndrome components were 42.2% for central obesity, 34.3% for hypertriglyceridemia, 26.8% for low HDL-C, 71.7% for elevated blood pressure and 22.5% for elevated FPG. According to the elevated serum potassium quartiles, the prevalence rates of metabolic syndrome and its related components were showed in Fig. 1. The prevalence rates of metabolic syndrome, insulin resistance, central obesity, hypertriglyceridemia and low HDL-C were tended to decrease with the increased serum potassium quartiles (all p for trend < 0.0001). However, no obvious trend differences were detected with the elevated FPG and the elevated blood pressure.

In order to assess the internal conformance of the above findings, we further analyzed the direct relationship between the serum potassium level and the number of metabolic syndrome components. As shown in Fig. 2, serum potassium level significantly decreased with the increasing number of metabolic syndrome components after adjusted for age and sex (p for trend < 0.0001). Serum potassium level was independently associated with risk of prevalent metabolic syndrome in both univariate and multivariate analyses.

Table 1

| Characteristics of study population by serum potassium (mmol/L) quartiles. |
|---------------------------------|------------------|------------------|------------------|------------------|------------------|
| n (%)
| Quartile 1 (2.54–3.85)
| 2638
| 2593
| 2530
| 2580
| Quartile 2 (3.86–4.11)
| 59.4 ± 9.7
| 58.4 ± 9.7*
| 58.0 ± 9.7*
| 58.2 ± 9.7*
| Quartile 3 (4.12–4.39)
| 959 ± 36.5
| 935 ± 36.6
| 926 ± 36.0
| 1127 ± 43.4
| Quartile 4 (4.40–5.50)
| 3.21 ± 3.24
| 3.02 ± 3.23
| 2.99 ± 3.09
| 2.95 ± 3.21
| p for trend
| < 0.0001
| < 0.0001
| < 0.0001
| < 0.0001
| p Values
| 0.0001
| 0.0001
| 0.0001
| 0.0001

Data were means ± SD or medians (interquartile ranges) for skewed variables or numbers (proportions) for categorical variables.

p < 0.05 compared with Quartile 1.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate.
multivariate logistic regression analyses (Table 2). Compared with subjects in quartile 4 of serum potassium level, multivariate adjusted OR for prevalent metabolic syndrome in quartile 2 and quartile 1 were 1.43 (95% CI, 1.13–1.81) and 1.48 (95% CI, 1.16–1.87), respectively. Each 1-SD decrease of serum potassium was still associated with a higher risk of prevalent metabolic syndrome (OR 1.17, 95% CI, 1.08–1.27).

Compared with subjects without central obesity, hypertriglyceridemia, low HDL-C and elevated FPG, those with each of these metabolic syndrome components have significant lower serum potassium level after adjusted for age and sex (Table 3, all \( p < 0.05 \)). However, no statistical difference was found in the presence of elevated blood pressure (\( p = 0.290 \)). Low serum potassium level was independently associated with risk of prevalent central obesity, low HDL-C and hypertriglyceridemia after controlled for related confounding factors and other metabolic syndrome components. Compared with subjects in the highest potassium quartile, subjects in the lowest quartile had 32%, 13% and 22% increased risk of prevalent central obesity, hypertriglyceridemia and low HDL-C, respectively.

### 3.3. Serum potassium level and risk of prevalent metabolic syndrome in different subgroups

As shown in Fig. 3, the associations between metabolic syndrome and serum potassium level were inconsistent in different subgroup. Significant relation between serum potassium level and metabolic syndrome was detected in relatively old subjects, subjects overweight and obesity and subjects receive no diuretic medications treatment. The difference in the subgroups analysis was accompanied by a statistically significant interaction term between quartiles of serum potassium level and age (\( p < 0.0001 \)).

### 4. Discussion

We found an inverse relationship between serum potassium level and prevalence of metabolic syndrome in the present study. To our current knowledge, this is the largest population-based study to explore the association of serum potassium level with metabolic syndrome. Early intervention is of great importance for metabolic syndrome, the present findings may just give insights into potential mechanisms for prevention and early detection of the disease.

Previous studies have shown that low potassium level and disorder of glucose-lipid metabolism are related. By collecting data from randomized controlled trials, a meta-analysis demonstrated that lower potassium value was associated with higher glucose value in people with thiazide diuretics therapy. Recently, Ranee et al. has reported an inverse correlation between serum potassium level and incident of diabetes independent of thiazide use. In their study, individuals with lower serum potassium level seemed to have more serious insulin resistance. Actually, the consequences of acute and chronic hypokalemia could worsen diabetic control by impairing insulin release and reducing tissue sensitivity to insulin. Evidence also suggests that certain patients with low plasma potassium level have high prevalence of central obesity and NAFLD.

In the present analyses, examination of the relationship between serum potassium level and metabolic disorders indicated that decreased serum potassium level was strongly associated with prevalence of central obesity, dyslipidemia and insulin resistance. However, we did not find a significant association between serum potassium level and prevalence of elevated blood pressure.
Moreover, a positive association of serum potassium with FPG was found in the present study. This obscure data was also detected in a previous study. Nevertheless, both OGTT 2 h plasma glucose and prevalent diabetes were inversely associated with serum potassium levels, which was consistent with our conclusion. Given the current inconsistencies between serum potassium level and metabolic syndrome, further investigations are needed.

The impact of potassium depletion on metabolic disorders mediated partly by deterioration of endothelial function and decrease of nitric oxide level. Potassium has been proven to play a role as an endothelium derived hyperpolarizing factor and regulate nitric oxide to maintain endothelial function. Potassium depletion will attenuate endothelium dependent vascular reactivity which might be beneficial in the management of metabolic syndrome.

The metabolic syndrome independently predicts cardiovascular risk and its related mortality. Previous studies in both human and animal models have suggested that low potassium level could also predict increased cardiovascular morbidity and mortality. In this context, low serum potassium level was related to many cardiovascular risk factors, such as high level of TG, WC and low level of HDL-C, which may increase the risk of cardiovascular events. We concerned that the mutual effect between serum potassium level and metabolic syndrome may provide a reasonable explanation for the high cardiovascular risk in these people. Consequently, to prevent and reduce the risk of cardiovascular events, further studies are necessary to establish an applicable range of serum potassium level in patients with metabolic syndrome.

Several potential limitations should be mentioned. First, results from the present study may not be representative of the general population because we invited subjects aged 40 years and older. Moreover, given the evidence that low serum potassium contributes to the excess risk of diabetes in African Americans than in whites, it will be important to explore the racial disparity between serum potassium level and risk of metabolic syndrome. Second, the present study including only single measurement of serum potassium level and has no relevant assessment for dietary potassium intake. However, compared with other testing items, intra-individual variation of serum potassium level is relatively low.

Table 2
The risk of prevalent metabolic syndrome according to quartiles of serum potassium level.

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th>p for trend</th>
<th>1 SD decrease of serum potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.25 (1.12–1.40)</td>
<td>1.40 (1.25–1.57)</td>
<td>1.76 (1.57–1.97)</td>
<td>&lt;0.0001</td>
<td>1.25 (1.20–1.30)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.31 (1.12–1.57)</td>
<td>1.74 (1.47–2.06)</td>
<td>2.19 (1.85–2.59)</td>
<td>&lt;0.0001</td>
<td>1.35 (1.27–1.43)</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1.10 (0.87–1.39)</td>
<td>1.43 (1.13–1.81)</td>
<td>1.48 (1.16–1.87)</td>
<td>0.0002</td>
<td>1.17 (1.08–1.27)</td>
<td></td>
</tr>
</tbody>
</table>

Data are odds ratios (95% confidence interval). Participants without metabolic syndrome are defined as 0 and with metabolic syndrome as 1.
Model 1 is unadjusted.
Model 2 is adjusted for age, sex, BMI, current smoking and drinking status, physical activity, and use of anti-diabetic medications, hypolipidemic and anti-hypertension medication.
Model 3 is further adjusted for age and sex.

Table 3
Association of serum potassium level with the prevalence of individual metabolic syndrome component.

<table>
<thead>
<tr>
<th>Components</th>
<th>Status</th>
<th>n</th>
<th>Potassium levelb</th>
<th>p</th>
<th>Model 1a</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td>Yes</td>
<td>4361</td>
<td>4.11 ± 0.42</td>
<td>&lt;0.0001</td>
<td>1.16 (1.12–1.21)</td>
<td>1.40 (1.26–1.46)</td>
<td>1.32 (1.22–1.42)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5980</td>
<td>4.16 ± 0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Yes</td>
<td>3548</td>
<td>4.10 ± 0.41</td>
<td>&lt;0.0001</td>
<td>1.15 (1.10–1.20)</td>
<td>1.18 (1.12–1.25)</td>
<td>1.13 (1.06–1.19)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>6793</td>
<td>4.15 ± 0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>Yes</td>
<td>2766</td>
<td>4.07 ± 0.45</td>
<td>&lt;0.0001</td>
<td>1.26 (1.21–1.32)</td>
<td>1.28 (1.19–1.37)</td>
<td>1.23 (1.14–1.32)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7575</td>
<td>4.16 ± 0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated FPG and diabetes</td>
<td>Yes</td>
<td>2328</td>
<td>4.12 ± 0.41</td>
<td>0.043</td>
<td>1.06 (1.01–1.11)</td>
<td>1.09 (1.01–1.16)</td>
<td>1.05 (0.98–1.13)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>8013</td>
<td>4.14 ± 0.41</td>
<td></td>
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<tr>
<td>Elevated blood pressure</td>
<td>Yes</td>
<td>7414</td>
<td>4.14 ± 0.41</td>
<td>0.290</td>
<td>1.00 (0.96–1.05)</td>
<td>0.97 (0.91–1.03)</td>
<td>0.95 (0.90–1.01)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2927</td>
<td>4.13 ± 0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1 is unadjusted.
Model 2 is adjusted for age, sex, BMI, current smoking and drinking status, physical activity, and use of anti-diabetic medications, hypolipidemic and anti-hypertension medication.
Model 3 is further adjusted for age and sex.

Data are odds ratios (95% confidence interval) of 1 SD decrease of serum potassium. Participants without the component of metabolic syndrome are defined as 0 and with the component of metabolic syndrome as 1.
confounding factors, other unmeasured confounders, such as specific drugs that influence potassium metabolism and hormones of the RAS, should be also considered to evaluate to strength the findings of the present study.

In summary, we found evidence that low potassium level have an independent association with the prevalence of metabolic syndrome in a large Chinese population. Further prospective studies are necessary to verify our findings and determine whether therapies targeting at correcting potassium disorders could alter the progression of the disease.

Statement of authorship

All authors believe that the manuscript represents valid work and have reviewed and approved the final version. The work described was original research that has not been published previously, and not under consideration for publication elsewhere, in part or in whole.

Conflict of interest

The funders did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. All of the authors have no relevant conflict of interests.

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