Abstract  Metabolic syndrome (MetS) and chronic kidney disease (CKD) are individual risk factors for cardiovascular disease (CVD). Abnormal hemorheology may be associated with CVD in both disorders. The present study investigated the impact of MetS and CKD on hemorheology. We studied 138 adults (women/men 63/75, mean age 52.2 years), who included 87 participants with MetS and 33 with CKD. The hemorheology was assessed by the index of ‘whole blood passage time (WBPT)’ using the Micro Channel array Flow ANalyzer (MC-FAN). The WBPT values of MetS participants were significantly higher than those of non-MetS participants (52.5 ± 13.1 vs. 46.3 ± 7.7 sec, p = 0.03). The WBPT values of CKD participants were significantly higher than those of non-CKD (55.5 ± 12.7 vs. 48.6 ± 11.0 sec, p = 0.003). The significant influence of MetS and CKD on WBPT was qualified by their effect modification to WBPT (p = 0.04). There was a significantly greater influence of the combination of MetS and CKD on WBPT (59.9 ± 13.4 sec) in comparison to the influence of non-MetS and CKD (46.6 ± 3.5) or non-CKD and MetS (50.0 ± 12.2). The influence of the combination of MetS and CKD was clearer in men, relative to women. Abnormal hemorheology as assessed using MC-FAN may be enhanced by the combination of MetS and CKD. J Physiol Anthropol 29(5): 157–160, 2010 http://www.jstage.jst.go.jp/browse/jpa2 [DOI: 10.2114/jpa2.29.157]

Keywords: metabolic risk, renal function, eGFR, MC-FAN, preventive cardiology

Introduction  Metabolic syndrome (MetS: a cluster of obesity, increased blood pressure [BP], dyslipidemia, and hyperglycemia) (Sánchez-Torres and Delgado-Osorio, 2005) and chronic kidney disease (CKD: an entity of renal function decline, regardless of cause) (Meisinger et al., 2006) are respectively associated with an elevated risk of cardiovascular disease (CVD) such as coronary heart disease. Because of the prevalence of CVD and its sociomedical burden, these disorders, which can be coexistent, have been regarded as a common health problem. Accordingly, it is crucial to elucidate the pathophysiology of CVD development in both disorders. Hemorheologic abnormalities are considered to be a possible contributor to the CVD formation in MetS (Kotani et al., 2007; Satoh et al., 2009) and CKD (Simpson et al., 1987).

The microchannel method using a Micro Channel array Flow ANalyzer (MC-FAN) is currently considered to be useful to test hemorheology (Kikuchi et al., 1994; Kotani et al., 2007; Kotani et al., 2008; Satoh et al., 2009). This system has a unique feature in assuming the microthrombus formation in blood flow through the minute watercourses produced on a siliconized chip (similar to the microvessel) (Kikuchi et al., 1994). Despite increased attention to this system, very limited data on MetS (Kotani et al., 2007) and no data on CKD using MC-FAN are yet available. The present study was aimed to investigate the association of MetS and CKD with hemorheology using MC-FAN in considering sex differences in this relationship.

Subjects and Methods  This study enrolled 138 adult volunteers (63 women/75 men, mean 52.2 ± 14.5 [SD] years) with no features of CVD, relatively severe real dysfunction (defined as serum creatinine ≥97 μmol/L), hematological disorders, and acute disease conditions such as the common cold. Participants taking drugs known to affect blood cell counts were not included. The study procedures were approved by the ethics committees of Kyoto Medical Center, and each subject gave informed consent.

Current smoking habits were self-reported. The presence of MetS was determined in ≥3 out of 5 components according to the NCEP-ATPIII criteria with a minor modification of obesity for Japanese as follows (Expert Panel on Detection, Evaluation,
and Treatment of High Blood Cholesterol in Adults, 2001); 1) obesity identified as body mass index (BMI) \( \geq 25 \text{kg/m}^2 \) (a surrogate for waist circumference), 2) raised systolic BP \( \geq 130 \text{mmHg} \) and/or diastolic BP \( \geq 85 \text{mmHg} \), 3) raised fasting plasma glucose \( \geq 6.1 \text{mmol/L} \), 4) raised fasting serum triglyceride (TG) \( \geq 1.7 \text{mmol/L} \), 5) reduced fasting serum high-density lipoprotein (HDL)-cholesterol \( \leq 1.3 \text{mmol/L} \). BP was measured in the seated upper arm using a mercury sphygmomanometer. The presence of CKD was defined as \( \geq 60 \text{mL/min/1.73 m}^2 \) using the estimated glomerular filtration rate (eGFR) by the following formula of the new 4-variable Modification of Diet in the Renal Disease Study Group equation: \( 0.741 \times 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.201} \) \((>0.742 \text{ if women})\) (Imai et al., 2007). The glucose, TG, and creatinine were enzymatically determined, and HDL-cholesterol was determined using a homogeneous method. Hemorheology was assessed by the index of the ‘whole blood passage time (WBPT)’ of 100 \( \mu \text{L} \) of heparinized sample blood with the MC-FAN system (Hitachi Haramachi Electronics Co., Ltd., Osaka, Japan) (Kikuchi et al., 1994; Kotani et al., 2007; Kotani et al., 2008; Satoh et al., 2009). The WBPT values were determined by correction with the saline passage time.

Data were expressed as the subject number or mean \( \pm \) standard deviation (SD). A simple comparison between the groups was performed by the \( t \)-test or one-way analysis of variance (ANOVA) with post-hoc (Bonferroni) test for multiple comparisons. A general linear model for WBPT values (as a dependent variable) was used to examine the influence of MetS and CKD (as fixed variables) as well as the effect modification by their interaction between MetS and CKD. Covariates such as age, sex, and/or smoking habits were also entered into the adjusted models. All statistical analyses were performed with the Statistical Package for Social Science (SPSS) version 11.0 for Windows (SPSS Inc., Chicago, USA). A value of \( p \leq 0.05 \) was considered to be significant.

**Results**

As a result, the study population included 122 participants with obesity, 115 with raised BP, 63 with hyperglycemia, 75 with hypertriglyceridemia, and 19 with reduced HDL-cholesterolemia; and thus, 87 participants with MetS and 51 without MetS. They included 30 current smokers. The average values of eGFR were 79.8 \( \pm \)22.8 \( \text{mL/min/1.73 m}^2 \), and 33 participants had CKD and 105 did not have CKD. The average values of WBPT were 50.2 \( \pm \)11.8 sec, and the values of MetS participants were significantly higher than those of non-MetS participants (52.5 \( \pm \)13.1 vs. 46.3 \( \pm \)7.7 sec, \( p = 0.03 \)). The WBPT values of CKD participants were significantly higher than those of non-CKD (55.2 \( \pm \)12.7 vs. 48.6 \( \pm \)11.0 sec, \( p = 0.003 \)). These differences in the WBPT values between MetS and non-MetS participants as well as between CKD and non-CKD participants were unchanged even after adjusting for age and sex, as well as for age, sex, and smoking habits (data not shown).

In the subanalysis by sex, the averaged WBPT values were 51.8 \( \pm \)12.4 sec in men, and the values of MetS participants were significantly higher than those of non-MetS participants (54.4 \( \pm \)13.5 \([n=27]\) vs. 47.0 \( \pm \)8.4 sec \([n=48]\), \( p = 0.01 \)). The WBPT values of CKD participants were significantly higher than those of non-CKD (56.2 \( \pm \)12.5 \([n=28]\) vs. 49.1 \( \pm \)11.6 sec \([n=47]\), \( p = 0.016 \)). In women, the averaged WBPT values were 48.3 \( \pm \)10.9 sec (vs. those in men, \( p > 0.05 \)), and the values of MetS participants were nonsignificantly higher than those of non-MetS participants (50.1 \( \pm \)12.5 \([n=39]\) vs. 45.6 \( \pm \)6.9 sec \([n=24]\), \( p > 0.05 \)). The WBPT values of CKD participants were nonsignificantly higher than those of non-CKD (51.4 \( \pm \)15.0 \([n=5]\) vs. 48.1 \( \pm \)10.6 sec \([n=58]\), \( p > 0.05 \)).

In all participants, the significant influence of MetS and CKD on WBPT values was qualified by their effect modification to WBPT (in analyzing in the product-term: MetS\( \times \)CKD, \( p = 0.04 \)). This effect modification was unchanged after adjusting for age and sex, as well as for age, sex, and smoking habits (data not shown). As shown in Table 1, a significantly greater influence of the combined presence of MetS and CKD on WBPT was observed in comparison to the influence of non-MetS and CKD or that of non-CKD and MetS. After adjusting for age and sex, as well as for age, sex, and smoking habits, the results were unchanged (as described in the footnote to Table 1). In the subanalysis by sex, both men and women showed similar trends; however, in men, but women, a significant influence of the combined presence of MetS and CKD on WBPT was observed in comparison to the influence of non-MetS and CKD or that of non-CKD and MetS. After adjusting for age and sex, as well as for age, sex, and smoking habits, the results were unchanged (as described in the footnote to Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The influence of MetS and CKD on whole blood passage time (a hemorheological index) by sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ( \pm ) standard deviation</td>
</tr>
<tr>
<td>All (n=138)</td>
<td></td>
</tr>
<tr>
<td>MetS(-), CKD(-) (n=40)</td>
<td>46.3 ( \pm )8.5*</td>
</tr>
<tr>
<td>MetS(-), CKD(+) (n=11)</td>
<td>46.6 ( \pm )3.5a</td>
</tr>
<tr>
<td>MetS(+), CKD(-) (n=65)</td>
<td>50.0 ( \pm )12.2c,b</td>
</tr>
<tr>
<td>MetS(+), CKD(+) (n=22)</td>
<td>59.9 ( \pm )13.4a,b</td>
</tr>
<tr>
<td>Men (n=75)</td>
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</tr>
<tr>
<td>MetS(-), CKD(-) (n=18)</td>
<td>46.9 ( \pm )10.1</td>
</tr>
<tr>
<td>MetS(-), CKD(+) (n=9)</td>
<td>47.3 ( \pm )3.4c</td>
</tr>
<tr>
<td>MetS(+), CKD(-) (n=29)</td>
<td>50.5 ( \pm )12.4d</td>
</tr>
<tr>
<td>MetS(+), CKD(+) (n=19)</td>
<td>60.4 ( \pm )13.0d</td>
</tr>
<tr>
<td>Women (n=63)</td>
<td></td>
</tr>
<tr>
<td>MetS(-), CKD(-) (n=22)</td>
<td>45.8 ( \pm )7.1</td>
</tr>
<tr>
<td>MetS(-), CKD(+) (n=2)</td>
<td>43.2 ( \pm )1.4</td>
</tr>
<tr>
<td>MetS(+), CKD(-) (n=36)</td>
<td>49.5 ( \pm )12.1</td>
</tr>
<tr>
<td>MetS(+), CKD(+) (n=3)</td>
<td>56.9 ( \pm )18.3</td>
</tr>
</tbody>
</table>

MetS: metabolic syndrome, CKD: chronic kidney disease.

A general linear model analysis to examine the effect modification by the interaction between MetS and CKD: Model 1 unadjusted, Model 2 age-(and sex-) adjusted, Model 3 age-, (sex-) and current smoking habits-adjusted: Model 1 \( p = 0.001 \), \( p = 0.001 \), \( p = 0.006 \), \( p = 0.005 \); Model 2 \( p = 0.001 \), \( p = 0.001 \), \( p = 0.008 \), \( p = 0.024 \); Model 3 \( p = 0.001 \), \( p = 0.009 \), \( p = 0.026 \).
MetS and CKD on WBPT was observed in comparison to the influence of non-MetS and CKD or non-CKD and MetS.

Discussion

In the present study, MetS and CKD seemed to be respectively associated with an abnormal hemorheology as assessed by the microchannel method using MC-FAN. These influences on WBPT were likely consistent with previous reports showing that MetS could impair hemorheology measured by this method (Kotani et al., 2007) and that CKD could have an abnormal hemorheology (Simpson et al., 1987). The more important finding of the present study is that the hemorheological impact might be significantly amplified by the combination of MetS and CKD, in men in particular. This finding can partly support the concept that the hemorheological viewpoint of coexistent conditions is necessary for understanding and managing the pathophysiology of CVD formation in relation to MetS and CKD.

In general, men have a higher incidence of CVD, coronary heart disease in particular, than women (Shu et al., 2007). To date, there are no reports on the effects of the combination of MetS and CKD on CVD occurrence. The influence of CKD on CVD incidence can reportedly be greater in men than in women (Ishizaka et al., 2007). A number of reports suggest that MetS, defined by NCEP-ATPIII criteria, as in our study, may influence the incidence of CVD, coronary heart disease in particular, in men relative to women (Qiao, 2006). Our present study result of a clear impact of the combination of MetS and CKD on WBPT in men, as a feature of sex difference, might be a reason for a higher incidence of CVD in men. Unfortunately, although the precise mechanisms of this phenomenon are unclear, sex-specific differences in physiological properties of blood (e.g., sex hormones and subsequent hemodynamics as well as endothelial conditions) and/or lifestyle-related factors may be considered as an underlying mechanism (Kameneva et al., 1999; Mercurio et al., 2003).

Furthermore, our study had a number of limitations. The present findings are inherently restricted with regard to causal correlations because of the cross-sectional study design. The small sample size might mean that our study findings could not be considered to be conclusive. Whereas CKD was defined using eGFR, eGFR may not always provide an accurate estimate of the true GFR (though it is more accurate than serum creatinine or the Cockcroft-Gault formula (Froissart et al., 2005)). While a single eGFR measurement has been a common approach in many epidemiological studies (Onat et al., 2007; Gatti et al., 2008; Lee et al., 2008), we also acknowledge that this eGFR measurement, without information on continuous eGFR decline and micro-albuminuria, is a weakness in mentioning CKD. In addition, since hemorheology can be modified by serum concentrations of protein and blood cell counts, future studies including these factors must be conducted.

In summary, abnormal hemorheology as assessed using MC-FAN may be enhanced by the combination of MetS and CKD. Further investigation into hemorheological roles in CVD development in MetS, CKD, and their combined association is therefore required.

Acknowledgements

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