Abdominal obesity is the most significant metabolic syndrome component predictive of cardiovascular events in chronic hemodialysis patients

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Abstract

Background. Five components of metabolic syndrome (MetS) have been identified as predictive of cardiovascular events (CVEs) in the general population: impaired fasting glucose, abdominal obesity, hypertriglyceridemia, hypertension and low high-density lipoprotein cholesterol. Whether MetS and its components are also predictive of CVEs in chronic hemodialysis (HD) patients remains unclear. We therefore investigated the role of MetS and its components in patients on chronic HD.

Methods. MetS at baseline was diagnosed in 91 HD patients based on the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF) definitions. During a 3-year period, all hospitalizations, CVEs and deaths were recorded and analyzed using Kaplan–Meier survival analysis and Cox regression.

Results. There were no differences in the number of CVEs, hospitalizations or deaths between patients with and without AHA/NHLBI-defined MetS; however, patients with IDF-defined MetS were found to be at a higher risk for CVEs (P = 0.006). Cox regression analysis showed that, of the MetS components, abdominal obesity was the single most significant predictor of CVEs (hazard ratio 6.25; 95% confidence interval: 1.65–23.6; P = 0.007).

Conclusions. IDF-defined MetS was more predictive of CVEs than AHA/NHLBI-defined MetS. Of the MetS components, abdominal obesity was the single most significant predictor of CVEs in chronic HD patients.

Keywords: hemodialysis; metabolic syndrome; obesity

Introduction

Metabolic syndrome (MetS) refers to a cluster of cardiovascular (CV) risk factors thought to be more reliable than its individual components at predicting CV risk in the general population [1]. There are multiple definitions of MetS, and most current MetS definitions recognize five components: hypertension, impaired fasting glucose, hypertriglyceridemia, abdominal obesity and low high-density lipoprotein cholesterol (HDLC). The most common definitions in current use are the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) [2] definition (2001), the International Diabetes Federation (IDF) [3] definition (2005) and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) definition (2005) [4].

The core components of MetS, as defined by the World Health Organization (WHO) in 1998 [5], include impaired glucose regulation or diabetes, or insulin resistance (under hyperinsulinemic euglycemic conditions), together with two or more of the following: central obesity, raised arterial pressure, raised plasma triglyceride (TG), low HDLC and microalbuminuria.

The NCEP/ATP III definition does not include insulin resistance as a criterion, thereby making the diagnosis of MetS easier and more practical. The IDF definition assigns a lower cutoff value for impaired fasting glucose than do other definitions (from 110 mg/dL to 100 mg/dL). In addition, abdominal obesity is a mandatory component with ethnicity-specific cutoff values for waist circumference (WC). The AHA/NHLBI definition includes the same criteria as the NCEP-ATP III definition, with the exception of impaired fasting glucose (identical with the IDF definition: 100 mg/dL); it also assigns the same ethnicity-specific cutoff values for WC as does the IDF.
definition. Cardiovascular disease (CVD) is the leading cause of death in the hemodialysis (HD) population [6]. Insulin resistance, thought to be the common denominator of MetS, is a predictor of CV mortality in HD patients [7].

Although several studies [8, 9] have compared the different definitions of MetS in the general population, few have compared the definitions of MetS in HD patients [10–12]. To date, the reported prevalence of MetS in chronic HD patients ranges from 40–60%; most of these studies were cross-sectional in design and none analyzed the relationships between the individual components of MetS or the development of CVD in chronic HD patients [10–14]. In this study, we used IDF and AHA/NHLBI definitions because they share identical cutoff values for the five criteria used to diagnose MetS; a prerequisite criterion of abdominal obesity in the IDF definition is the sole difference between the two. The purpose of the current study was to evaluate the validity and reliability of these two MetS definitions and their individual components for predicting hospitalization, cardiovascular events (CVEs) and mortality in chronic HD patients.

Patients and methods

Study design and population

This was a prospective cohort study conducted in the HD unit of the E-DA hospital in Taiwan. We initially recruited 104 patients who had received chronic HD treatment, 4 h each session, three times a week for >3 months at our hospital. Exclusion criteria included irregular or inadequate HD therapy with a mean Kt/V <1.2 within 3 months before entry, inability to measure WC and evidence of hypercatabolic disease. WC cutoff points were based on those for the Chinese population [3].

AHA/NHLBI-defined MetS was diagnosed in patients with three or more of the following components: impaired fasting glucose (≥100 mg/dL) or a preexisting diagnosis of impaired glucose tolerance or diabetes; abdominal obesity (WC ≥90 cm in men or ≥80 cm in women); hypertriglyceridemia (≥150 mg/dL); hypertension (≥130/85 mmHg) and low HDL-C levels (<40 mg/dL in men, <50 mg/dL in women). IDF-defined MetS was diagnosed in patients with abdominal obesity who met two or more of the other above-mentioned criteria. Patient follow-ups lasted 3 years or until the patient died. Our study protocol was approved by the E-DA Hospital Institutional Review Board, and written informed consent was obtained from each patient.

Data collection

Patient characteristics taken into consideration for this study included age, gender, duration of HD and smoking status. An 8-h fasting blood sample was obtained from each patient immediately before the midweek HD session for a complete blood cell count and analysis of biochemistry data at baseline. WC measurement was taken after the same HD session by our specialist dietitian. WC was measured at the midpoint between the iliac crest and the lowest rib at the end of a normal expiration in upright position. Blood pressure (BP) at baseline was measured with the patient in a sitting position immediately before HD. Hypertension was diagnosed in patients on antihypertensive drugs or with two of three BP measurements ≥130/85 mmHg.

Patients were then followed up for 3 years, during which time major CVEs, all-cause hospitalizations and deaths were recorded. Major CVEs included ischemic heart disease, congestive heart failure and cerebrovascular disease.

Statistical analysis

All values are expressed as means ± SDs as well as medians and interquartile ranges. Between-group differences in continuous variables were analyzed using Student’s t-test or the Mann–Whitney U-test, depending on the normality of the variables. The Cohen’s kappa coefficient was used to evaluate the agreement of the two MetS definitions. Kaplan–Meier analysis with the log-rank test was used to evaluate the all-cause mortality rate and predictability of CVEs and hospitalization.

Patients who received a kidney transplantation were transferred to other HD units or were shifted to peritoneal dialysis; their survival data were censored. Cox regression analysis was used to identify the variables that were most predictive of mortality, CVEs and hospitalization. Variables with a P-value <0.1 in univariate analysis were then analyzed using multivariate analysis. All data were analyzed on a personal computer using SPSS for Windows 15.1 (SPSS Inc., Chicago, Ill) or MedCalc for Windows 10 (MedCalc Software bvba, Mariakerke, Belgium). Except in univariate analysis, significance was set at P < 0.05.

Results

Characteristics of the study population

Thirteen patients were excluded because of (i) poor compliance with their HD schedule (n = 2), (ii) unwillingness to have their WC measured (n = 4), (iii) an inability to measure WC because they were bedridden with either cirrhosis with ascites or autosomal dominant polycystic kidney disease (n = 5) and (iv) acute infectious illness at the beginning of the study (n = 2). The final study population was 91 patients: 50 men and 41 women. The mean age was 58.7 ± 12.5 years (range: 25–80 years) when the study began. The median HD duration was 25 months (interquartile range: 6–30). Causes of chronic renal failure in our patients were type 2 diabetes (26.4%), hypertension (14.3%), glomerulonephritis (11%) and other causes (48.3%). Twenty-six patients had diabetes, and all were identified as type 2 diabetes.

Thirty patients were being treated with regular antihypertension drugs: calcium channel blockers (CCBs) (n = 23), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) (n = 12), beta-adrenergic blockers (beta-blockers) (n = 11) and others (n = 2). Thirteen of these 30 patients were taking two or more antihypertension drugs.

There were no differences in age, gender, smoking status or duration of HD between the two groups of patients (Table 1). Statistical agreement between the two MetS definitions in our study was significant (Cohen’s kappa coefficient = 0.61; P < 0.001).

Prevalence of MetS and its components

The prevalence of AHA/NHLBI-defined MetS was 50.5% (n = 46) and that of IDF-defined MetS was 30.8% (n = 28) for patients participating in this study.

Overall, 96% (n = 87) of our chronic HD patients had at least one MetS component. Of the patients with AHA/NHLBI-defined MetS, 17 (37%) had three components, 14 (30.4%) had four components and 15 (32.6%) had five components of MetS.

In patients with AHA/NHLBI-defined MetS, hypertension was the most prevalent MetS component (80.2%), followed by hyperglycemia (54.9%), low HDL-C (54.9%), hypertriglyceridemia (45.1%) and abdominal obesity (34.1%). In patients with IDF-defined MetS, all of whom uniformly had abdominal obesity (100%), hypertension and low HDL-C (both 89.3%) were the second most
prevalent symptoms followed by hypertriglyceridemia (85.7%) and hyperglycemia (82.1%).

All-cause mortality, the probability of CVEs and hospitalization

During the 3-year follow-up period, 15 patients died because of arrhythmia (n = 3), sepsis (n = 8), sudden death (n = 3) and hepatoma with liver failure (n = 1). There were no significant differences in all-cause mortality between patients with and without AHA/NHLBI-defined MetS (P = 0.12) or between patients with and without IDF-defined MetS (P = 0.32). Older age, lower hemoglobin, lower serum albumin and a greater level of high-sensitivity C-reactive protein (hs-CRP) were found to be significant predictors of all-cause mortality in univariate Cox regression analysis. But after adjusting for each of these factors, only older age [hazard ratio (HR) 1.09; 95% confidence interval (CI): 1.0–1.2, P = 0.001] and a greater level of hs-CRP (HR 1.04; 95% CI: 1.01–1.07, P = 0.006) were significant predictors of all-cause mortality (Table 2). None of the MetS components was significantly predictive of mortality. Other factors, such as the causes of chronic renal failure, dialysis adequacy and treatment with beta-blockers, CCB or ACEI/ARB, were not significantly associated with all-cause mortality.

During the 3-year follow-up period, there were 19 CVEs in 11 patients. There was no significant difference in the number of CVEs between patients with and patients without AHA/NHLBI-defined MetS (P = 0.12) during that time; however, the number of CVEs was greater among patients with IDF-defined MetS than among those without it (P = 0.01). Kaplan–Meier analysis showed no significant difference in the number of CVEs between patients with and patients without AHA/NHLBI-defined MetS (P = 0.076). Patients with IDF-defined MetS, however, were more likely to have CVEs than patients without IDF-defined MetS (P = 0.006) (Figure 1). Of the five MetS components, only abdominal obesity indicated a higher probability of CVEs (P = 0.002) (Figure 2).

In univariate Cox regression analysis, only abdominal obesity proved to be a significant predictor of CVEs (HR: 6.25; 95% CI: 1.65–23.6; P = 0.007). However, when we focused on preexisting diabetes only, instead of impaired fasting glucose, patients with preexisting diabetes had a higher risk of CVEs (HR: 5.56; 95% CI: 1.6–19.1; P = 0.021). After adjusting for the multivariate model, both abdominal obesity (HR: 4.91; 95% CI: 1.3–18.9; P = 0.021) and preexisting diabetes (HR: 4.24; 95% CI: 1.2–14.8; P = 0.023) continued to be significantly predictive of CVEs.

Treatment with antihypertensive drugs was not significantly associated with CVEs in our patients, even when considered in the subgroup of patients with hypertension.

Fifty-nine patients were hospitalized during the study period. The total number of hospitalizations was 155. Reasons for hospitalization included CVD (n = 19), infection (45), intervention of HD vascular access (14) and others (n = 77). The number of hospitalizations did not differ significantly between patients with and without AHA/
NHLBI-defined and those with and without IDF-defined MetS. Neither AHA/NHLBI-defined MetS (P = 0.57) nor IDF-defined MetS (P = 0.12) was predictive of hospitalization. However, patients with abdominal obesity showed a significantly higher probability of being hospitalized (P = 0.038) (Figure 3). In univariate Cox regression analysis, older age, lower serum albumin and abdominal obesity were all risk factors for all-cause hospitalization. After adjusting for the multivariate model, a lower serum albumin level (HR: 3.3; 95% CI: 1.0–10.2; P = 0.02) continued to be significant for predicting all-cause hospitalization.

The more components of MetS are evident, the higher the CV mortality rate becomes for patients in the general population [15]. In our study, the more components of MetS that were evident also predicted a greater number of CVEs (HR: 1.68; 95% CI: 1.1–2.6; P = 0.02) but not more all-cause mortality or hospitalization.

### Table 2. Results of the univariate and multivariate Cox regression models of all-cause mortality, cardiovascular events and all-cause hospitalization in chronic HD patients

<table>
<thead>
<tr>
<th>Criteria of MetS (yes versus no)</th>
<th>All-cause mortality</th>
<th>CVEs</th>
<th>All-cause hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.67</td>
</tr>
<tr>
<td>Gender</td>
<td>0.47</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Male versus female</td>
<td>0.69</td>
<td>(0.2–1.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>HD duration (months)</td>
<td>0.27</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Hb (mg/dL)</td>
<td>0.003</td>
<td>0.09</td>
<td>0.48</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>0.002</td>
<td>0.10</td>
<td>0.28</td>
</tr>
<tr>
<td>Pre-existing DM</td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Yes versus no</td>
<td>0.43</td>
<td>(0.1–0.6)</td>
<td>0.35</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.79</td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>spKt/V</td>
<td>1.31</td>
<td>(0.2–9.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>1.03</td>
<td>(0.5–2.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Antihypertension drugs (yes versus no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>0.45</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>CCB</td>
<td>0.46</td>
<td>(0.1–3.1)</td>
<td>2.89</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>0.25</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>Criteria of MetS (yes versus no)</td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>HTN</td>
<td>1.04</td>
<td>(0.1–1.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>IFG</td>
<td>0.04</td>
<td>(0.01–18.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>High TG</td>
<td>1.38</td>
<td>(0.5–3.9)</td>
<td>2.49</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>0.87</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>1.09</td>
<td>(0.4–3.0)</td>
<td>1.58</td>
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<tr>
<td>AHA/NHLBI-MS</td>
<td>0.21</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Yes versus no</td>
<td>2.54</td>
<td>(0.8–8.0)</td>
<td>2.55</td>
</tr>
<tr>
<td>IDF-MS</td>
<td>0.13</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Yes versus no</td>
<td>2.3</td>
<td>(0.8–6.8)</td>
<td>3.13</td>
</tr>
</tbody>
</table>

aData are expressed as P-value and hazard ratio (95% CIs). A P-value <0.05 is considered significant. DM, diabetes mellitus; Hb, hemoglobin; HTN, hypertension; IFG, impaired fasting glucose; spKt/V, single-pool Kt/V.
We examined the effect of AHA/NHLBI-defined and IDF-defined MetS and its five components on the rate of any-cause mortality, CVEs and all-cause hospitalization in chronic HD patients. We found that neither AHA/NHLBI-defined nor IDF-defined MetS had a significant effect on the any-cause mortality or all-cause hospitalization rates but that IDF-defined MetS had prognostic value for CVEs in chronic HD patients. Of the five MetS components, only abdominal obesity predicted CVEs, and its predictive power was stronger than that of IDF-defined MS in chronic HD patients.

It is well known that patients on chronic HD experience metabolic disturbances such as uremia, oxidative stress due to the dialysis procedure, acidosis, malnutrition and microinflammation. We hypothesize that this occurs because the current standard criteria for diagnosing MetS in the general population are inappropriate or have different cutoff values for chronic HD patients.

Interdialytic ambulating blood pressure (ABP) monitoring provides more accurate information than clinic BP measurement [17]. However, neither predialysis nor postdialysis BP readings can estimate ABP precisely in HD patients [18]. It has been suggested that an average of multiple BP values improves BP determination when interdialytic ABP monitoring is not available [19].

In this study, we used the average of three BP readings as the BP reference; however, BP was not found to be a significant risk factor for CVEs or all-cause mortality in our HD patients. Our findings support another study [20] that found no correlation between an average of six BP measurements and the prevalence of coronary heart disease or cerebrovascular disease in a cohort of 995 Taiwanese HD patients. We believe that the extremely high prevalence of hypertension in chronic HD patients confounds its possible significance between patients with and without MetS. Pulse pressure has been reported [21] as a risk factor for all-cause mortality and CVEs in chronic HD patients; however, when we used pulse pressure as the BP reference in our study, we found no correlation with CVEs or all-cause mortality.

Diabetes is an independent risk factor for CVD in patients undergoing maintenance HD [21]. Hyperglycemia, before blood glucose is high enough to be diagnosed as diabetes, also increases the risk of CVD [16]. Our study found that a preexisting diagnosis of diabetes mellitus, rather than the hyperglycemia criterion of MetS, was predictive of CVEs.

We also showed that abdominal obesity was a significant risk factor for CVD and all-cause hospitalization in chronic HD patients. A paradoxical relationship between survival and obesity in chronic HD patients has been reported in...
several studies [22–24]. However, an association in Asian populations has yet to be found [25, 26]. An ethnicity-specific phenomenon is therefore suspected [27]. Abdominal obesity, defined using WC, is a significant risk factor for both all-cause and CV mortality in patients with end-stage renal disease [28]. Our study found that obesity correlated only with a poor CV outcome and all-cause hospitalization. The lack of an association between abdominal obesity and survival may be due to our small study population. Intra-abdominal fat and insulin resistance are acknowledged as important causative factors of MetS [29], and WC is considered a simple anthropometric index of intra-abdominal fat accumulation [30]. Abdominal obesity was thought to be associated with higher CVD risk independent of other MetS components; thus, the IDF includes abdominal obesity as a prerequisite criterion of MetS. Because abdominal obesity was the most distinguishing component of MetS in our chronic HD patients, we conclude that it explains why the IDF definition of MetS outperformed the AHA/NHLBI definition in predicting CVEs in our chronic HD patients.

In addition to increased energy intake, low energy expenditure is an important factor of obesity. There are several determinants of energy expenditure, including climate, age, hormones and physical activity. Whether a metabolic disturbance of related hormones or peptides by uremic toxins, HD procedures and limited physical activity causes obesity in chronic HD patients remains unclear. We also do not know whether adequate body weight reduction by increased physical activity or exercise provides positive benefits for obese HD patients.

Of the dyslipidemia components of MetS, neither elevated TG nor low HDL-C was found to be a risk factor in predicting all-cause mortality, CVEs or all-cause hospitalization in our study. Elevated TG and low HDL-C are characteristics of dyslipidemia in MetS and also in end-stage renal disease treated with HD. However, the association between survival and elevated TG, low HDL-C and even total cholesterol have not been clearly demonstrated [31–34]. Other complicated mechanisms, like recurrent reperfusion injury during HD or sympathetic overactivity and autonomic nerve dysfunction other than plaque rupture due to atherogenic dyslipoproteinemias, may also attenuate the association of dyslipidemia to CVEs and survival [35, 36].

Although only abdominal obesity was shown to be a significant criterion in predicting CVEs, other MetS components still demonstrated a tendency toward a higher incidence of CVEs in our study.

There were some limitations to this study. First, our study population was relatively small and end point events were few, which may have attenuated the effect of some important risk factors. Second, most data were collected at a single point in time, which may not have been a true reflection of patient circumstances.

Conclusion

In conclusion, we showed a high prevalence of MetS and its components in chronic HD patients. The IDF definition was more predictive than the AHA/NHLBI definition of CVEs in chronic HD patients. Of the five components of MetS, abdominal obesity was the single most significant predictor of long-term CVEs and all-cause hospitalization.

Conflict of interest statement. None declared.

References

Impact of dialysate calcium concentration on the progression of aortic stiffness in patients on haemodialysis

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Abstract

Background. Higher dialysate calcium (DCA) can result in an acute and transient increase in arterial stiffness. The aim of the present study is to evaluate the impact of DCA on the progression of arterial stiffness, calcium balance and bone metabolism in haemodialysis (HD) patients over a 6-month period.

Method. We randomly assigned 30 patients on chronic HD to be dialysed with a DCA of 1.12 or 1.37 mmol/L for a period of 6 months. Aortic stiffness and brachial stiffness were respectively measured by carotid-femoral pulse wave velocities (cf-PWV) and carotid-radial pulse wave velocity (cr-PWV) at baseline and at 3 and 6 months. Central pulse pressure (PP) and augmentation index were determined by radial artery tonometry. Dialysis calcium balance and parathyroid hormone (PTH) were measured monthly. Pro-collagen type-1 amino-terminal propeptide (P1NP) and C-terminal telopeptide of type-I collagen (CTX) were used as markers of bone formation and resorption, respectively. Data was analysed by linear mixed model.

Results. Twenty-seven patients (66 ± 13 years old) with a mean duration of HD of 5.8 ± 3.6 months completed the study. At baseline, the groups were similar with respect to age, serum levels of calcium, phosphate and PTH, blood pressure (BP), cf-PWV and cr-PWV. The cf-PWV at baseline and 3 and 6 months were, respectively, 13.4 ± 4.2,