An integrative view on the carotid artery alterations in metabolic syndrome

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ABSTRACT

Backgrounds Metabolic syndrome (MetS) is a multiple risk factor paradigm widely considered in risk management. We aimed to investigate carotid artery alterations in MetS and the underlying risk factors.

Materials and methods A total of 400 Chinese subjects were recruited, divided into control (n = 200) and MetS (n = 200) groups. Clinical and laboratory characteristics were collected. All subjects underwent carotid ultrasonography.

Results Cardiovascular risk profiles were worse in the MetS than control group (all \( P < 0.05 \)). After adjusting for MetS and age, the MetS group showed significantly increased mean intima-media thickness (IMTmean) and significantly impaired carotid elastic properties (all \( P < 0.05 \)), as compared to control group. Waist circumference (WC) was positively correlated with IMTmean (\( r = 0.130, P = 0.038 \)), systolic carotid diameter (\( r = 0.139, P = 0.026 \)) and diastolic carotid diameter (\( r = 0.168, P = 0.007 \)). Systolic blood pressure (SBP) and diastolic blood pressure were positively correlated with IMTmean (\( r = 0.201, P = 0.004; r = 0.168, P = 0.008 \), respectively), but negatively with arterial compliance coefficient (\( r = -0.421, P < 0.001; r = -0.230, P < 0.001 \), respectively). Serum level of high-density lipoprotein (HDL) negatively correlated with IMTmean (\( r = -0.195, P = 0.002 \)). Plaque index was positively correlated with fasting blood glucose (\( r = 0.205, P = 0.001 \)) after adjusting for the other risk factors. Significantly impaired carotid elastic properties (all \( P < 0.05 \)) independently correlated with IMTmean. Furthermore, age (\( \beta = 0.255, P < 0.001 \)), SBP (\( \beta = 0.224, P < 0.001 \)), WC (\( \beta = 0.202, P < 0.001 \)) and high-density lipoprotein cholesterol (HDL-C) (\( \beta = -0.163, P = 0.001 \)) were independently associated with IMTmean.

Conclusion Carotid alterations consequent upon MetS ultimately developed subclinical and clinical atherosclerosis, the underlying risk factors for which were abdominal obesity, hypertension, ageing and low level of HDL-C.

Keywords Carotid alterations, metabolic syndrome, ultrasonography.

Introduction

With the increasing affluence and ageing of the world population, the prevalence of obesity has been associated with a pandemic metabolic syndrome (MetS) [1]. The syndrome, the most devastating conditions being type 2 diabetes mellitus and atherosclerotic cardiovascular disease (CVD), is reaching epidemic proportions and causing a parallel rapid growth in CVDs [2,3].

As multiple risk factors raise risk of atherosclerotic CVD more than the sum of accompanying single risk factors [4], a more effective prediction tool is to identify atherosclerotic burden through non-invasive imaging. Increased carotid intima-media thickness (IMT) has been found directly associated with risk of vascular events [5]. However, to what extent MetS per se exerts a direct effect or indirect effects on alterations of carotid artery warrants further investigation.

Lifestyle therapies in accordance with current guidelines are recommended for MetS. Drug therapy is a secondary consideration guided by global risk assessment [6]. The present therapeutic strategies that target multiple risk factors commonly lead to the use of multiple medications (polypharmacy), which
carries the risk of adverse drug interactions and interferes with therapy compliance, and for many patients, the cost is prohibitive [7]. Therefore, attacking multiple risk factors with a single drug or a drug combination is attractive. However, the predominant components of MetS that cause carotid artery alterations must be assessed to determine the focus of drug therapy. Therefore, we aimed to investigate the alterations of carotid artery in MetS and the corresponding underlying components.

**Materials and methods**

**Subjects**
Four hundred Chinese subjects ranging from 30 to 74 years old were recruited from the Qilu Hospital of Shandong University: 200 subjects (86 men; mean age 52.2 ± 9.3 years) with MetS [8]; 200 subjects (controls; 90 men; mean age 51.3 ± 9.7 years) without CVDs or elevated fasting plasma glucose (≥ 5.6 mM) and with waist circumference (WC) < 90 cm for men and 80 cm for women. Written informed consent was obtained from all subjects before enrolment in the study, and procedures were approved by the ethics committees of Qilu Hospital of Shandong University and followed the Helsinki Declaration criteria. Reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.

Subjects fasted for at least 12 h before the screening visit. Screening included the completion of standardised questionnaires collecting personal information and data on age, sex, personal medical history, and history of CVDs, dyslipidemia and diabetes. Blood pressure was measured twice in the right arm at 2 min intervals. Waist circumference was measured at the mid-point between the iliac crest and the lower rib margin and hip circumference around the maximum circumference of the buttocks posteriorly and the symphysis pubis anteriorly.

**Laboratory measurements**

Blood samples were separated into serum and plasma preserved with EDTA immediately by centrifugation at 2500 × g for 10 min. Glucose measurements involved the glucose oxidase method. Total cholesterol (TC) and total triglyceride levels were determined by enzymatic methods. High-density lipoprotein cholesterol (HDL-C) was measured in the supernatant after precipitation of apo B-containing lipoproteins with use of phosphotungstic acid and magnesium chloride. Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula. LDL-C was not calculated for individuals with triglyceride level > 4.5 mM. Serum concentration of insulin was determined by a radioimmunometric assay kit (Dongya Ltd, Haidian District, Beijing, China). Intra- and interassay coefficients of variation for insulin were 10% and 15%, respectively; no cross-reactivity was observed between insulin and proinsulin. Insulin resistance (IR) was determined from glucose and insulin concentrations according to the homeostasis model assessment (HOMA) equation [9].

**Carotid ultrasonography**

All B-mode ultrasonography of the carotid arteries was performed by single trained clinical technician. Ultrasound images of both the right and left common carotid arteries were acquired by use of a 7.5-MHz linear array transducer and a commercially available ultrasound machine (Vivid 7 dimension; General Electric Medical Systems, Horten, Norway). IMT, plaque extent of the near and far walls of the common and internal carotid arteries and bifurcations were measured according to the ACAPS protocol [10]. Maximal and mean IMT (IMTmax and IMTmean) were defined as the greatest and mean values, respectively, of IMT measured from three contiguous sites at 1-cm intervals. IMTmax represented the highest single measurement at any site with plaque.

Plaque was evaluated by ultrasonography in the proximal common, distal common, carotid bulb, internal carotid and external carotid. For each segment, the degree of plaque was graded as follows: 0 = no plaque; 1 = one small plaque < 30% of vessel diameter; 2 = one medium plaque between 30% and 50% of the vessel diameter or multiple small plaques; and 3 = one large plaque > 50% of the vessel plaque or multiple plaques with at least one medium plaque. The grades were then summed across right and left carotid arteries for an overall measure of the extent of focal plaque, termed the plaque index [11].

Stiffness of the common carotid artery was evaluated by M-mode ultrasonography and determined by the stiffness index (β) [12]. Specifically, the stiffness index was β = ln(SBP/DBP)/(D2s-D2d)/Dd, where Ds and Dd are the end-systolic and end-diastolic diameters of the common carotid artery, respectively, and SBP and DBP are the systolic and diastolic blood pressures, respectively.

Arterial compliance coefficient (ACc) [13] to show absolute change in lumen area during systole for a given pressure change, was determined as follows: ACc = ∆A/∆p, where ∆A equal to [π(D2s-D2d)/4] is the stroke change in lumen area, and ∆p is pulse pressure.

Pressure strain elastic modulus (Ep) [14] was calculated from carotid strain and the changes in brachial artery pressure by the following formula: Ep = (SBP−DBP)/(D2s−D2d)/Dd, pressure strain normalised by diastolic pressure (Ep’) was calculated as follows: Ep’ = Ep/DBP. Ep’ is a dimensionless ratio, whereas Ep has dimension and is represented with unit kPa.

Reproducibility of ultrasound measures was 95%.
Statistical analysis

The Kolmogorov-Smirnov test was used to test for normal distribution. Normally distributed data are presented as means ± SD, and non-normally distributed data are presented as medians (interquartile range). Continuous variables were compared between groups by unpaired Student’s t test or Mann–Whitney U test and categorical variables by chi-square test. ANCOVA was used to compare alterations of carotid artery between groups, adjusting for MetS and age. Multiple linear regression analysis was used to evaluate the contribution of risk factors. The correlation between two variables was assessed by Pearson or Spearman correlation coefficient analysis. After controlling for covariates, bivariate correlations underwent partial correlation analysis. A P value < 0.05 was considered statistically significant. Analyses involved SPSS v. 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline demographic features

The clinical and biochemical characteristics of the two groups of the subjects are in Table 1. The two groups did not differ by age and gender. As expected, cardiovascular risk profile was worse for the MetS than control group (P-values in Table 1).

Alterations of carotid artery related to MetS

Compared with the control group, the MetS group showed significantly increased IMTmean, IMTmax, plaque index, $D_o$, Ep*, β and decreased ACc (Table 2; all $P < 0.05$). Even after adjusting for WC, SBP, DBP, triglycerides (TG), HDL, fasting blood glucose (FBG) and age, the MetS group still showed significantly increased IMTmean, Ep*, β and decreased ACc (Table 2; all $P < 0.05$), but no difference was detected in IMTmax plaque index, and $D_o$ (Table 2; all $P > 0.05$).

Relationship of MetS components and carotid artery alterations

MetS is a cluster of cardiovascular risk factors. Abdominal obesity is the most prevalent manifestation of MetS. In the present study, WC is positively correlated with IMTmean, IMTmax plaque index, $D_o$, Ep* and β (Table 3; all $P < 0.005$), but negatively associated with ACc (Table 3; $P < 0.005$). After controlling for age, gender, SBP, DBP, TG, HDL, LDL, FBG, fasting insulin and HOMA-IR, partial correlation analysis showed that WC was still positively correlated with mean IMTmean ($r = 0.130, P = 0.038$) and $D_o$ ($r = 0.139, P = 0.026$).

Hypertension plays a prominent role in MetS. Here, systolic BP is positively correlated with IMTmean, IMTmax plaque index, $D_o$, Ep* and stiffness index (Table 3; all $P < 0.005$), but negatively associated with ACc (Table 3; $P < 0.005$). It is the same with DBP. After adjusting for age, gender, BMI, WC, TC, TG, HDL, LDL, FBG, fasting insulin and HOMA-IR, partial correlation analysis showed that SBP was still positively correlated with IMTmean ($r = 0.201, P = 0.004$), Ep* ($r = 0.281, P < 0.001$) and stiffness index ($r = 0.370, P < 0.001$), but negatively associated with ACc ($r = -0.421, P < 0.001$). As for DBP, it was still positively correlated with IMTmean ($r = 0.168, P = 0.008$), but negatively associated with ACc ($r = -0.230, P < 0.001$).

MetS is characterised by hypertriglyceridaemia as well. In our study, serum TG is positively correlated with IMTmean, IMTmax plaque index, $D_o$, Ep* and stiffness index (Table 3; all $P < 0.005$), but negatively associated with ACc (Table 3; $P < 0.005$). After adjusting for age, gender, BMI, WC, SBP, DBP, TC, HDL, LDL, FBG, fasting insulin and HOMA-IR, partial correlation analysis showed that serum TG was no longer correlated with any carotid artery variables.

Low HDL is a risk factor for CVDs. In our study, HDL is positively correlated with IMTmean, IMTmax plaque index, $D_o$.

Table 1 Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 200)</th>
<th>MetS (n = 200)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>90/110</td>
<td>86/114</td>
<td>0.687</td>
</tr>
<tr>
<td>Age (years)</td>
<td>513 ± 9.7</td>
<td>52.2 ± 9.3</td>
<td>0.344</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.43 ± 2.91</td>
<td>29.00 ± 4.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>84.21 ± 8.51</td>
<td>98.15 ± 10.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WHR</td>
<td>0.86 ± 0.06</td>
<td>0.93 ± 0.06</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116 ± 11</td>
<td>150 ± 23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 ± 7</td>
<td>94 ± 14</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TC (mM)</td>
<td>4.60 ± 0.80</td>
<td>5.36 ± 1.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TG (mM)</td>
<td>0.97 (0.56)</td>
<td>2.08 (1.22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL-C (mM)</td>
<td>1.54 ± 0.34</td>
<td>1.25 ± 0.40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LDL-C (mM)</td>
<td>2.88 ± 0.71</td>
<td>3.60 ± 0.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>UA (µM)</td>
<td>259.39 ± 75.70</td>
<td>330.60 ± 89.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FBG (mM)</td>
<td>4.86 ± 0.57</td>
<td>6.62 ± 2.52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Insulin (uU/mL)</td>
<td>9.88 (4.89)</td>
<td>17.98 (10.99)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.00 (1.25)</td>
<td>5.02 (3.80)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>4.61 ± 0.30</td>
<td>5.48 ± 1.24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>29%</td>
<td>40%</td>
<td>0.021</td>
</tr>
</tbody>
</table>

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment for insulin resistance.
Plaque index 0 (0) 0 (2) < 0 < 0.01

\[ \text{IMTmax} = 0 \pm 0.75 \pm 0.75 \]

\[ \text{D_s} = 0.65 \pm 0.07 \pm 0.68 \pm 0.10 \pm 0 < 0 < 0.01 \]

\[ \text{Ep*} = 7.97 \pm 4.49 \pm 23.04 \pm 15.05 \pm 0 < 0 < 0.001 \]

\[ \beta = 6.69 \pm 3.15 \pm 17.54 \pm 10.67 \pm 0 < 0 < 0.01 \]

\[ \text{ACc} = 0.85 \pm 0.35 \pm 0.35 \pm 0.23 \pm 0 < 0 < 0.001 \]

\[ P^*, \text{adjusted for WC, SBP, DBP, TG, HDL, FBG and age.} \]

\[ \text{ACc, arterial compliance coefficient; } \beta, \text{ stiffness index; } D_s, \text{ end-systolic diameters; } \text{Ep*}, \text{ normalised pressure strain elastic modulus; IMT, intima-media thickness.} \]

Ep* and stiffness index (Table 3; all \( P < 0.005 \)), but negatively associated with ACc (Table 3; \( P < 0.005 \)). After controlling for age, gender, BMI, WC, SBP, DBP, TC, TG, LDL, FBG, fasting insulin, and HOMA-IR, partial correlation analysis showed that serum HDL had a negative correlation with IMTmean (\( r = -0.195, P = 0.002 \)).

Elevated FBG is a major factor in dysmetabolism. In our study, FBG is positively correlated with IMTmean, IMTmax, plaque index, \( D_s \), Ep* and stiffness index (Table 3; all \( P < 0.005 \)), but negatively associated with ACc (Table 3; \( P < 0.005 \)). After adjusting for age, gender, BMI, WC, SBP, DBP, TC, TG, HDL, LDL, fasting insulin and HOMA-IR, partial correlation analysis showed that FBG was still significantly correlated with plaque index (\( r = 0.205, P = 0.001 \)).

### Clinical outcomes of carotid alterations and the underlying determinants

Correlation coefficients between IMTmean and the other measured parameters of carotid artery are shown in Table 4. Stepwise multivariable regression analysis revealed that ACc (\( \beta = -0.414, P < 0.001 \)) was independently associated with IMTmean. Furthermore, stepwise multivariable regression analysis suggested that age (\( \beta = 0.255, P < 0.001 \), Table 4), SBP (\( \beta = 0.224, P < 0.001 \), Table 4), WC (\( \beta = 0.202, P < 0.001 \), Table 4), HDL-C (\( \beta = -0.163, P = 0.001 \), Table 4) and TC (\( \beta = 0.096, P = 0.046 \), Table 4) were independently associated with IMTmean.

### Discussion

MetS is a multiple-risk factor paradigm that is widely considered in risk management. We aimed to compare carotid alterations in 200 Chinese people with MetS and 200 without MetS and the underlying risk factors. Alterations of the carotid artery in MetS covered the whole wall, which ultimately results in atherosclerosis. The risk factors for carotid alterations were abdominal obesity, hypertension, age and low HDL-C. Therefore, to prevent carotid atherosclerosis caused by MetS, the fundamental approaches are weight loss, lowering blood pressure and increasing HDL-C besides regular therapy.

### Relationship of MetS and carotid artery alterations

All features of metabolic syndrome are risk factors for atherosclerosis, CVD and type 2 diabetes mellitus [4]. The condition, exacerbated by advancing age, is progressive, beginning with borderline risk factors that eventually progresses to categorical risk factors. Furthermore, in many patients, MetS culminates in type 2 diabetes, which further increases risk for CVDs, especially atherosclerosis. As for carotid artery, before carotid

### Table 2 Carotid ultrasound parameters between the groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 200)</th>
<th>MetS (n = 200)</th>
<th>P</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IMT (mm)</td>
<td>0.53 ± 0.15</td>
<td>0.76 ± 0.17</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Maximal IMT (mm)</td>
<td>0.75 ± 0.75</td>
<td>1.22 ± 0.86</td>
<td>&lt; 0.01</td>
<td>0.141</td>
</tr>
<tr>
<td>Plaque index</td>
<td>0 (0)</td>
<td>0 (2)</td>
<td>&lt; 0.01</td>
<td>0.083</td>
</tr>
<tr>
<td>( D_s ) (cm)</td>
<td>0.65 ± 0.07</td>
<td>0.68 ± 0.10</td>
<td>&lt; 0.01</td>
<td>0.522</td>
</tr>
<tr>
<td>Ep*</td>
<td>7.97 ± 4.49</td>
<td>23.04 ± 15.05</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( \beta )</td>
<td>6.69 ± 3.15</td>
<td>17.54 ± 10.67</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACc (mm² / kPa)</td>
<td>0.85 ± 0.35</td>
<td>0.35 ± 0.23</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\( P^*, \text{ adjusted for WC, SBP, DBP, TG, HDL, FBG and age.} \)

\( \text{ACc, arterial compliance coefficient; } \beta, \text{ stiffness index; } D_s, \text{ end-systolic diameters; } \text{Ep*}, \text{ normalised pressure strain elastic modulus; IMT, intima-media thickness.} \)

### Table 3 Pearson correlation coefficients between risk factors and carotid alterations

<table>
<thead>
<tr>
<th></th>
<th>WC</th>
<th>TG</th>
<th>SBP</th>
<th>DBP</th>
<th>HDL</th>
<th>FBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r )</td>
<td>0.436</td>
<td>&lt; 0.001</td>
<td>0.341</td>
<td>&lt; 0.001</td>
<td>0.497</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( r )</td>
<td>0.192</td>
<td>&lt; 0.001</td>
<td>0.258</td>
<td>&lt; 0.001</td>
<td>0.291</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( r )</td>
<td>0.156</td>
<td>0.003</td>
<td>0.261</td>
<td>&lt; 0.001</td>
<td>0.260</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( r )</td>
<td>0.272</td>
<td>&lt; 0.001</td>
<td>0.147</td>
<td>0.004</td>
<td>0.240</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( r )</td>
<td>0.353</td>
<td>&lt; 0.001</td>
<td>0.470</td>
<td>&lt; 0.001</td>
<td>0.588</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( r )</td>
<td>0.356</td>
<td>&lt; 0.001</td>
<td>0.318</td>
<td>&lt; 0.001</td>
<td>0.583</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>( r )</td>
<td>−0.368</td>
<td>&lt; 0.001</td>
<td>−0.373</td>
<td>&lt; 0.001</td>
<td>−0.625</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\( \text{IMT, intima-media thickness; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; ACc, arterial compliance coefficient; } \beta, \text{ stiffness index; } D_s, \text{ end-systolic diameters; } \text{Ep*}, \text{ normalised pressure strain elastic modulus.} \)
plaque was detected, sub-clinical atherosclerosis has initiated and developed.

The carotid arterial changes we found related to MetS suggested carotid atherosclerosis. As reported previously, IMT in MetS increased significantly [15]. Simultaneously, large arteries underwent stiffness, which probably preceded thickness of IMT and appearance of plaques [16]. In this study, stiffness of the carotid wall was significantly increased in MetS subjects, exhibiting significantly increased $E_p$ and stiffness index, and decreased $A_c$. Arterial mechanical properties, particularly in larger arteries, are regarded as a marker of cardiovascular risk and diseases [17]. However, IMT might be the earliest morphological marker of carotid atherosclerosis. Here, it has been revealed that arterial mechanical properties contributed to thickened IMT, especially $A_c$.

Increased IMT and impaired wall mechanics associated with CVD risk factors and events are considered to result from changes in the intrinsic structural and functional properties of artery. Recent studies, furthermore, have revealed a cross-talk of the vascular smooth muscle cells and adventitia in pulmonary artery [18,19]. Also, it is found in our study that $E_p$, stiffness index and $A_c$, describing the elastic properties, were associated with IMTmean. Therefore, the thickened IMT, representing subclinical atherosclerosis, might result from the alterations through endothelium, media and adventitia, which emphasises the contributions of thinning and fracturing of elastic fibres, and increased deposition of more collagen caused by the MetS. Claridge et al. [16] found that changes in indices of arterial stiffness were much higher than changes in IMT and diameter. Indices of arterial stiffness may be a sensitive early marker of atherosclerosis.

Arterial aberrations might be consequent upon the MetS. However, MetS is combination of several cardiometabolic risk factors. This raised the question whether certain components of MetS exacerbate the arterial aberrations. In the present study, it has been suggested that abdominal obesity, hypertension, low HDL-C, FBG and ageing play dominant roles in the alterations of carotid wall.

Waist circumference had a strong association with atherosclerosis progression. This observation may suggest increased WC is a marker that reflects long-term deviations in several metabolic risk factors. As is known, various morphological adaptations in the cardiovascular structure and function occurred in obese individuals [20]. Besides, central obesity predisposes to MetS and CVDs. Furthermore, individuals with a central deposition of adipose tissue are at increased risk of cardiovascular morbidity and mortality [21], including stroke, congestive heart failure, myocardial infarction and cardiovascular death.

Hypertension has been demonstrated to be one of the strongest risk factors contributing to atherosclerosis. Hypertension can cause impairment of the endothelium and distention of the carotid artery, resulting in atherosclerosis and stroke [22]. The benefits of blood pressure reduction for reducing major CVD have been well established through many clinical trials [23], including for patients with type 2 diabetes [24]. Despite improved management of hypertension, it is still the major risk factor for atherosclerosis.

High-density lipoprotein cholesterol can protect against atherosclerosis. Low HDL-C has been demonstrated to be one of CVDs’ risk factors [25], although controversy exists as to quantity or quality of HDL-C [26]. Low HDL-C, especially low HDL$_3$ [27], makes cardiovascular system exposed to an atherogenic lipid profile, which will induce changes in arteries that contribute to the development of atherosclerosis. Furthermore, low HDL-C would impair elastic properties through cellular accumulation of cholesterol, oxidative stress and inflammation in the arterial wall [27].

Ageing renders the endothelium more susceptible to damage by insults. Epidemiological studies have revealed that ageing was recognised as a well-established CVD risk factor. Furthermore, viscoelastic properties, such as arterial wall thickening, increased elasticity, reduced compliance and increased stiffness, deteriorate with ageing. Therefore, the buffering capacity is decreased, which causes insufficient damping of the pulse pressure, with viscoelastic deterioration caused by ageing and hypertension forming a vicious circle.

Although type 2 diabetes mellitus might be a significant CVD risk factor, the independent contribution of the hyperglycaemia with type 2 diabetes mellitus to CVD is rather weak. Significant reductions in cardiovascular outcomes have not been achieved with intensive glycemic control [28]. In the present study, FBG was revealed to positively correlate with plaque index, which suggests that hyperglycaemic state might exacerbate the established atherosclerosis in the particular period. Furthermore, hyperglycaemia is commonly restrained to the post-prandial state and is typically asymptomatic for many years, which explains the weak correlation between fasting plasma glucose,

| Table 4 Multiple regression analysis to evaluate the contribution of risk factors to mean intima-media thickness |
|--------------------------------------------------|--------------------------------------------------|
| $\beta$ | $p$ |
| Age | $0.255$ | $< 0.001$ |
| SBP | $0.224$ | $< 0.001$ |
| WC | $0.202$ | $< 0.001$ |
| HDL-C | $-0.163$ | $0.001$ |
| TC | $0.096$ | $0.046$ |

WC, waist circumference; SBP, systolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; $\beta$, standard coefficient.
or IR, estimated by means of HOMA-index and the extent of atherosclerosis.

Thus, the components of MetS might exert different effects on carotid artery. However, a lively debate is currently ongoing as to whether MetS per se could impact carotid artery. Previous studies showed that multiple risk factors increase risk more than the sum of accompanying single risk factors [29]; risk increased geometrically instead of linearly, which suggests MetS per se, beyond the components, could have a deleterious effect on carotid artery beyond its components. In the present study, significant differences were detected between the control and MetS groups in carotid artery factors even after controlling for the components of MetS, so MetS per se has an adverse effect on carotid artery. The underlying mechanism remains obscure. Inflammation is involved in MetS and might be an important factor.

Potential therapeutic targets for atherosclerosis in patients with MetS

As for an individual at high risk of MetS, the modifiable risk factors must be reduced simultaneously to reduce the absolute risk of CVD. However, therapeutic strategies towards several risk factors imply increased number of drugs, and therefore worse compliance, drug interactions and cost. Therefore, the number of risk factors to be controlled must be reduced, before drugs targeting the MetS as a whole are designed. Clinical management should focus on the underlying risk factor besides an individual’s risk status, including central obesity, hypertension, low HDL-C level and hyperglycaemia, which contribute much to the carotid aberrations resulting in atherosclerosis.

Study limitations: This was a cross-sectional study. The cardiovascular end-points were not available, but surrogates of arterial health. Moreover, study population is racially homogenous, so the findings cannot be thoroughly generalised.

Conclusion

Carotid alterations consequent upon MetS ultimately lead to subclinical and clinical atherosclerosis, the underlying risk factors for which were abdominal obesity, hypertension, ageing and lower HDL-C. Therefore, the primary strategy for management of MetS is to mitigate the modifiable, underlying risk factors through lifestyle changes, among which obesity interventions is connected to better blood pressure, HDL-C and glucose homoeostasis. Then, incorporate drug therapy to the regimen towards the aforementioned risk factors.

Acknowledgements

This work was supported by the research grants from Key Technologies R & D Program of Shandong Province (2006GG2202020 and 2010G0020262), the Natural Science Foundation of Shandong Province (Y2005C11, ZR2009CM022, ZR2009CM025 and BS20091Y026), the National Natural Science Foundation of China (30871038, 30971215, 81070192, 81070141 and 81100605) and the National Basic Research Program of China (973 Program, Grant No.: 2009CB521904). There is no conflict of interests.

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