Original Article

The impact of visceral fat on multiple risk factors and carotid atherosclerosis in chronic haemodialysis patients

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Abstract

Background. There has been recent interest in the importance of visceral fat (VF) for the development of atherosclerosis. The purpose of this study was to examine associations between VF and multiple risk factors as well as the prevalence of carotid atherosclerosis in chronic haemodialysis patients.

Methods. We classified 77 non-diabetic haemodialysis patients into ‘low VF’, ‘middle VF’ and ‘high VF’ groups after determining VF area using computed tomography. Systemic atherosclerosis was assessed from intima-media thickness (IMT), plaque score (PS) and stiffness parameter β (stiffness/C12) measured by high-resolution B-mode ultrasonography.

Results. Compared with the low VF group, the high VF group exhibited (i) significantly higher fasting plasma insulin (11.0±6.8 vs 7.1±2.9 μU/ml, P = 0.0061); (ii) significantly higher plasma triglycerides (141.8±94.0 vs 86.5±32.5 mg/dl, P = 0.0032); and (iii) significantly lower plasma high-density lipoprotein cholesterol (42.1±14.5 vs 53.0±15.7 mg/dl, P = 0.0134). Moreover, the high VF group had a higher prevalence and extent of carotid atherosclerosis: IMT was 0.69±0.13 vs 0.61±0.12 mm (P = 0.0239), PS was 4.8±3.2 vs 2.4±3.6 (P = 0.0236) and stiffness-β was 11.4±3.1 vs 8.5±3.0 (P = 0.0082) in the high and low VF groups, respectively.

Conclusion. We show that VF is associated with the prevalence of carotid atherosclerosis as well as with hyperinsulinaemia and lipid abnormalities in chronic haemodialysis patients.

Keywords: carotid atherosclerosis; haemodialysis; intima-media thickness; multiple risk factors; ultrasonography; visceral fat

Introduction

More than 20 years have passed since Lindner et al. [1] reported a high incidence of coronary deaths in patients receiving chronic haemodialysis and proposed the term ‘accelerated atherosclerosis’. However, the cause of atherosclerosis is multifarious and the mechanism by which it is accelerated in haemodialysis remains to be clarified. In the general population, obesity is one of the most important lifestyle factors contributing to the development of systemic atherosclerosis. However, it is well known that malnutrition remains widely prevalent in haemodialysis patients. Numerous studies have shown that malnutrition is a serious risk factor for morbidity and mortality in chronic haemodialysis patients. In contrast, few studies have examined nutrition excess, obesity or both in haemodialysis patients.

In recent decades, the development of renal replacement therapy has improved both the physical condition and survival rate of haemodialysis patients. Therefore, obesity may present a risk factor for atherosclerosis, especially in contemporary healthy haemodialysis patients. In support of this, recent studies have demonstrated a strong association between visceral fat (VF) accumulation and systemic atherosclerosis in the general population [5]. Furthermore, Odakaki et al. [6], while investigating abdominal fat distribution in haemodialysis patients, found that they had an excessive VF accumulation relative to healthy subjects. Thus, VF in haemodialysis patients may accelerate systemic atherosclerosis, as it does in the general population.

The purpose of the present study was to investigate associations between VF as well as multiple risk factors and the prevalence of carotid atherosclerosis in stable haemodialysis patients. We evaluated VF accumulation in haemodialysis patients by the computed tomography (CT) scanning technique and determined the prevalence and extent of carotid...
atherosclerosis using high-resolution B-mode ultrasound.

**Subjects and methods**

**Patients**

At the time of the study, 122 patients were undergoing daytime haemodialysis at Toshima Chuo Hospital. We selected currently healthy outpatients from the hospital. Excluded from the study were seven patients that had been hospitalized within the past 6 months and two immobilized patients that were not able to come to the hospital. Twenty-two diabetic patients were excluded because their disease may have confounded the results. Also excluded were nine patients that had initiated haemodialysis therapy within 1 year and one patient with residual renal function that required only 6 h of dialysis therapy per week. Of the remaining patients, none had continuously positive plasma C-reactive proteins. We could not obtain informed consent from four patients. We finally had 77 stable outpatients to participate in the study. Informed consent was obtained from all these patients before study onset. The study protocol was approved by the Ethics Committee of Nihon University School of Medicine. End-stage renal failure was due to glomerulonephritis in 59 patients (76.6%), polycystic kidney disease in six (7.8%), an unknown cause in five (6.5%), renal sclerosis in four (5.2%), interstitial nephritis in two (2.6%) and lupus nephritis in one (1.3%).

The patients were maintained on regular haemodialysis three times a week for 4.4.5 h/day using hollow-fibre dialysers with a bicarbonate-buffered dialysate. The blood flow rate ranged from 180 to 260 ml/min, with a dialysate flow rate of 500 ml/min. Body weight was measured before and after each dialysis, and the post-dialysis body weight served as the dry weight.

**Measurement of body fat mass and VF**

Body-mass index (BMI) was calculated as the post-dialysis dry weight in kilograms divided by the square of the height in metres. The percentage fat was measured by bioelectrical impedance analysis. The body fat distribution was determined using the CT scanning technique, according to the procedure of Tokunaga et al. [7]. All CT scans were performed with the subject in the supine position using a slip ring CT scanner (Radix-Pratico, Hitachi, Tokyo, Japan). The subcutaneous fat layer was clearly defined as the extraperitoneal fat between skin and muscle, with attenuation ranging from −40 to −140 HU. The intraperitoneal portion, having the same density as the subcutaneous fat layer, was defined as the visceral fat area (VFA). The subcutaneous fat area (SFA) and intra-abdominal VFA were measured at the level of the umbilicus.

**Evaluation of carotid atherosclerosis by B-mode ultrasonography**

Ultrasonography of the carotid arteries was performed with an echotomography system (Logic 400, GE Yokogawa Medical Systems, Tokyo, Japan) and an electrical linear transducer (midfrequency of 11 MHz).

**Carotid intima-media thickness.** Carotid intima-media thickness (IMT), as defined by Salonen et al. [8,9], was measured as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first line represented the lumen–intima interface, and the second line represented the collagen-containing upper layer of the adventitia. Three IMT measurements were made in the far wall of both the right and left common carotid arteries (CCAs) at the site of the greatest IMT for each recording and vessel. The mean of these six IMT measurements was used to derive an estimate of the overall IMT in the CCAs. Atherosclerotic lesions were defined as plaques when IMT was ≥1.0 mm in the CCAs below the carotid bulb.

**The plaque score.** The plaque score (PS), as defined by Handa et al. [10], was computed by summing the maximum thickness of the intima-media complex (plaque thickness), measured in millimetres, on the near and far walls of each of four divisions on both sides of the carotid arteries: S1 was the region of the internal carotid artery (ICA) <15 mm distal to its bifurcation from CCAs; S2 was the region of ICA and CCAs <15 mm proximal to the bifurcation; S3 was the region of CCAs >15 mm and <30 mm proximal to the bifurcation; and S4 was the region of CCAs >30 mm proximal to the bifurcation below the flow divider. The length of the individual plaques was not considered in determining the PS.

**The stiffness parameter β.** The stiffness parameter β (stiffness-β) is a quantitative index of the elastic properties of large arteries. We measured the vascular internal diameter of the carotid artery and calculated stiffness-β according to the method of Kawasaki et al. [11] using the following equation:

\[
\beta = \frac{\log_e P_s/P_d \times D_a(D_s - D_a)}{\log_2 P_s/P_d}
\]

where \(P_s\) is systolic pressure, \(P_d\) is diastolic pressure, \(D_s\) is the inner diameter at systole and \(D_a\) is the inner diameter at diastole. \(β\) is a coefficient when the constitutive stress–strain relation is expressed as an exponential function, representing the stiffness of the vascular wall.

**Analytical procedures**

Blood samples were drawn for biochemical analysis after an overnight fast. Plasma triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C) concentrations were determined using standard enzymatic techniques with an automatic analyser. Plasma glucose concentrations were measured using the glucose oxidase method. Plasma insulin was assayed using a double antibody radioimmunoassay.

**Statistical analysis**

Given the small number of reports examining VF in haemodialysis patients, we separated our patients into three equal groups, designated ‘low VF’, ‘middle VF’ and ‘high VF’, based on the ranking of VFA of males and females, respectively. Results are shown as means ± SD. Differences between groups were analysed by one-way ANOVA followed by Fisher’s PLSD tests. Spearman’s rank correlations evaluated relationships between BMI, SFA or VFA and variables obtained by blood samplings and B-mode ultrasonography. Multiple regression models of BMI, SFA or VFA were performed with various parameters. \(P\)-values of <0.05 were considered to be statistically significant.
Results

Characteristics of the three haemodialysis patient groups stratified according to VFA are shown in Table 1. Although there were no significant intergroup differences for age, haemodialysis duration, Kt/V and plasma albumin concentration, all the body-fat-related indices, including BMI, %fat, whole fat area, SFA and VFA, were significantly higher in the high VF group than in the low VF group.

In order to clarify the relationship between VF and metabolic disorders, clinical variables in the three groups are compared in Table 2. Fasting plasma insulin and plasma triglycerides values were significantly higher in the high VF group than in the low VF group. In contrast, plasma HDL-C was lower in the high VF group than in the low VF group.

The indices of systemic atherosclerosis, evaluated by B-mode ultrasonography among the three groups, are shown in Figure 1. All three indices were significantly higher in the high VF group than in the low VF group: IMT was 0.61 ± 0.12, 0.66 ± 0.12 and 0.69 ± 0.13 mm (P = 0.0239); PS was 2.4 ± 3.6, 4.6 ± 3.9 and 4.8 ± 3.2 (P = 0.0236); and stiffness–β was 8.5 ± 3.0, 11.1 ± 5.0 and 11.4 ± 3.1 (P = 0.0082) in the low, middle and high VF groups, respectively.

Simple correlations between BMI, SFA or VFA and ultrasonography data and clinical variables are shown in Table 3. None of the ultrasonography-detected indices of carotid atherosclerosis was correlated with BMI or SFA. However, VFA was significantly correlated with PS and stiffness–β. The correlation between VFA and IMT was of borderline significance.

While analysing the clinical variables, we found that BMI significantly correlated with fasting plasma insulin and that SFA correlated only with plasma triglycerides. In contrast, VFA was strongly correlated with both plasma lipids and carbohydrates. A multivariate regression model including BMI, SFA and VFA was performed to clarify which was most strongly related to ultrasonography-detected fat-related parameters and the clinical variables. VFA was found to be the strongest predictor of PS, triglycerides and HDL-C (Table 4).

Discussion

We found that the high VF group had (i) significantly higher levels of fasting plasma insulin, (ii) significantly higher levels of plasma triglycerides and (iii) significantly lower levels of plasma HDL-C than the low VF group. Moreover, the high VF group had a higher prevalence and extent of carotid atherosclerosis. Carotid atherosclerosis is thought to provide an indication of systemic atherosclerosis in both the

Table 1. Characteristics of the low, middle and high visceral fat (VF) haemodialysis patient groups

<table>
<thead>
<tr>
<th></th>
<th>Low VF</th>
<th>Middle VF</th>
<th>High VF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>14/12</td>
<td>15/11</td>
<td>14/11</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.3 ± 13.1</td>
<td>59.2 ± 12.0</td>
<td>61.0 ± 9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Haemodialysis duration (years)</td>
<td>11.7 ± 8.5</td>
<td>11.9 ± 9.6</td>
<td>10.9 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.16 ± 0.17</td>
<td>1.12 ± 0.13</td>
<td>1.15 ± 0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9 ± 0.3</td>
<td>3.8 ± 0.3</td>
<td>3.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>18.8 ± 1.7</td>
<td>20.8 ± 2.4</td>
<td>22.7 ± 2.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%fat</td>
<td>16.7 ± 4.3</td>
<td>19.0 ± 5.8</td>
<td>23.1 ± 4.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Whole fat area (mm²)</td>
<td>8945 ± 4599</td>
<td>18 654 ± 5650</td>
<td>28 500 ± 8469</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subcutaneous fat area (mm²)</td>
<td>6609 ± 3976</td>
<td>12 261 ± 5121</td>
<td>15 848 ± 5443</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Visceral fat area (mm²)</td>
<td>2336 ± 1079</td>
<td>6393 ± 2266</td>
<td>12 652 ± 4875</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD. All P-values were determined using Fisher’s PLSD test after justification by one-way ANOVA compared to low and high VF groups. NS, not significant.

Table 2. Comparison of clinical variables among the the low, middle and high visceral fat (VF) haemodialysis patient groups

<table>
<thead>
<tr>
<th></th>
<th>Low VF</th>
<th>Middle VF</th>
<th>High VF</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td></td>
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<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>83.8 ± 11.0</td>
<td>84.9 ± 10.0</td>
<td>88.2 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma insulin (µU/ml)</td>
<td>7.1 ± 2.9</td>
<td>9.3 ± 4.4</td>
<td>11.0 ± 6.8</td>
<td>0.0061</td>
</tr>
<tr>
<td>Plasma total cholesterol (mg/dl)</td>
<td>166.8 ± 32.8</td>
<td>173.6 ± 28.3</td>
<td>173.5 ± 32.7</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma triglycerides (mg/dl)</td>
<td>86.5 ± 32.5</td>
<td>110.0 ± 51.5</td>
<td>141.8 ± 94.0</td>
<td>0.0032</td>
</tr>
<tr>
<td>Plasma HDL-C (mg/dl)</td>
<td>53.0 ± 15.7</td>
<td>47.1 ± 13.3</td>
<td>42.1 ± 14.5</td>
<td>0.0134</td>
</tr>
<tr>
<td>Plasma HDL-C (mg/dl)</td>
<td>144.3 ± 24.5</td>
<td>137.6 ± 23.0</td>
<td>135.6 ± 20.3</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.0 ± 12.9</td>
<td>75.0 ± 13.3</td>
<td>73.4 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma uric acid (mg/dl)</td>
<td>7.2 ± 1.5</td>
<td>7.4 ± 1.6</td>
<td>7.3 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma Ca × P</td>
<td>57.2 ± 13.7</td>
<td>55.4 ± 11.9</td>
<td>52.6 ± 15.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD. All P-values were determined using Fisher’s PLSD test after justification by one-way ANOVA compared to low and high VF groups. NS, not significant. *HDL-C, high-density lipoprotein cholesterol.
Thus, our findings suggest that VF accumulation in haemodialysis patients may be closely correlated with systemic atherosclerosis that is associated with multiple risk factors such as hyperinsulinaemia and lipid abnormalities.

Nakamura et al. [5] described the ‘visceral fat syndrome’ in the general population as a highly...
atherogenic state associated with multiple risk factors that stems from VF accumulation. Our findings indicate that this syndrome is also present in the dialysis population.

Prior to our study, only Odamaki et al. [6] had evaluated VF parameters in the dialysis population using CT scanning techniques that were similar to the techniques used by our group. As in our study, they demonstrated that VF accumulation correlated well with serum lipid abnormalities. In addition, we found that VF accumulation had a good correlation with abnormalities in carbohydrates.

The main objective of the present study was to examine whether systemic atherosclerosis is associated with VF accumulation in haemodialysis patients, as it is in the general population. We found a good correlation between VF accumulation and carotid atherosclerosis, which may be representative of systemic atherosclerosis. VF may contribute to the ‘accelerated atherosclerosis’ in haemodialysis patients and may thus represent an additional risk for atherosclerotic disease in this patient population.

Recently, Leavey et al. [17] reported that increasing body size (BMI) was correlated with a decreased mortality risk even in ‘healthier’ haemodialysis patients. This correlation does not contradict our result, since BMI itself was not correlated with any indices of carotid atherosclerosis in our population. Moreover, our study suggests the possibility of an increased mortality risk from systemic atherosclerosis, particularly among haemodialysis patients that are relatively obese but have VF accumulation.

Compared with the general population, haemodialysis patients are already characterized by abnormalities in lipid and carbohydrate metabolism. For example, repeated use of heparin during haemodialysis produces alterations in lecithin cholesterol acyltransferase activity that may contribute to lipid abnormalities specific to haemodialysis conditions [18]. Similarly, accumulation of uraemic toxins, metabolic acidosis and reductions in insulin clearance are thought to contribute to insulin resistance in haemodialysis patients [19,20]. Even though haemodialysis therapy has been improved recently, it remains difficult to eliminate these disadvantages. On the other hand, it may be easier to modify patient lifestyle to prevent the accumulation of VF along with its associated risk factors to thereby slow the development of atherosclerosis, especially in contemporary healthy haemodialysis patients. It is therefore important for these patients to avoid high-fat diets and to exercise according to their physical abilities.

In summary, we have shown that VF accumulation in haemodialysis patients is correlated with several metabolic risk factors and the prevalence of carotid atherosclerosis. Thus, VF accumulation may contribute to atherosclerosis in haemodialysis patients, especially if they are relatively healthy patients. However, because the present study represented a cross-sectional investigation in a smaller population, further longitudinal investigations in larger populations will be required to clarify the contribution of VF to systemic atherosclerosis in haemodialysis patients.

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Conflict of interest statement. None declared.

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