Interrelationship among lipid profiles, arterial stiffness, and nitroglycerin-mediated vasodilation in the community-based setting of the Japanese women

Kazumi Fujioka¹*, Minoru Oishi², Akira Fujioka³, Tomohiro Nakayama⁴, Masahiro Okada¹

¹Department of Radiology, Nihon University School of Medicine, Tokyo, Japan; ²Department of Internal Medicine, Izutobu General Hospital, Shizuoka, Japan; ³Department of Dermatology, Fujioka Dermatological Clinic, Tokyo, Japan; ⁴Department of Pathology and Microbiology, Division of Laboratory Medicine, Tokyo, Japan

ABSTRACT

Objective: The purpose of this study is to evaluate whether interrelationship among lipid profiles including non-high-density lipoprotein cholesterol (non-HDL-C) and lipid ratio, arterial stiffness and vascular smooth muscle cell function are demonstrated in a cross-sectional setting of the community-based Japanese women.

Methods: We studied 42 women were enrolled in this study. The lipid parameters were assessed including non-HDL-C, triglyceride/HDL-C (TG/HDL-C) ratio, total cholesterol/HDL-C (TC/HDL-C) ratio and low density lipoprotein cholesterol /HDL-C (LDL-C/HDL-C) ratio. Arterial stiffness was evaluated by brachial-ankle pulse wave velocity (bapwv) procedure. Brachial artery measures including flow-mediated vasodilation (FMD), nitroglycerin-mediated vasodilation (NMD), brachial artery diameter (BAD), FMD/NMD ratio and post-nitroglycerin brachial artery diameter (P-NITGD) examinations were studied in all subjects by using brachial artery ultrasonography. Vascular smooth muscle cell (VSMC) function was assessed by NMD.

Results: There were significantly positive correlations between non-HDL-C and right bapwv (r= 0.47, p=0.003), between TG/HDL-C and right bapwv (r=0.42, p=0.01), and between TC/HDL-C and right bapwv (r=0.44, p=0.006). There were significantly positive correlations between non-HDL-C and left bapwv (r= 0.48, p=0.003), between TG/HDL-C and left bapwv (r=0.35, p=0.035), and between TC/HDL-C and left bapwv (r=0.37, p=0.026). There were significantly negative correlations between non-HDL-C and NMD (r=-0.45, p=0.003), between TG/HDL-C and NMD (r=-0.35, p=0.025), and between TC/HDL-C and NMD (r=-0.36, p=0.021).Correlations between NMD and right bapwv (r=-0.42, p=0.009) and between NMD and left bapwv (p=-0.31, r=0.001) were also significantly recognized. Interrelationship among non-HDL-C, bapwv, and NMD and among lipid ratios including TC/HDL-C, TC/HDL-C, bapwv, and NMD was found.

Conclusion: Interrelationship among lipid fractions, arterial stiffness and VSMC function was shown and lipid profiles may be respectively associated with structure and function alterations of VSMC rather than endothelial dysfunction.

We will suggest that lipid fractions may reflect the structure and function changes of VSMC in the cross-sectional setting of the community-based Japanese women.

Keywords: Lipid profile; Brachial-ankle PWV; Nitroglycerin-mediated vasodilation; Arterial stiffness; Vascular smooth muscle cell function


*Correspondence to: Kazumi Fujioka, MD, Department of Radiology, Nihon University School of Medicine, 30-1 Oyaguchi Kamicho Itabashiku, Tokyo, Japan Tel: +81-3-5732-1241, Fax: +81-3-5732-1234; Email: spbk2xp9@ninus.ocn.ne.jp

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INTRODUCTION

Dyslipidemia, such as elevated LDL-C and triglyceride (TG) or decreased HDL-C is an established risk factor and play a role in the occurrence and progression of cardiovascular disease (CVD) and ischemic stroke [1]. The Adult Treatment Panel of the National Education Program has also provided the availability of non-HDL-C as a secondary target of therapy and the studies have indicated that non-HDL-C is more closely associated with CVD compared with other lipid markers [2-4]. While, the possibility that lipid-related ratios such as TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C may be better parameters of CVD risk than any other single lipid marker has been reported [2]. On the other hand, arterial stiffness estimated by baPWV occurs as a result of structural changes in the medial layer of the elastic arteries, including fragments and degeneration of elastin [2]. Meta-analyses have recently established baPWV as an independent risk factor for cardiovascular events in subjects both with and without preexisting CVD [5,6]. Several studies have shown a close relation between lipid levels (non-HDL-C, high TG/HDL-C and TC/HDL-C ratio) and baPWV [5, 7-10].

The significant procedure for evaluating vascular endothelial and vascular smooth muscle cell (VSMC) function are flow-mediated vasodilatation (FMD), an endothelium-dependent function, and nitroglycerin-mediated vasodilation (NMD), an endothelium-independent function in the brachial artery [11-15]. Some reports, suggesting the correlation between NMD and lipid fractions including oxidized LDL parameter have been studied [16-19]. It has been reported that the impaired NMD may attribute to the increased oxidative stress or VSMC dysfunction in children at risk for atherosclerosis [17]. The report has been also suggested that reduced NMD is due to the VSMC dysfunction and surrounding extracellular matrix in the medial layer of the arterial wall in subjects with accelerating risk factors for atherosclerosis such as dyslipidemia [19]. Majority role of NMD value [11-19] are affected and determined by VSMC function change, while baPWV is primarily due to the VSMC structure alteration [2,20,21]. We have studied that whether interrelationship among lipid profiles including non-HDL-C and lipid ratio, arterial stiffness and VSMC function are recognized.

MATERIALS AND METHODS

Study population

Forty-two women in community-based population were enrolled in this study (including: 11 cerebral infarction, 10 migraine, 3 cervical spondylosis, and 18 not otherwise) between April 2008 and April 2014.

Biochemical analysis

Analyses were performed for total cholesterol (TC), triglyceride (TG), and HDL-C by standard enzymatic laboratory techniques. LDL-C was calculated using the Friedewald formula in subjects whose triglycerides levels were less than 400 mg/dL (LDL-C= TC-HDL-C-1/5TG) [22].

Vascular reactivity

FMD of the brachial artery was determined using high resolution B-mode ultrasonographic system (UNEXEF 18G, Japan) with a linear transducer mid frequency of 7.5MHz, using the technique described previous report [12-15]. Parameters including FMD, NMD and P-NTGD [23,24] were examined as previously described [11-15].

Carotid ultrasonography

The intima-media thickness (IMT) of the bilateral common carotid arteries (CCA) was measured by ultrasonography with a 10-MHz probe using an ultrason sound system (Aplo S8 SSD-70AA, Toshiba Medical System, Tochigi, Japan). Measurement of IMT were performed as previously described [12,14, 25].

Brachial-ankle pulse wave velocity (baPWV) measurement

BaPWV was measured using a volume-plethysmographic apparatus (form PWV/ABI; Colin, Co., Ltd., Komaki, Japan) and ankle-brachial pressure index (ABI) is measured simultaneously by these machines in accordance with a described method [12,14,26].

STATISTICAL ANALYSIS

Numerical variables were expressed as mean±SD. Spearman’s bivariable correlation analysis was used to test the relationships between the numerical variables when appropriate. Statistical significance was defined as a p value of less than 0.05. The statistical analyses were performed using the SPSS software package (version 16.0; SPSS Inc., Chicago, IL).

Table 1: The Clinical and Biochemical Characteristics of the Participant (mean±SD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>57.3±14.3</td>
</tr>
<tr>
<td>Heart rate beats/min</td>
<td>70.1±12.7</td>
</tr>
<tr>
<td>SBP mmHg</td>
<td>136.8±25.0</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>80.2±15.0</td>
</tr>
<tr>
<td>Weight kg</td>
<td>55.6±9.5</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>22.8±3.6</td>
</tr>
<tr>
<td>Waist cm</td>
<td>75.7±11.0</td>
</tr>
<tr>
<td>TC mg/dL</td>
<td>211.0±41.6</td>
</tr>
<tr>
<td>TG mg/dL</td>
<td>101.9±60.2</td>
</tr>
<tr>
<td>LDL-C mg/dL</td>
<td>65.4±19.1</td>
</tr>
<tr>
<td>HDL-C mg/dL</td>
<td>125.2±39.3</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>3.4±1.0</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>2.1±0.8</td>
</tr>
<tr>
<td>Non-HDL-C mg/dL</td>
<td>145.6±42.9</td>
</tr>
<tr>
<td>TG/HDL-C</td>
<td>1.8±1.5</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>95.3±9.3</td>
</tr>
<tr>
<td>HbA1c (NGSP) %</td>
<td>5.3±0.3</td>
</tr>
<tr>
<td>PLT 10³/UL</td>
<td>22.59±4.51</td>
</tr>
<tr>
<td>AST U/L</td>
<td>20.2±6.8</td>
</tr>
<tr>
<td>ALT U/L</td>
<td>16.1±8.8</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>0.09±0.04</td>
</tr>
<tr>
<td>UA mg/dL</td>
<td>4.4±1.2</td>
</tr>
<tr>
<td>BUN mg/dL</td>
<td>13.5±4.3</td>
</tr>
<tr>
<td>Cre mg/dL</td>
<td>0.6±0.1</td>
</tr>
<tr>
<td>eGFR mL/min/1.73m²</td>
<td>79.5±16.4</td>
</tr>
<tr>
<td>Urine alb mg/day</td>
<td>179.1±790.9</td>
</tr>
<tr>
<td>Renin pg/mL</td>
<td>9.6±10.2</td>
</tr>
</tbody>
</table>
RESULTS

Baseline characteristics of study population are summarized in Table 1. Mean age of the participants was 57.3±14.3 years (range: 19 to 80 years).

Table 2 shows Spearman’s rank correlation coefficients of the brachial artery measures in participants. BAD was significantly correlated with FMD% (r=-0.45, p=0.004). Significant correlations between BAD and P-NTGD (r=0.91, p<0.001) and between BAD and NMD (r=0.47, p=0.002) were recognized.

Table 3 shows Spearman’s rank correlation coefficients of the atherosclerotic parameters in participants. Correlations between NMD and rt bpawv (p=0.42, p=0.009) and between NMD and lt ba PWV (p=0.51, r=0.001) were significantly correlated.

Table 4 shows Spearman’s rank correlation coefficients for FMD, BAD, P-NTGD, and FMD/NMD with clinical and biochemical parameters in participants. Negative correlations between non-HDL-C and NMD (r=-0.45, p=0.003), between TG/HDL-C and rt baPWV (r=0.42, p=0.01), and between TC/HDL-C and rt baPWV (r=0.44, p=0.006) were detected. There were significantly positive correlations between non-HDL-C and rt baPWV (r=0.47, p=0.003), between TG/HDL-C and lt baPWV (r=0.35, p=0.035), and between TC/HDL-C and lt baPWV (r=0.37, p=0.026). There was significant correlation between LDL-C/HDL-C and rt baPWV (r=0.39, p=0.017), a tendency of the correlation between LDL-C/HDL-C and lt baPWV (r=0.32, p=0.051) was shown. There were correlations between TC and rt baPWV (r=0.42, p=0.01) and between TC and lt baPWV (r=0.46, p=0.005). Significant correlations between TG and rt baPWV (r=0.44, p=0.006) and between TG and lt baPWV (r=0.43, p=0.009) were recognized. There were also correlations between LDL-C and rt baPWV (r=0.41, p=0.012) and between LDL-C and lt baPWV (r=0.42, p=0.010).

DISCUSSION

Dyslipidemia, such as elevated LDL-C and TG or decreased HDL-C, is an established risk factor and play a role in the occurrence and progression of CVD and ischemic stroke [1]. Non-HDL-C quantifies all atherogenic apolipoprotein B-containing lipoproteins, including LDL, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), chylomicrons (CM), and their TG-rich lipoprotein remnants [27]. The Adult Treatment Panel of the National Education Program has provided the availability of non-HDL-C as a secondary target of therapy and a research has indicated that non-HDL-C is more closely associated with CVD compared with other lipid markers [27]. International Atherosclerosis Society (IAS) guideline [28], National Lipid Association (NLA) guideline and National Institute for Health and Care Excellence (NICE) guideline [29] have flagged non-HDL-C as a secondary target of therapy.

Table 2: Spearman’s rank correlation coefficients of the brachial artery measures in participants.

<table>
<thead>
<tr>
<th>BAD-b</th>
<th>BAD-m</th>
<th>P-NTGD</th>
<th>FMD mm</th>
<th>FMD%</th>
<th>NMD%</th>
<th>FMD/NMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAD-b</td>
<td>0.98</td>
<td>0.91</td>
<td>-0.24</td>
<td>-0.45</td>
<td>-0.47</td>
<td>0.01</td>
</tr>
<tr>
<td>BAD-m</td>
<td>0.98</td>
<td>0.90</td>
<td>-0.11</td>
<td>-0.33</td>
<td>-0.45</td>
<td>0.09</td>
</tr>
<tr>
<td>P-NTGD</td>
<td>0.91</td>
<td>0.90</td>
<td>-0.21</td>
<td>-0.40</td>
<td>-0.24</td>
<td>-0.15</td>
</tr>
<tr>
<td>FMD mm</td>
<td>-0.24</td>
<td>-0.11</td>
<td>-0.21</td>
<td>0.97*</td>
<td>0.04</td>
<td>0.75*</td>
</tr>
<tr>
<td>FMD%</td>
<td>-0.45</td>
<td>-0.33</td>
<td>-0.40</td>
<td>0.97*</td>
<td>0.15</td>
<td>0.68*</td>
</tr>
<tr>
<td>NMD%</td>
<td>-0.47</td>
<td>-0.45</td>
<td>-0.24</td>
<td>0.04</td>
<td>0.15</td>
<td>-0.52*</td>
</tr>
<tr>
<td>FMD/NMD</td>
<td>0.01</td>
<td>0.09</td>
<td>-0.15</td>
<td>0.75*</td>
<td>0.68*</td>
<td>-0.52*</td>
</tr>
</tbody>
</table>

*p<0.001.

Table 3: Spearman’s rank correlation coefficients of the atherosclerotic parameters in participants.

<table>
<thead>
<tr>
<th>FMD</th>
<th>NMD</th>
<th>FMD/NMD</th>
<th>Rt IMT</th>
<th>Lt IMT</th>
<th>Rt PWV</th>
<th>Lt PWV</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD</td>
<td>0.15</td>
<td>-0.68</td>
<td>0.61</td>
<td>-0.48</td>
<td>-0.27</td>
<td>-0.32</td>
</tr>
<tr>
<td>NMD</td>
<td>0.15</td>
<td>-0.524*</td>
<td>-0.004</td>
<td>-0.101</td>
<td>-0.42</td>
<td>-0.51</td>
</tr>
<tr>
<td>FMD/NMD</td>
<td>0.68*</td>
<td>-0.524*</td>
<td>-0.515</td>
<td>-0.48</td>
<td>0.45</td>
<td>0.42</td>
</tr>
<tr>
<td>Rt IMT</td>
<td>-0.61*</td>
<td>-0.004</td>
<td>-0.515</td>
<td>0.65*</td>
<td>0.45</td>
<td>0.53</td>
</tr>
<tr>
<td>Lt IMT</td>
<td>-0.48</td>
<td>-0.101</td>
<td>-0.31</td>
<td>0.65*</td>
<td>0.54</td>
<td>0.53</td>
</tr>
<tr>
<td>Rt PWV</td>
<td>-0.27</td>
<td>-0.42</td>
<td>-0.04</td>
<td>0.45</td>
<td>0.54</td>
<td>0.96*</td>
</tr>
<tr>
<td>Lt PWV</td>
<td>-0.32</td>
<td>-0.51</td>
<td>-0.01</td>
<td>0.42</td>
<td>0.53</td>
<td>0.96*</td>
</tr>
</tbody>
</table>

*p<0.001.
Rt: Right, Lt: Left, IMT: Intima-Media Thickness, PWV: Pulse Wave Velocity
as a primary therapeutic target for patients with coronary heart disease (CHD) [27]. The possibility that lipid-related ratios such as TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C may be better parameters of CVD risk than any other single lipid marker has been also reported [2]. TG/HDL-C parameter has been linked to insulin resistance and it has been regarded as an independent risk factor for cardiovascular events in subjects with and without preexisting CVD [5,6]. Several studies have shown a close relation between lipid levels (non-HDL-C, high TG/HDL-C and TC/HDL-C ratio) and baPWV [5,7-10]. Wen et al. [5] reported that their study showed significant positive association of non-HDL-C, TG, and the TC/HDL-C ratio with arterial stiffness irrespective of LDL-C level.

On the other hand, arterial stiffness occurs as a result of structural changes in the medial layer of the elastic arteries, including fragments and degeneration of elastin, increase in collagen, and thickening of the arterial wall [2]. Meta-analyses have recently established baPWV as an independent risk factor for cardiovascular events in subjects both with and without preexisting CVD [5,6]. Several studies have shown a close relation between lipid levels (non-HDL-C, high TG/HDL-C and TC/HDL-C ratio) and baPWV [5,7-10]. Wen et al. [5] reported that their study showed significant positive association of non-HDL-C, TG, and the TC/HDL-C ratio with arterial stiffness irrespective of LDL-C level.

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Now, Wen et al. [2] also described that the lipoprotein ratios such as TG/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and TG are superior to conventional lipid parameters for predicting arterial stiffness in young men and especially, they indicated that the TG/HDL-C ratio has the strongest association with arterial stiffness [2]. Chung et al. [1] also suggested that the occurrence of cardiometabolic disorders can be in part explained by deficient or absent estrogen production [34]. Ma et al. also reported the relationship between non-HDL-C and carotid atherosclerosis among community based female subjects [8]. As our data indicated the relationship between non-HDL and baPWV, we will speculate that non-HDL-C may, in part, reflect the VSMC structure change.

Alvim et al. [34] have also reported that non-HDL-C is a good predictor of the risk of increased arterial stiffness in postmenopausal women. Their resulting showed that a decrease in estrogen facilitates the developing increased arterial stiffness, which is an independent risk factor for CVD in postmenopausal women. It is also putative that the occurrence of cardiometabolic disorders can be in part explained by deficient or absent estrogen production [34]. Ma et al. also reported the relationship between non-HDL-C and carotid atherosclerosis among community based female subjects [8]. As our data indicated the relationship between non-HDL and baPWV, we will speculate that non-HDL-C may, in part, reflect the VSMC structure change.

This suggests that arterial stiffness may be a primary therapeutic target for patients with coronary heart disease (CHD). The possibility that lipid-related ratios such as TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C may be better parameters of CVD risk than any other single lipid marker has been also reported [2]. TG/HDL-C parameter has been linked to insulin resistance and it has been regarded as an independent risk factor for cardiovascular events in subjects with and without preexisting CVD [5,6]. Several studies have shown a close relation between lipid levels (non-HDL-C, high TG/HDL-C and TC/HDL-C ratio) and baPWV [5,7-10]. Wen et al. [5] reported that their study showed significant positive association of non-HDL-C, TG, and the TC/HDL-C ratio with arterial stiffness irrespective of LDL-C level.

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metabolism in vascular smooth muscle and endothelium in postmenopausal phase, resulting in various detrimental metabolic and vascular change, due to high TG with low HDL-C. Meanwhile, the increased TG/HDL-C was independently associated with baPWV abnormality in apparently healthy individuals [35] or in adolescents and young adults [36]. As our result showed the correlations between TG/HDL-C and baPWV and between TC/HDL-C and baPWV, we suggest that lipid fractions may be in part an indicator of VSMC structure alteration. Our result may indicate that raised non-HDL-C and high TG/HDL-C and LDL-C/HDL-C ratio, in physiological range, suggest the elevated baPWV value.

The correlation between NMD and lipid fractions including oxidized LDL parameter has been studied [16-19]. Adams et al. reported that decreased NMD is associated with serum cholesterol concentration in asymptomatic healthy adults [16]. The study that a trend toward an impaired NMD has been reported, indicating that some of the deleterious effects of dyslipidemia may be mediated by altered smooth muscle activity, rather than by endothelial dysfunction [18]. It has been reported that the impairment of NMD may include accelerated inactivation of NO by increased oxidative stress or VSMC dysfunction in children at risk for atherosclerosis [17]. There have been also some reports with regards to impaired NMD studies including CVD [16], type 2 diabetic patients (DM) [19] and obesity [37]. The report has been also suggested that reduced NMD is due to the VSMC dysfunction and surrounding extracellular matrix in the medial layer of the arterial wall in subjects with accelerating risk factors for atherosclerosis such as dyslipidemia [19]. The accelerating risk factors for atherosclerosis, such as hyperglycemia, dyslipidemia, hypertension, and uremia, may exert long-term cumulative effects on VSMC and the surrounding matrix in the medial layer rather than on the endothelium [19]. As relationships between non-HDL-C and NMD and between lipid ratio and NMD were identified, we will indicate that lipid profile may be a significant predictor, reflecting the VSMC function. Our data suggests that raised non-HDL-C and high TG/HDL-C and LDL-C/HDL-C ratio, in physiological range, may be an indicator, reflecting impaired NMD, namely VSMC function change.

Brachial-ankle pulse wave velocity (baPWV), a non-invasive parameter both central and peripheral arterial stiffness is widely used in clinical practice and a significant association between baPWV and carotid-femoral pulse wave velocity (PWV) [5]. Except for dyslipidemia, DM and obesity status, decreased NMD has been shown in chronic kidney disease (CKD). In CKD, different vascular pathologies, namely, atherosclerosis and arteriosclerosis are present [20]. Endothelial dysfunction also cause arteriosclerosis, a disease affecting the media of large and middle sized arteries with an increased collagen-elastin ratio, calcification and hyperplasia and hypertrophy of VSMCs [20]. While increased arterial stiffness is caused primarily by structural changes, there is also a major functional component from the vascular endothelium. Marked increases in arterial stiffness as measured by pulse wave velocity have been demonstrated in response to NOS inhibitors, with reductions in response to exogenous NO donors [21]. As the arterial media is composed of smooth muscle cells and extracellular matrix including collagen and elastin, these constituents of the media and their interactions are major determinants of structural arterial stiffness [38]. While it has been noted that PWV reflects arterial stiffening that is increased by adverse structural and functional alterations including impaired endothelial-dependent dilation, medial hypertrophy, and elevated smooth muscle tone in the vessel wall [39].

Now, as FMD, NMD and baPWV examinations were measured by using different artery tree at different sites, a strong correlation between NMD and baPWV were observed. Our results have provided that structural and functional alterations of VSMC may be affected by lipid profiles.

Study limitation: there were some limitations in this study. Our results indicated that interrelationship among lipid profiles, arterial stiffness and VSMC function was recognized in a cross-sectional setting of the community-based Japanese women. But several confounding factors related to arterial stiffness as well as VSMC function was present. The significant differences in risk factors are important to address as they are likely independently related to arterial stiffness as well as VSMC dysfunction. However, our study sample size is relatively small and we have studied in the cross-sectional and retrospective research, we did not have adjusted using confounding factors. Future prospective researches are warranted to clarify more accurate conclusion.

SUMMARY

Interrelationship among non-HDL-C, baPWV, and NMD and among lipid ratios including TG/HDL-C, TC/HDL-C, baPWV, and NMD was detected in community-based setting of Japanese women. Lipid profiles may be respectively associated with arterial stiffness and VSMC dysfunction rather than endothelial dysfunction. Our result may suggest that raised non-HDL-C and high TG/HDL-C and LDL-C/HDL-C ratio, in physiological range, may reflect elevated baPWV and impaired NMD, suggesting structural and functional alteration of VSMC.

CONCLUSIONS

Lipid profiles may be respectively associated with the structural and functional alteration of vascular smooth muscle cell rather than endothelial dysfunction.

We will indicate that lipid fractions may reflect the structural and functional change of vascular smooth muscle cell in a cross-sectional setting of the community-based Japanese women.

Compliance with ethical standards

Informed consent was obtained from patients in this study and the study was approved by the Ethics Committee of Niilihon University School of Medicine.

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