Original Article

Association of Changes in Neck Circumference with Cardiometabolic Risk in Postmenopausal Healthy Women

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***Aim*: Although neck circumference (NC) is thought to predict obesity-related metabolic abnormality, its causal role in cardiometabolic risk is unclear. The aim of this study was to clarify the impact of changes in NC on cardiometabolic risk in healthy postmenopausal women through a community-based longitudinal study.**

***Methods*: From a local community in Japan, 63 generally healthy postmenopausal women were recruited. All participants received an assessment of obesity-related anthropometric markers, biochemical parameters, and hemodynamic measures and were followed on average for 3 years.**

***Results*: At baseline analysis, larger NC was positively associated with atherosclerosis-related markers, brachial-ankle pulse wave velocity (baPWV) and blood pressure, as well as some lipid parameters. After the follow-up period, change in NC was associated with changes in body mass index (BMI), body fat percentage, and waist circumference (WC). Interestingly, significant correlations of change in NC with changes in baPWV and blood pressure were observed, whereas changes in WC and BMI were only associated with changes in low-density lipoprotein cholesterol and/or total cholesterol. In multivariate linear regression analysis, change in NC was significantly associated with changes in baPWV and systolic blood pressure, independent of changes in BMI, WC, and biochemical parameters. In addition, an increase in NC was associated with a 2.69-fold increased odds ratio of accelerated baPWV.**

***Conclusions*: Change in NC was independently associated with changes in atherosclerosis-related markers. These observations suggest that NC is an important predictor of the risk of developing obesity-related atherosclerosis in healthy postmenopausal women.**

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Key words: Neck circumference, Obesity, Brachial-ankle pulse wave velocity, Atherosclerosis

Introduction

Despite advances in medical and surgical procedures, coronary artery disease (CAD) is the leading cause of death in the elderly. Although CAD is rare in young women, the incidence of CAD rapidly rises postmenopause because of estrogen deficiency[1, 2]. However, an early diagnosis of CAD is difficult in some women because older women with CAD often present with atypical symptoms, and noninvasive analysis for detecting CAD, such as exercise ECG, is less accurate[3, 4]. Consequently, the incidence of sudden cardiac death without CAD history and silent myocardial infarction is higher in women than in

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Table 1. Clinical characteristics of study participants

	Baseline values (mean ± SD)	Follow-up values (mean ± SD)	*p* value
Age (years)	62.4 ± 7.1	65.2 ± 7.1	0.001
Height (cm)	153.5 ± 4.9	153.2 ± 4.8	0.004
Body weight (kg)	52.0 ± 8.0	52.0 ± 8.6	0.873
Body fat percentage (%)	33.0 ± 6.1	32.7 ± 7.5	0.373
Body mass index	22.1 ± 3.3	22.2 ± 3.5	0.519
Waist circumference (cm)	79.1 ± 9.6	81.8 ± 10.2	0.001
Neck circumference (cm)	33.1 ± 1.5	33.1 ± 1.9	0.730
baPWV (cm/sec)	1518.1 ± 274.2	1572.6 ± 333.8	0.025
Systolic blood pressure (mmHg)	128.2 ± 19.2	130.3 ± 21.5	0.243
Diastolic blood pressure (mmHg)	73.4 ± 11.1	72.9 ± 12.3	0.712
Triglyceride (mg/dL)	106.8 ± 58.3	108.9 ± 47.5	0.703
Total cholesterol (mg/dL)	212.1 ± 26.5	218.7 ± 29.2	0.048
LDL-cholesterol (mg/dL)	118.4 ± 24.4	127.7 ± 26.4	0.001
HDL-cholesterol (mg/dL)	71.1 ± 17.6	71.64 ± 18.0	0.858
HbA1c (%)	5.62 ± 0.37	5.65 ± 0.47	0.490

baPWV, brachial-ankle pulse wave velocity; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c.

men[5, 6]. Therefore, the management of CAD in postmenopausal women is an imperative clinical problem. Responses to postmenopausal estrogen loss are linked to the pathophysiology of metabolic syndrome[1, 2]. Estrogen level is negatively correlated with body mass index (BMI) and abdominal fat accumulation in postmenopausal women, leading to an increased incidence of metabolic syndrome during and after menopause[1]. In addition, several clinical studies have reported the importance of obesity as a determinant of CAD in women[7]. To enable early therapeutic intervention against the development of CAD, risk assessment of obesity-related atherosclerosis in postmenopausal women is important in clinical practice because cardiovascular diseases mainly occur because of atherosclerosis progression.

Obesity is a potent mediator of an adverse metabolic profile and increases the risk of metabolic disorders including CAD[7-9]. However, obesity-related risk can be restored by early therapeutic intervention such as exercise for weight loss. To identify obesity in individuals, BMI, waist circumference (WC), and waist-to-hip ratio are widely available as simple surrogate measures because the accurate assessment of fat distribution using magnetic resonance imaging (MRI) or computed tomography (CT) is impractical in a clinical setting. However, these markers do not completely characterize fat topology and exhibit problems in reproducibility[10-12]. Therefore, additional methods capable of improving metabolic disease risk assessment beyond traditional anthropometric measures are awaited. Recently, the neck fat depot has emerged as a potent predictor of metabolic disease independent of visceral and whole body obesity, and measurement of neck circumference (NC) was confirmed to reflect the amount of neck fat depot as assessed using CT or MRI[13-17]. Indeed, our previous study also showed the ability of NC measurement to identify obesity-related metabolic abnormality[18].

On the basis of these observations, we thought that NC measurement would be useful for clinical screening to evaluate the risk of atherosclerosis in postmenopausal healthy women. However, the causal role of NC in the development of cardiovascular risk in postmenopausal women is unclear because several previous studies were conducted in a cross-sectional setting. The aim of this study was to clarify whether changes in NC influence cardiometabolic risk and whether NC measurement can predict atherosclerosis progression for the primary prevention of CAD in postmenopausal women, through a community-based longitudinal study.

Methods

Study Population

The participants were 63 generally healthy postmenopausal women who were recruited from a local community, Mihara city, in Japan. All subjects participated on their own free will and attended our medical

Table 2. Correlations among anthropometric markers and cardio-metabolic risk factors at baseline, adjusted for age

	NC		WC		BMI	
	r	p	r	p	r	p
Height	−0.057	0.658	−0.088	0.495	−0.103	0.420
Body weight	0.689	0.001	0.812	0.001	0.922	0.001
Body fat percentage	0.741	0.001	0.863	0.001	0.922	0.001
BMI	0.744	0.001	0.883	0.001		
WC	0.739	0.001			0.883	0.001
NC			0.739	0.001	0.744	0.001
baPWV	0.349	0.005	0.194	0.128	0.206	0.105
SBP	0.359	0.004	0.309	0.014	0.261	0.039
DBP	0.278	0.027	0.259	0.040	0.200	0.115
TG	0.155	0.230	0.053	0.685	0.018	0.892
TC	−0.182	0.157	−0.154	0.232	−0.193	0.132
LDL-C	−0.036	0.782	0.018	0.887	−0.028	0.830
HDL-C	−0.286	0.024	−0.257	0.044	−0.283	0.026
HbA1c	0.404	0.001	0.282	0.027	0.324	0.010

BMI, body mass index; WC, waist circumference; NC, neck circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol.

center for risk-screening tests of metabolic syndrome. These participants underwent the assessment of cardiometabolic risk factors twice a year and were followed on average for 3.03±0.46 years between December 2010 and June 2014. All participants were free of clinical chronic disease and medication use such as estrogen replacement therapy and diuretics. Written informed consent was obtained from all participants, and the study protocol was approved by the local Ethics Committee.

Anthropometric Measurements

Height, body weight, BMI, body fat percentage, WC, and NC were evaluated in all participants as anthropometric measurements. Height was measured to the nearest 1 mm using a stadiometer with no shoes and the head held in the Frankfurt horizontal plane, and weight was assessed to the nearest 0.1 kg using a digital scale with no outerwear or shoes. BMI was calculated as weight divided by height squared (kg/m^2). Body fat percentage was determined by bioelectrical impedance analysis using a body fat meter. Both WC and NC were measured to the nearest 1 mm using a flexible tape measure. WC was measured at the level of the umbilicus in a standing position. NC was measured in a seated position at the level of the mid-neck, positioned just below the laryngeal prominence and spinous process of the 7th cervical vertebra.

Laboratory Assessments

After an overnight fast, a blood sample was collected from each participant for the measurement of biochemical parameters related to metabolic disorders. Serum triglyceride (TG), total-cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured for lipid profile analysis. Hemoglobin A1c (HbA1c) was measured to evaluate glucose metabolism using a standard biochemical procedure.

Measurement of Blood Pressure and Pulse Wave Velocity

Every participant was rested in a supine position for at least 5 min in a quiet room before measuring blood pressure and brachial-ankle pulse wave velocity (baPWV). Blood pressure was measured at both brachial arteries using a digital sphygmomanometer, and the mean of these measurements was used as the average blood pressure. baPWV was measured using a volume-plethysmographic system (Form/ABI; Colin Co. Ltd., Japan) according to the manufacturer's protocol, and the average of bilateral recordings of baPWV was used for analysis.

Statistical Analysis

All values are expressed as mean±standard division (SD). All tests were two-sided, and $p<0.05$ was considered significant. Anthropometric measurements, including NC, WC, and BMI, were normally distrib-

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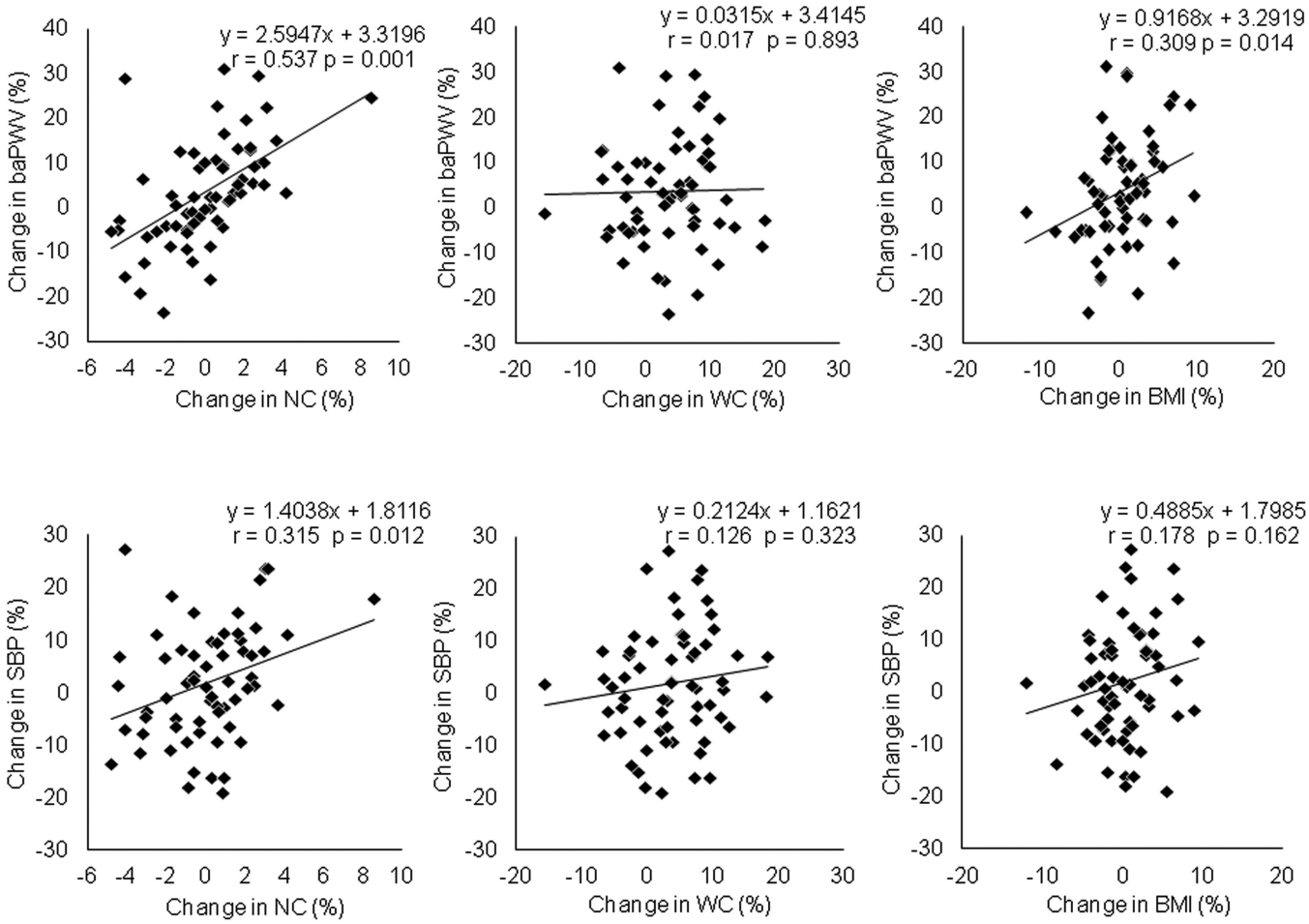

Fig. 1. Correlations between changes in anthropometric markers and hemodynamic measures

Change in baPWV was positively associated with changes in NC and BMI, and change in SBP correlated with change in NC only.
NC, neck circumference; WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; baPWV, brachial-ankle pulse wave velocity.

uted. TC, TG, and HbA1c were log-transformed to improve the normality of their distribution. For statistical analysis, Student's *t* test was used for comparison of continuous variables. Associations among the anthropometric measurements and cardiometabolic risk factors or their changes were assessed using an age-adjusted Pearson's correlation coefficient. To adjust for the effects of covariates and further clarify independent relationships, we performed a multivariate linear regression analysis. In this model, we initially adjusted for covariates (age and changes in heart rate and/or mean blood pressure) and then evaluated independent variables to estimate the relative contribution of these variables and the variability of the dependent variables. Finally, we performed a multivariate logistic regression of dichotomous data for baPWV (increase or no increase during the follow-up period) after adjusting for age and change in heart rate to determine the size of the effect of variables as odds ratios and 95% confidence intervals. In this model, independent variables were changes in NC, WC, BMI, and biochemical parameters. Statistical analysis was performed using SPSS 20.0 (SPSS Inc., IL).

Results

Subject Characteristics

The characteristics of the 63 participants in this study are presented in **Table 1**. All subjects were postmenopausal women in the local community and had a history of natural menopausal transition. All participants were nonsmokers and had similar lifestyles and backgrounds including age. Amongst these participants, 4 subjects had WC of 90 cm or greater, 11 had

Table 3. Associations of changes in anthropometric markers with changes in cardio-metabolic risk factors, adjusted for age

	Change in NC		Change in WC		Change in BMI	
	r	p	r	p	r	p
Height	−0.007	0.954	−0.130	0.308	−0.085	0.506
Body weight	0.372	0.003	0.474	0.001	0.957	0.001
Body fat percentage	0.278	0.027	0.352	0.005	0.684	0.001
BMI	0.385	0.002	0.522	0.001		
WC	0.254	0.045			0.522	0.001
NC			0.254	0.045	0.385	0.002
baPWV	0.537	0.001	0.017	0.893	0.309	0.014
SBP	0.315	0.012	0.126	0.323	0.178	0.162
DBP	0.168	0.188	0.142	0.268	0.111	0.385
TG	0.065	0.616	0.085	0.510	0.120	0.355
TC	0.211	0.100	0.081	0.529	0.387	0.002
LDL-C	0.176	0.172	0.264	0.038	0.517	0.001
HDL-C	0.154	0.231	0.149	0.247	0.192	0.136
HbA1c	−0.090	0.485	0.013	0.921	−0.080	0.535

systolic blood pressure (SBP) of >140 mmHg, and 14 had dyslipidemia (TG >150 mg/dL or HDL-C <40 mg/dL) at baseline. Mean BMI, WC, and NC were 22.1, 79.1 cm, and 33.1 cm respectively, and mean baPWV was 1518.1 cm/second at baseline. Although the presence of peripheral arterial disease affects baPWV, there were no subjects with low ankle brachial index (<0.9).

After the follow-up period, WC, baPWV, TC, and LDL-C were significantly increased, and height was decreased as compared with baseline values. In contrast, there were no significant changes in body weight, BMI, body fat percentage, NC, TG, HDL-C, HbA1c, and blood pressure.

Correlations Among Anthropometric Markers and Metabolic Risk Factors at Baseline

We investigated the correlations among obesity-related anthropometric measurements using baseline values (**Table 2**). Age-adjusted Pearson's correlation coefficient demonstrated that NC and WC were significantly associated with anthropometric markers of whole body adiposity, BMI, and body fat percentage. In addition, a strong association between NC and WC was found at baseline. These observations indicate that NC was related to not only upper-body subcutaneous fat accumulation but also whole body and visceral fat accumulation.

The associations of anthropometric markers with hemodynamic measures and biochemical parameters were also investigated after adjusting for age (**Table 2**). Whereas both SBP and diastolic blood pressure (DBP) were correlated with NC and WC, baPWV was associated with NC only. Analysis of lipid and glucose metabolism demonstrated that NC, WC, and BMI negatively correlated with HDL-C, and HbA1c positively associated with these anthropometric markers.

Correlations Among Changes in Anthropometric Markers and Metabolic Risk Factors

To further clarify the ability of NC measurements to identify metabolic risk, we investigated the associations among changes in anthropometric markers, biochemical parameters, and hemodynamic measures using an age-adjusted Pearson's correlation coefficient. Although significant associations among changes in NC, WC, and BMI were observed, correlation coefficients were lower than those of baseline analysis. Interestingly, changes in NC, WC, and BMI were related to different medical conditions. Although subclinical atherosclerosis was evaluated by measuring baPWV and blood pressure, change in baPWV was associated with changes in NC ($r=0.537$, $p=0.001$) and BMI ($r=0.309$, $p=0.014$), and change in SBP correlated with change in NC only ($r=0.315$, $p=0.012$). In addition, change in baPWV was also associated with change in SBP ($r=0.448$, $p=0.001$). There were no associations between change in DBP and anthropometric markers (**Fig. 1** and **Table 3**). In contrast, changes in lipid parameters correlated with changes in WC and BMI but not with change in NC. Change in WC was only associated with change in LDL-C, whereas change in BMI correlated with changes in TC and LDL-C. No significant association

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Table 4. Multivariate linear regression analysis between changes in hemodynamic markers and cardio-metabolic risk factors

	Change in baPWV			Change in SBP		
	β	p	R^2	β	p	R^2
Model 1						
NC	0.411	0.001	0.392	0.346	0.008	0.073
Model 2						
NC	0.372	0.002	0.424	0.314	0.029	0.046
WC	−0.216	0.066		0.044	0.769	
BMI	0.240	0.051		0.052	0.737	
Model 3						
NC	0.335	0.002	0.461	0.376	0.007	0.036
LDL-C	0.112	0.298		−0.081	0.572	
HDL-C	0.200	0.062		−0.061	0.665	
HbA1c	−0.134	0.207		0.021	0.881	

Change in baPWV, adjusted for age and changes in mean blood pressure and heart rate; Change in SBP, adjusted for age and change in heart rate.

was observed between changes in anthropometric measures and change in HbA1c (**Table 3**).

Based on the correlation analysis, we focused on the association of changes in NC and atherosclerosis-related factors; subsequently, we performed multivariate linear regression analysis after adjusting for age and changes in heart rate and mean blood pressure (**Table 4**). In this analysis, change in NC was independently associated with changes in baPWV and SBP. However, changes in WC, BMI, and biochemical parameters were not associated with changes in atherosclerosis-related factors. In contrast, change in WC, but not change in NC, was independently correlated with change in LDL-C (β=0.277, p=0.026), and change in BMI was independently associated with changes in TC (β=0.314, p=0.004) and LDL-C (β=0.493, p=0.001).

Finally, we performed multivariate logistic regression analysis to assess the influence of change in NC on baPWV. After adjusting for age and change in heart rate, an increase in NC was associated with a 2.69-fold increased odds ratio of accelerated baPWV, and an increase in SBP was also associated with a 1.13-fold increased odds ratio of accelerated baPWV (**Table 5**).

Table 5. Multivariate logistic regression of risk factors for increased baPWV

	OR	95% CI	p value
Change in NC	2.694	1.348−5.387	0.005
Change in WC	0.881	0.727−1.067	0.195
Change in BMI	1.297	0.907−1.855	0.154
Change in SBP	1.125	1.020−1.241	0.018
Change in LDL	0.993	0.921−1.071	0.856
Change in HDL	1.064	0.973−1.163	0.173

OR, odds ratio; CI, confidence interval.

Discussion

In this study, we examined the correlations of NC and its change with metabolic risk factors in community-based postmenopausal women in Japan and found that change in NC, but not changes in WC and BMI, was independently associated with changes in arteriosclerosis-related factors, baPWV, and blood pressure. These observations suggest that NC is an important surrogate marker to identify the early phase of atherosclerosis associated with obesity in healthy postmenopausal women.

The measurement of WC is a first step to recognize metabolic syndrome because it reflects the adverse metabolic profile associated with excess visceral fat accumulation[19, 20]. However, recent studies demonstrated that NC is also an independent predictor of metabolic abnormality[13-18]. Indeed, the present study showed that NC was related to an adverse metabolic profile including low HDL-C and high HbA1c levels at baseline. In addition, we investigated the associations of NC with atherosclerosis-related factors because the primary prevention of CAD is based on the assessment of subclinical atherosclerosis in individuals.

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In this study, we utilized baPWV and blood pressure to assess atherosclerosis noninvasively, and NC was significantly associated with baPWV, SBP, and DBP at baseline. PWV is well known to reflect the elasticity of segmental arteries, providing an estimate of arterial stiffness[21]. Accelerated arterial stiffness is mainly due to the degeneration of the elastic layer, increased collagen in the central arterial wall and vascular dysfunction. Arterial stiffness reflects advanced arteriosclerosis, which precedes overt atherosclerosis, and arteriosclerosis progression is closely related to the incidence of cardiovascular diseases[22, 23]. In addition, a large part of the structural and functional changes of arterial stiffness is thought to be linked to the early phase of atherosclerosis[24, 25]. Carotid-femoral PWV (cfPWV) is widely used to assess central arterial stiffness. However, the measurement of cfPWV has some limitations for use in clinical screening because it is necessary to have relatively high skills and to expose the inguinal region for measurement, resulting in a lengthy measuring time. In contrast, because baPWV is calculated by measuring the pulse wave of the brachial and tibial arteries, the measurement can be easily and quickly performed compared with cfPWV and shows high reproducibility[26]. In addition, several clinical studies showed a strong association between baPWV and cfPWV or aortic PWV, and baPWV has been shown to predict future cardiovascular events, cardiovascular mortality, and all-cause mortality above and beyond traditional risk factors[27-29]. Therefore, the measurement of baPWV is thought to be suitable for clinical practice and screening to detect subclinical atherosclerosis.

To clarify the impact of increased NC on metabolic risk, we evaluated the changes in anthropometric measurements and metabolic risk factors in the same subject. As a result, change in NC was independently associated with changes in baPWV and SBP, and an increase in NC was associated with a 2.69-fold increased odds ratio of accelerated baPWV. However, changes in WC or BMI were not associated with change in baPWV despite the fact that a significant association was found among changes in NC, WC, and BMI. A large part of the effect of increased NC on metabolic risk is thought to relate to the whole body or visceral adiposity. However, the associations between changes in NC, WC, and BMI were reduced as compared with those of baseline analysis. Therefore, NC could rapidly increase in response to an increase in upper-body adiposity as compared with WC and BMI.

The accuracy of NC measurement might make it possible that change in NC can predict changes in baPWV and SBP. In the present study, measurement of NC was performed using two anatomic landmarks. This procedure can easily determine the location for measuring NC, resulting in high reproducibility and accuracy with a short measurement time. In addition, although the measurement of WC is influenced by postprandial and respiratory abdominal expansion, the value of NC is not affected by these physiological problems. Consequently, NC measurement could actually detect a slight increase in neck fat accumulation associated with upper-body obesity.

Recently, the role of subcutaneous adipocytes in metabolic abnormalities has received considerable attention. Excess upper-body subcutaneous adipose tissue can increase the secretion of angiotensinogen and proinflammatory cytokines, such as IL-6 and TNF-α. Several studies demonstrated that these inflammatory biomarkers are significantly associated with arterial stiffness[30-32]. In addition, recent studies using FDG-PET/CT demonstrated that metabolic activity and inflammation in upper-body subcutaneous adipose tissue, including the neck fat depot, were increased in obese individuals[33]. Furthermore, the inflammation of neck subcutaneous adipose tissue was significantly associated with increased inflammatory activity in the arterial wall[34]. Inflammatory stimuli enhance the secretion and activation of several proteases and cytokines in the arterial wall. These inflammatory factors are thought to induce medial degeneration, such as the destruction of the elastic layer and collagen deposition, leading to accelerated arteriosclerosis[32]. Therefore, the accumulation of neck or upper-body adipose tissue might be associated with obesity-related atherosclerosis progression through inducing an inflammatory response in the arterial wall.

On the other hand, dyslipidemia plays an important role in the process of atherogenesis. The pathology of atherosclerotic lesions is characterized by lipid deposition in the arterial wall, and this structural change results from increased lipid concentrations in blood. Therefore, lipid parameters are considered to be atherosclerosis markers. However, change in NC was not significantly associated with changes in lipid parameters during the follow-up period (3 years), although some lipid parameters correlated with NC at the baseline. In contrast, changes in WC and BMI were associated with changes in TC and/or LDL-C. Free fatty acids and glycerol can be stored as TG in subcutaneous adipocytes in nonobese subjects, and the visceral fat depot is thought to be increased after the disruption of this buffering effect of subcutaneous adipose tissue[30]. Therefore, changes in lipid parameters are closely associated with visceral fat accumulation.

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These observations suggest that NC is a more sensitive predictor of arteriosclerosis than are WC and BMI, and WC is mainly associated with atherosclerosis progression.

This study has one limitation. In contrast to our study, it has been reported that change in NC was associated with changes in lipid parameters[16]. This opposing result might be explained by the distinct age, menopausal state, or ethnicity of the study population. However, because of the small sample size in our study, we cannot exclude the possibility that the associations of changes in anthropometric measurements with lipid parameters were underestimated in the statistical analysis. Therefore, a longitudinal cohort study with a large population will be needed to clarify the precise role of NC in cardiovascular risk estimates.

Conclusion

NC was independently and sensitively predictive of arteriosclerosis progression among obesity-related anthropometric indices. Measurement of NC could be useful to identify individuals with a high risk of developing obesity-related atherosclerosis amongst healthy postmenopausal women, leading to the determination of an appropriate time for therapeutic intervention against the development of CAD.

Conflicts of Interest

The authors report no conflict of interest.

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