Acta Med. Nagasaki 62: 7－14

Single nucleotide polymorphism as an indicator of short stature and dyslipidemia in community-dwelling elderly Japanese subjects

Kazuhide TEZUKA[1], Yuji SHIMIZU[1,2], Yuko NOGUCHI[2], Shimpei SATO[2], Jun KOYAMATSU[3], Hirotomo YAMANASHI[3], Mako NAGAYOSHI[2], Shin-Ya KAWASHIRI[2], Yasuhiro NAGATA[4], Takahiro MAEDA[2,3]

1) Department of Cardiovascular Disease Prevention, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka, Japan.
2) Department of Community Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan.
3) Department of Island and Community Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan.
4) Center for Comprehensive Community Care Education, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Aims: We previously reported an inverse association between adult height and dyslipidemia in subjects with low, but not high, body mass index (BMI) by elucidating genetic influences. However, the genetic factors that are associated with short stature and dyslipidemia in subjects with a low BMI are unknown.

Methods: We conducted a cross-sectional study of 877 elderly Japanese subjects aged ≥60 years who underwent a national health check-up in 2014 and 2015. We focused on single nucleotide polymorphism (SNP) rs3782886, since this variant was reported to be associated with metabolic syndrome. Short stature was defined as the lowest 20% of the height distribution (<157.8cm for men and <145.0cm for women), and dyslipidemia was defined by the Japan Atherosclerosis Society (JAS) guidelines as follows: triglycerides (TG) ≥150mg/dL and/or low density lipoprotein-cholesterol (LDL) ≥140mg/dL, and/or high density lipoprotein-cholesterol (HDL) <40mg/dL, and/or lipid lowering medication use.

Results: Of the study population, 62.3% were major homo, 33.0% were hetero and 4.8% minor homo. With non-minor homo (major homo and hetero) as reference groups, minor homo was significantly positively associated with short stature independent of known cardiovascular risk factors. The multivariable odds ratio (OR) and 95% confidence interval (CI) of short stature for minor homo was 2.23 (1.07, 4.67). Minor homo also showed a significant positive association with dyslipidemia in subjects with a BMI<23kg/m^2, 3.20 (1.08, 9.51), but not in those with a BMI≥23kg/m^2 ,0.77 (0.32, 1.89).

Conclusion: SNP rs3782886 is associated with short stature and dyslipidemia in elderly Japanese subjects with a BMI<23kg/m^2.

ACTA MEDICA NAGASAKIENSIA 62: 7−14, 2018

Key words: Body mass index, Dyslipidemia, rs3782886, short stature, SNP,

---

Introduction

We previously reported an inverse association between height and dyslipidemia in middle aged Japanese men with a low, but not high body mass index (BMI) [1]. Generally, adult height is regarded as a marker of childhood social and physical condition, including genetic factors [2-5]. On the other hand, BMI has been reported to be positively associated with increased risk of disease [6] and is largely influenced by current circumstances. An analysis limited to subjects with a lower BMI might elucidate the potential risk of child circumstances (including genetic status). A detailed concept of the above has been described elsewhere [1,7].

Genetically determined shorter height and increased risk of coronary artery disease was reported by a European study, which also found that part of this inverse association may be driven by the association between shorter height and an adverse lipid profile [8].

Address correspondence: Yuji Shimizu, MD, PhD, Department of Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki-shi, Sakamoto 1-12-4, Nagasaki 852-8523, Japan
Tel.: +81-95-819-2523, Fax: +81-95-819-8509, E-mail: shimizuyuji@nagasaki-u.ac.jp

Received December 12, 2017; Accepted March 26, 2018

However, no studies have reported that the genetic factor associated with short stature also has a BMI status-specific association with dyslipidemia.

The single nucleotide polymorphism (SNP) rs3782886 in the breast cancer suppressor protein associated protein (BRAP) gene is likely to present only in Asian populations [9]. This SNP rs3782886 is reported to be positively associated with coronary artery disease [9], short stature [10] and inversely associated with metabolic syndrome [11]. We therefore focused on SNP rs3782886 to investigate the genetic factors associated with short stature and dyslipidemia accounting for BMI status.

Applying the above, we conducted a cross-sectional study of 877 elderly Japanese aged ≥60 years who underwent a national health check-up in 2014 and 2015.

Materials and Methods

Subjects and methods

The study population comprised 996 subject residents aged ≥60 years from the western rural communities of Goto city, who undertook an annual medical check-up in 2014 and 2015 as recommended by the Japanese government.

To avoid the influence of chronic disease and malnutrition, those with low body mass index (BMI) (<19.0kg/m^2) (n=84) were excluded, as were persons with missing data (blood pressure data (n=1) and laboratory data (n=34)). The remaining participants, comprising 877 subjects with a mean age of 72.8 years (standard deviation (SD): 7.4; range: 60-92), were enrolled in the study.

Data collection and laboratory measurements

Trained interviewers obtained information on smoking status, drinking status, and medical history. Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan), and body mass index (BMI;kg/m^2) was calculated. Systolic and diastolic blood pressure were recorded at rest. Triglycerides (TG) and creatinine were measured enzymatically. High Density Lipoprotein-cholesterol (HDL) and Low Density Lipoprotein-cholesterol (LDL) were measured using a direct method at SRL, Inc. (Tokyo, Japan). Genomic DNA was extracted from 2ml blood samples with GENE PREP STAR NA-480 (KURABO). Subject genetic DNA was typed with regard to SNP rs3782886 (BRAP on chromosome 12q24.12) using the HybProbe method with LightCycler 480 (Roshe).

Short stature was defined as the lowest 20% with regard to height (<157.8cm for men and <145.0cm for women).

Since a previous Asian study that reported a higher minor allele (G) frequency for SNP rs3782886 as being inversely associated with metabolic syndrome [11] defined abdominal obesity as a waist circumference ≥90cm for men and ≥85 cm for women, we followed this definition when diagnosing abdominal obesity. Dyslipidemia has been defined by the Japan Atherosclerosis Society (JAS) Guidelines as follows: LDL≥140mg/dL and/or HDL<40mg/dL and/or TG≥150mg/dL and/or taking lipid lowering medication [12], as in a previous study [1].

Statistical analysis

Clinical characteristics of the SNP rs3782886 genotype were compared. Differences in mean values or prevalence of potential confounding factors by SNP rs3782886 genotype were calculated. A trend test was performed with a generalized linear regression model for mean values, and a logistic regression model was used for proportion.

Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to determine the association of SNP rs3782886 with short stature and dyslipidemia. We also used logistic regression models to calculate ORs and 95% CIs to determine the association of short stature with abdominal obesity.

In addition, to evaluate the influence of BMI on the association between SNP rs3782886 and dyslipidemia, subjects were stratified by BMI status, since in our previous study, height was inversely associated with dyslipidemia in non-overweight but not in overweight men [1]. Since the World Health Organization (WHO) identified BMI≥23kg/m^2 as an indicator for enhanced risk of disease in Asian populations [6], 23kg/m^2 was set as the BMI cutoff point.

Adjustments for confounding factors were made into three models. The first model (Model1) adjusted only for sex and age. The second (Model 2) included other possible confounding factors, namely, BMI (kg/m^2), smoking status (never-smoker, former smoker, current smoker), alcohol consumption [never-drinker, former drinker, current drinker (<23g/week, 23g/week≤ <46g/week, 46g/week≤ <69g/week, 69g/week≤)], systolic blood pressure (mmHg), HbA1C (%) and serum creatinine (mg/dL). And Model 3 further adjusted for serum triglycerides (mg/dL), serum HDL-cholesterol (mg/dL) and LDL-cholesterol (mg/dL).

All statistical analyses were performed with the SAS system for Windows (version 9.3; SAS Inc., Cary, NC). All p-values for statistical tests were two-tailed, with values of <0.05 regarded as being statistically significant.

Results

Characteristics of the study population

Characteristics of the study population are shown in Table 1. Among 877 elderly Japanese subjects, 546 were major homo (A/A), 289 were hetero (A/G), and 42 were minor homo (G/G). Current drinker status was significantly associated with these genotypes.

Association between the rs3782886 genotype and short stature.

Table 2 shows the association between genotype and short stature. With major homo (A/A) as the reference group, no significant association was observed for hetero (A/G), while a significant association was observed for minor homo (G/G). When we compared the analysis between the two categories (non-minor homo and minor homo), a significant association was observed.

Table 1. Characteristics of the study population by genotype of rs3782886

	rs3782886			p for trend
	Major homo (A/A)	Hetero type (A/G)	Minor homo (G/G)	
No. of participants	546	289	42	
Gender (men), %	37.2	43.3	35.7	0.209
Age, years	72.3 ± 7.5	73.6 ± 7.4	72.6 ± 6.9	0.079
Current drinker, %	33.3	12.8	0.0	<0.001
Current smoker, %	6.8	5.2	2.4	0.392
Body mass index (BMI), kg/m^2	23.6 ± 2.9	24.0 ± 3.2	23.5 ± 2.9	0.105
Systolic blood pressure, mmHg	140 ± 18	140 ± 18	139 ± 15	0.852
Diastolic blood pressure, mmHg	82 ± 11	80 ± 12	81 ± 11	0.229
Serum HDL-cholesterol (HDL), mg/dL	59 ± 15	56 ± 14	57 ± 13	0.005
Serum LDL-cholesterol (LDL), mg/dL	119 ± 29	120 ± 29	119 ± 31	0.862
Serum triglycerides (TG), mg/dL	103 ± 59	106 ± 53	99 ± 41	0.655
Lipid lowering medication use, %	23.8	23.2	26.2	0.910
Hemoglobin A1c (HbA1c), %	5.7 ± 0.5	5.7 ± 0.5	5.8 ± 0.6	0.546
Serum creatinine, mg/dL	0.75 ± 0.20	0.78 ± 0.20	0.75 ± 0.19	0.135
Waist circumference (cm)	85.8 ± 9.0	86.2 ± 8.7	84.7 ± 8.4	0.556
Height, cm	154.9 ± 9.0	154.6 ± 8.4	152.7 ± 8.6	0.268

values: mean ± standard deviation.

Table 2. Odds ratios (OR) and 95% CI for short stature in relation to type of rs3782886.

	rs3782886			P value	minor allele frequencies
	Major homo (A/A)	Hetero type (A/G)	Minor homo (G/G)		
No. at risk	546	289	42		
Short stature					
No. of cases (percentage)	99 (18.1)	61 (21.1)	13 (31.0)		
Model.1	1	1.08 (0.74, 1.58)	2.22 (1.06, 4.63)	0.117	1.27 (0.94, 1.70)
	1		2.16 (1.05, 4.45)	0.037	
Model.2	1	1.13 (0.76, 1.70)	2.35 (1.10, 5.04)	0.079	1.33 (0.97, 1.82)
	1		2.22 (1.06, 4.64)	0.034	
Model.3	1	1.13 (0.75, 1.69)	2.36 (1.10, 5.06)	0.081	1.32 (0.97, 1.81)
	1		2.23 (1.07, 4.67)	0.033	

Model.1: adjusted only for sex and age. Model.2: further adjusted for body mass index, systolic blood pressure, alcohol consumption, smoking status, HbA1c and serum creatinine.

Model.3: further adjusted for triglycerides, HDL-cholesterol and LDL-cholesterol. Short stature is defined as the lowest 20% of height (<157.8cm for men and <145.0cm for women).

Association between short stature and abdominal obesity.

We performed a further analysis to evaluate the influence of short stature on abdominal obesity, which is one of the important components of metabolic syndrome [12]. Short stature was found to be significantly inversely associated with abdominal obesity (Table 3).

Association between the rs3782886 genotype and dyslipidemia accounting for BMI status.

We also evaluated the association between the rs3782886 genotype and dyslipidemia accounting for BMI status (Table 4). For subjects with a BMI<23kg/m^2, the rs3782886 genotype was significantly associated with dyslipidemia, while no significant association was observed for subjects with a BMI≥23kg/m^2.

Table 3. Odds ratios (OR) and 95% CI of abdominal obesity for short stature.

	Short stature		P value
	(-)	(+)	
No. at risk	704	173	
Abdominal Obesity			
No. of cases (percentage)	434 (61.6)	84 (48.6)	
Model.1	1	0.46 (0.31, 0.68)	<0.001
Model.2	1	0.26 (0.15, 0.47)	<0.001
Model.3	1	0.26 (0.15, 0.47)	<0.001

Model.1: adjusted only for sex and age. Model.2: further adjusted for body mass index, systolic blood pressure, alcohol consumption, smoking status, HbA1c and serum creatinine. Model.3: further adjusted for triglycerides, HDL-cholesterol and LDL-cholesterol. Short stature is defined as the lowest 20% of height (<157.8cm for men and <145.0cm for women). Abdominal obesity is defined as waist circumference ≥ 90cm for men and ≥ 85 cm for women.

Table 4. Odds ratios (OR) and 95% CI for dyslipidemia in relation to type of rs3782886.

	rs3782886			P value	minor allele frequencies
	Major homo (A/A)	Hetero (A/G)	Minor homo (G/G)		
Total subjects					
No. at risk	546	289	42		
No. of cases (percentage)	293 (53.7)	171 (59.2)	27 (64.3)		
Model.1	1	1.37 (0.99, 1.78)	1.56 (0.80, 3.03)	0.034	1.29 (1.02, 1.64)
	1		1.42 (0.74, 2.73)	0.298	
Model.2	1	1.24 (0.90, 1.71))	1.49 (0.75, 2.96)	0.112	1.23 (0.95, 1.59)
	1		1.46 (0.74, 2.88)	0.271	
BMI < 23kg/m^2					
No. at risk	250	109	19		
No. of cases (percentage)	108 (43.2)	52 (47.7)	14 (73.7)		
Model.1	1	1.25 (0.78, 1.98)	3.59 (1.23, 10.44)	0.028	1.50 (1.05, 2.15)
	1		3.36 (1.16, 9.68)	0.025	
Model.2	1	1.37 (0.82, 2.28)	3.57 (1.18, 10.77)	0.022	1.59 (1.07, 2.37)
	1		3.20 (1.08, 9.51)	0.036	
BMI ≥ 23kg/m^2					
No. at risk	296	180	23		
No. of cases (percentage)	185 (62.5)	119 (66.1)	13 (56.5)		
Model.1	1	1.26 (0.84, 1.87)	0.80 (0.33, 1.92)	0.614	1.09 (0.79, 1.50)
	1		0.74 (0.31, 1.74)	0.485	
Model.2	1	1.17 (0.77, 1.79)	0.73 (0.30, 1.82)	0.900	1.02 (0.73, 1.44)
	1		0.77 (0.32, 1.89)	0.572	

Model.1: adjusted only for sex and age. Model.2: further adjusted for body mass index, systolic blood pressure, alcohol consumption, smoking status, HbA1c and serum creatinine.

Dyslipidemia is defined as TG ≥ 150mg/dL and/or LDL-cholesterol ≥ 140mg/dL, and/or HDL-cholesterol<40mg/dL and/or lipid lowering medication use.

Interaction between the rs3782886 genotype and BMI categories on dyslipidemia

Since our study population comprised subjects with a BMI<23kg/m^2 (n=378) and a BMI≥23kg/m^2 (n=499), to avoid the influence of sample size bias on the correlation between height and dyslipidemia, we evaluated the interaction between the rs3782886 genotype and two BMI categories (BMI≥23kg/m^2 and BMI<23kg/m^2) on dyslipidemia. No significant interaction between genotype categories by tree type (major homo, hetero and minor homo) and BMI category was observed (fully adjusted p value for the effect of this interaction on dyslipidemia at p=0.154), whereas a significant interaction was seen between genotype categories with respect to two types (non-minor homo and homo) and BMI category (p=0.037).

Sex-specific analysis

With non-minor homo (major homo and hetero) as reference groups, the fully adjusted ORs and 95% CIs of short stature for minor homo were 3.72 (1.15, 12.07) for men and 1.54 (0.57, 4.22) for women.

And with non-minor homo (major homo and hetero) as reference groups, the fully adjusted ORs and 95% CIs of dyslipidemia for minor homo among men were 7.05 (0.65, 77.10) for a BMI<23kg/m^2 and 0.69 (0.18, 2.68) for a BMI≥23kg/m^2, with the corresponding values among women at 2.86 (0.84, 9.78) and 0.65 (0.20, 2.10), respectively.

Discussion

The major finding of present study is the association of SNP rs3782886 with short stature and dyslipidemia in elderly Japanese subjects with a BMI<23kg/m^2, independent of known classical cardiovascular risk factors.

Our previous cross-sectional study of middle aged Japanese men revealed an inverse association between height and dyslipidemia, particularly in subjects with a low BMI [1]. An additional study reported a positive association between genetically determined shorter height and increased risk of cardiovascular disease, and that this association can be partly explained by the association between shorter height and an adverse lipid profile [8]. In our previous study, the Asian population specific SNP rs3782886 [9] was revealed to be associated with short stature in the elderly Japanese population [10] which is compatible with present results. We also found further evidence that SNP rs3782886 is associated with dyslipidemia, particularly in subjects with a BMI<23kg/m^2.

Contradictory to our present results, higher minor allele (G) frequency of SNP rs3782886 is reported to have a beneficial association with regard to metabolic syndrome and abdominal obesity [11]. However, when the association between short stature and abdominal obesity is evaluated, the former is significantly inversely associated with the latter, which seems to be compatible with this previous study [11]. Since abdominal obesity as defined by waist circumference is one of the important components of metabolic syndrome [13], height should act as strong confounding factor for the diagnosis of metabolic syndrome, while the SNP rs3782886 genotype is associated with short stature.

In addition to the above, a positive association between the minor allele (G) frequency of SNP rs3782886 and coronary artery disease has been reported [9], while short stature is known to be positively associated with high inflammatory activity, as evaluated by white blood cell count and carotid atherosclerosis [4,7]. Atherosclerosis, which is a well-known risk factor for coronary artery disease, is acknowledged to be an inflammatory condition [14], and previous studies have reported an association between white blood cell count and carotid atherosclerosis [15,16]; therefore, these studies are compatible with our present results showing a positive association between SNP (rs3782886) and dyslipidemia. Furthermore, that SNP rs3782886 is known to be located in the BRAP gene on chromosome 12q24, and that higher expression of BRAP minor allele (G allele) is associated with increased risk of atherosclerosis [17] via enhancing the degree of inflammation through activation of NF-κB protein [18], also support the above-mentioned mechanism.

The background mechanism behind these associations has yet to be clarified, however.

In addition to above-mentioned factors, bone is also an important endocrine organ for the regulation of glucose/lipid metabolism [19,20], and it follows that this organ is smaller in those with a short stature. These compartments may form a complicated network that could explain our present results. Further investigation is necessary to elucidate these networks.

Atherosclerosis related inflammatory SNPs [17] were shown to be associated in our study with short stature as well as with dyslipidemia limited to subjects with low BMI. Since atherosclerosis [4] and active inflammation [7] are reportedly positively associated with short stature limited to subjects with high BMI, the notion that an analysis limited to subjects with a low BMI might be useful for elucidating the potential risk associated with childhood circumstances (including genetic status) [1,7] appears to be supported by the results presented here.

Potential limitations of this study warrant consideration. Due to the limited number of participants, meaningful sex-specific analysis was not possible. However, although statistical power did not reach significant values, essentially the same associations were observed for both men and women. Although we found that SNP rs3782886 is associated with short stature in elderly Japanese subjects, the background mechanism is not yet known; therefore, further investigation is necessary. As in previous studies of cardiovascular risk factors [21,22], no adjustments were made for confounding factors related to dietary intake. Because creatinine clearance data were not available, and estimated glomerular filtration rate (GFR) is not effective for evaluating kidney function when comparing the association with various body heights [1,3-5,7,23], we were not able to perform an analysis adjusted for precise renal function. However, our study showed that these associations remained significant even after adjusting for serum creatinine.

Conclusion

In conclusion, SNP rs3782886 is associated with short stature and dyslipidemia in elderly Japanese subjects with a BMI<23kg/m^2.

List of Abbreviations

BMI: body mass index; SNP: single nucleotide polymorphism; JAS: Japan Atherosclerosis Society; TG: triglycerides; LDL: low density lipoprotein-cholesterol; HDL: high density lipoprotein-cholesterol; OR: odds ratio; CI: confidence interval; BRAP: breast cancer suppressor protein associated protein; SD: standard deviation; WHO: World Health Organization; WBC: white blood cell; GFR: estimated glomerular filtration rate;

Declarations

Ethical approval and consent to participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki declaration and its later amendments for comparable ethical standards. The Ethics Committee for Human Use of Nagasaki University obtained ethical approval. This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences (project registration number 14051404). Written consent forms were available in Japanese to ensure comprehensive understanding of the study objectives, and informed consent was provided by the participants.

Consent for publication Not applicable

Availability of data and material The datasets generated during and/or analyzed during the current study are not publicly available due to ethical consideration but are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no conflict of interest.

Funding This study was supported by Grants-in-Aids for Scientific Research from the Japan Society for the Promotion of Sciences (No.17H03740, No.18k06448)

Acknowledgements We are grateful to staff from Goto City Hall for their outstanding support.

Reference

1. Shimizu Y, Yoshimine H, Nagayoshi M, Kadota K, Takahashi K, Izumino K, et al. Height correlates with dyslipidemia in non-overweight middle-aged Japanese men. J Physiol Anthropol. 2016;35:29.
2. Honjo K, Iso H, Inoue M, Tsugane S. Adult height and the risk of cardiovascular disease among middle aged men and women in Japan. Eur J Epidemiol. 2011;26:13-21.
3. Shimizu Y, Imano H, Ohira T, Kitamura A, Kiyama M, Okada T, et al; CIRCS Investigators. Adult height and body mass index in relation to risk of total stroke and its subtypes: the circulatory risk in communities study. J Stroke Cerebrovasc Dis. 2014;23:667-674.
4. Shimizu Y, Nakazato M, Sekita T, Kadota K, Arima K, Yamasaki H, et al. Relationship between adult height and body weight and risk of carotid atherosclerosis assessed in terms of carotid intima-media thickness: the Nagasaki Islands study. J Physiol Anthropol. 2013;32:19.
5. Shimizu Y, Sato S, Koyamatsu J, Yamanashi H, Nagayoshi M, Kadota K, et al. Height indicates hematopoietic capacity in elderly Japanese men. Aging (Albany NY). 2016;8:2407-2413.
6. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157-163.
7. Shimizu Y, Yoshimine H, Nagayoshi M, Kadota K, Takahashi K, Izumino K, et al. Short stature is an inflammatory disadvantage among middle-aged Japanese men. Environ Health Prev Med. 2016;21:361-367.
8. Nelson CP, Hamby SE, Saleheen D, Hopewell JC, Zeng L, Assimes TL, et al; CARDIoGRAM+C4D Consortium. Genetically determined height and coronary artery disease. N Engl J Med. 2015;372:1608-1618.
9. Ozaki K, Sato H, Inoue K, Tsunoda T, Sakata Y, Mizuno H, et al. SNPs in BRAP associated with risk of myocardial infarction in Asian populations. Nat Genet. 2009;41:329-333.
10. Shimizu Y, Sato S, Noguchi Y, Koyamatsu J, Yamanashi H, Higashi M, et al. Impact of single nucleotide polymorphism on short stature and reduced tongue pressure among community-dwelling elderly Japanese participants: a cross-sectional study. Environ Health Prev Med. 2017;22:62
11. Wu L, Xi B, Hou D, Zhao X, Liu J, Cheng H, et al. The single nucleotide polymorphisms in BRAP decrease the risk of metabolic syndrome in a Chinese young adult population. Diab Vasc Dis Res. 2013;10:202-207.
12. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, et al; Japan Atherosclerosis Society (JAS) Committee for Epidemiology and Clinical Management of Atherosclerosis. Diagnostic criteria

for dyslipidemia. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb. 2007;14:155-158.

13. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23:469-480.
14. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685-1695.
15. Ortega E, Gilabert R, Nuñez I, Cofán M, Sala-Vila A, de Groot E, et al. White blood cell count is associated with carotid and femoral atherosclerosis. Atherosclerosis. 2012;221:275-281.
16. Shimizu Y, Nakazato M, Kadota K, Sato S, Koyamatsu J, Arima K, et al. Association between white blood cell count and diabetes in relation to triglycerides-to-HDL cholesterol ratio in a Japanese population: The Nagasaki Islands study. Acta Med Nagasaki. 2014;59:91-97.
17. Liao YC, Wang YS, Guo YC, Ozaki K, Tanaka T, Lin HF, et al. BRAP activates inflammatory cascades and increases the risk for carotid atherosclerosis. Mol Med. 2011;17:1065-1074.
18. Karin M, Delhase M. The I kappa B kinase (IKK) and NF-kappa B: key elements of proinflammatory signalling. Semin. Immunol. 2000;12:85-98.
19. Sato M, Asada N, Kawano Y, Wakahashi K, Minagawa K, Kawano H, et al. Osteocytes regulate primary lymphoid organs and fat metabolism. Cell Metab. 2013;18:749-758.
20. Yoshizawa T. [Bone remodeling and glucose/lipid metabolism]. Clin Calcium. 2011;21:709-714. [Article in Japanese]
21. Kitamura A, Noda H, Nakamura M, Kiyama M, Okada T, Imano H, et al. Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). J Atheroscler Thromb. 2011;18:454-63.
22. Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Ohta H. Association between non-high-density lipoprotein cholesterol concentrations and mortality from coronary heart disease among Japanese men and women: the Ibaraki Prefectural Health Study. J Atheroscler Thromb. 2010;17:30-6.
23. Shimizu Y, Sato S, Koyamatsu J, Yamanashi H, Nagayoshi M, Kadota K, et al. Height is an indicator of vascular maintenance capacity in older men. Geriatr Gerontol Int. 2017;17:1729-1736.