Acta Med. Nagasaki 59: 77－82

Associations of carotid atherosclerosis and hyperuricemia with height in relation to drinking status of rural Japanese men: The Nagasaki Islands study.

Shimpei Sato,[1] Yuji Shimizu,[1,2] Naomi Hayashida,[3] Mako Nagayoshi,[1] Jun Koyamatsu,[2] Hirotomo Yamanashi,[2] Koichiro Kadota,[1] Mio Nakazato,[2] Keita Inoue,[4] Noboru Takamura,[3] Yoshiyuki Oozono,[4] Takahiro Maeda[1,2]

[1] Department of Community Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan
[2] Department of Island and Community Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan
[3] Department of Global Health, Medicine and Welfare, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan
[4] Department of General Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Background; Several studies have identified a positive, independent association between uric acid and atherosclerosis whereas uric acid was once considered to be a major antioxidant in human plasma with possible beneficial anti-atherosclerotic effects. Several other studies have found an inverse association between height and stroke, while a previous study of ours detected a positive association between height and hyperuricemia. However, even though uric acid levels may be strongly affected by alcohol consumption and serum creatinine, no published study has examined the possible associations between hyperuricemia and carotid atherosclerosis while taking both height and drinking status into account.

Methods; We conducted a cross-sectional study of 1,337 men aged 30-89 years undergoing a general health check-up to investigate the associations of hyperuricemia and carotid atherosclerosis with height in relation to drinking status.

Results; Of the total study population, 312 men were diagnosed with carotid atherosclerosis (carotid intima-media thickness (CIMT) ≥1.1 mm) and 365 men with hyperuricemia (serum uric acid>7.0mg/dL). For shorter non-drinkers, a significantly positive association between these two abnormalities was detected, which was independent of classical cardiovascular risk factors except for serum creatinine. However, this association ceased to exist after further adjustment for serum creatinine. However, while the age-adjusted model showed no significant association for taller drinkers, adjustment for serum creatinine produced a significantly inverse association.

Conclusion; Our study established that hyperuricemia is associated with carotid atherosclerosis for Japanese men, while body height, drinking status and serum creatinine are important determining factors for this association.

ACTA MEDICA NAGASAKIENSIA 59: 77－82, 2015

Key words: carotid atherosclerosis, hyperuricemia, height, drinking status, men

Introduction

Several studies reported the association between uric acid and carotid atherosclerosis [1,2], the latter being a known risk factor for stroke [3]. Moreover, several studies have identified an inverse association between height and stroke [4,5]. Finally, a previous study of ours found a positive association between height and hyperuricemia [6]. However, no published study has investigated the possible associations between hyperuricemia and carotid atherosclerosis, while taking body height into account.

For such an investigation, however, women might not be suitable subjects because height is confounded by vertebral compression fractures, which are mainly caused by post-

Address correspondence: Yuji Shimizu, MD, PhD, Department of Community Medicine, Nagasaki University Graduate school of Biomedical Science, Nagasaki-shi, Sakamoto 1-12-4, Nagasaki 852-8523, Japan.
Tel: +81-95-819-7578, Fax: +81-95-819-7189, E-mail: simizicyuu@yahoo.co.jp

Received March 20, 2014; Accepted June 27, 2014

menopausal osteoporosis [7]. We therefore limited our investigation to Japanese men. Other studies have found that alcohol consumption is associated with uric acid level [8] whereas while light to moderate alcohol consumption reportedly has a beneficial effect on atherosclerosis [9]. Since the prevalence of drinkers is high among Japanese men, [10,11], a study to investigate associations between hyperuricemia and carotid atherosclerosis in relation to body height of Japanese men should also take drinking status into account. To investigate those associations we conducted a cross-sectional study of Japanese men who participated in a general health check-up between 2005 and 2012.

Methods

Participants

The survey population included 1,538 men aged 30 to 89 years, all residents of the western rural Japanese community of the Goto Islands, who underwent a general health check-up between 2005 and 2012. A total of 45 individuals with missing data and 156 individuals with a history of cardiovascular disease were excluded, leaving 1,337 men for enrolment in this study. The mean age of the study population was 64.8 years (±10.7 SD; range 30-89). Written consent forms were available in Japanese to ensure comprehensive understanding of the study objectives, and informed consent was signed by the participants. This study was approved by the Ethics Committee for Use of Humans of Nagasaki University (project registration number: 0501120073).

Data collections and laboratory measurements

Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) when blood was drawn.

Fasting blood samples were obtained and the serum was separated and centrifuged after blood coagulation. Serum samples were also obtained in individual siliconized tubes.

Serum triglycerides, serum HDL cholesterol, serum aspartate aminotransferase (AST), serum uric acid, HbA_{1C}, and serum creatinine levels were measured with standard laboratory procedures.

Trained interviewers obtained information on smoking status, drinking status, medical history, use of antihypertensive agents, medication for diabetes mellitus, and medication for dyslipidemia. HbA_{1c}, as defined by the National Glycohemoglobin Standardization Program (NGSP), was calculated with the following equation, which was recently proposed by a working group of the Japanese Diabetes Society (JDS): HbA_{1c} (NGSP) = HbA_{1c} (JDS) + 0.4%. Presence of diabetes was defined as HbA_{1c} (NGSP) ≥ 6.5%, and/or initiation of glucose-lowering medication or insulin therapy [12]. Hyperuricemia was defined as a serum uric acid level >7mg/dL [13].

Carotid B-mode ultrasound imaging

Measurement of carotid intima-media thickness (CIMT) by ultrasonography of the left and right carotid arteries was performed by two medical doctors (N.T. and M.N.) using a LOGIQ Book XP with a 10-MHz transducer (GE Healthcare, Milwaukee, WI, USA). The protocol they used has been described in detail elsewhere [14]. The values of right and left CIMT without measurement of plaque were calculated and the higher CIMT value was used for analysis. Since a previous study reported normal CIMT value as <1.1mm, we defined atherosclerosis as CIMT≥1.1mm [15]. Intra-observer variation for CIMT (N.T.; n=32) was 0.91 ($p<0.01$), and interobserver variation (N.T. and M.N.; n=41) was 0.78 ($p<0.01$).

Statistical analysis

Differences in age-adjusted mean values or prevalence of potential confounding factors by height tertile were calculated by using covariance or general linear models, while logistic regression models were used for calculating odds ratios (OR) and 95% confidence intervals (CI) for the association of carotid atherosclerosis with hyperuricemia stratified by height level. In addition, subjects were stratified by drinking status because alcohol consumption not only influences uric acid levels [8] and development of hyperuricemia [16], but also atherosclerosis [9].

A previous study of ours found that height is positively associated with hyperuricemia independently from classical cardiovascular factors including serum creatinine [6], while another study of a community based population reported that uric acid may be related to glomerular damage [17]. So we established four types of adjusted models. For total subjects and non-drinkers, they were an age-adjusted model, a multivariable adjusted model that included smoking status (never smoker, former smoker, current smoker), alcohol consumption [non-drinker, current light to moderate drinker (1-6 times/week), current heavy drinker (every day)], body mass index (kg/m^2), diabetes mellitus (no, yes), systolic blood pressure (mmHg), antihypertensive medication use (no, yes), antihyperlipidemic agent use (no, yes),

serum triglycerides (mg/dL), serum HDL cholesterol (mg/dL), and serum AST (IU/L), and a fully adjusted model with the addition of serum creatinine (mg/dL). For drinkers, they were an age-adjusted model, an age-and-serum creatinine adjusted model, and a fully adjusted model that included the same variables as those of the fully adjusted model for total subjects and non-drinkers.

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, and values of <0.05 were regarded as statistically significant.

Results

Of the 1,337 men taking part in the general health check-up program, 312 were diagnosed with carotid atherosclerosis (carotid intima-media thickness (CIMT) ≥1.1 mm) and 365 with hyperuricemia (serum uric acid>7.0 mg/dL). Prevalence of current drinkers was 50.6%. Table 1 shows age-adjusted characteristics for this study population in relation to body height. The height tertiles were 'shorter': 155.9±3.7cm (<160.1cm;median:157cm), 'intermediate': 163.1±1.6cm (160.1-165.8cm;median:163.0cm),'taller':170.2±3.6(>165.8 cm;median:169.3cm). Current drinker, serum uric acid, and serum creatinine were significantly positively associated with body height.

As shown in Table 2, no significant associations between hyperuricemia and carotid atherosclerosis were observed for participants of either 'shorter' or 'intermediate' height. For 'taller' participants, no significant associations were noted in either the age-adjusted or the multivariable adjusted except for serum creatinine model, but after further adjustment for serum creatinine, a significantly inverse association was observed.

When the analysis of the above associations was limited to non-drinking men, the age-adjusted model and the multivariable adjusted except for serum creatinine model showed a significantly positive association between hyperuricemia and carotid atherosclerosis for 'shorter' participants but no significant associations were observed for 'intermediate' and 'taller' participants. However, when further adjustment was made for serum creatinine, the significant association for 'shorter' men ceased to exist (Table 3).

Table 4 shows the associations between hyperuricemia and carotid atherosclerosis for drinking men. The age-adjusted model showed no significant association for any of the height tertiles. However, when further adjustment was made for serum creatinine, a significantly inverse association was observed for 'taller' participants, but no significant associations for either 'intermediate' or 'shorter' participants. These association remained even after further adjustments for other classical cardiovascular disease risk factors.

Table 1. Age-adjusted clinical characteristics of the study population by height tertiles

Parameters	Height tertiles			
	Shorter	Intermediate	Taller	p for trend
No. at risk	457	428	452	
Height, cm	155.9 ± 3.7	163.1 ± 1.6	170.2 ± 3.6	
Age, years	69.4 ± 9.4	65.3 ± 9.7	59.8 ± 10.6	
Systolic blood pressure, mmHg	143	142	143	0.665
Diastolic blood pressure, mmHg	84	85	86	0.195
Antihypertensive medication, %	28.0	24.4	27.7	0.614
Body mass index, kg/m^2	23.6	23.7	23.7	0.898
Serum HDL-cholesterol, mg/dL	54	55	54	0.714
Serum triglycerides, mg/dL	120	129	127	0.294
Serum uric acid, mg/dL	5.9	6.2	6.2	0.002
Diabetes, %	9.1	9.5	9.5	0.973
Current drinker, %	43.4	53.6	55.1	0.001
Current smoker, %	26.5	25.1	24.9	0.857
Serum aspartate aminotransferase (AST), IU/L	25	26	24	0.037
Serum creatinine, mg/dL	0.85	0.90	0.91	<0.001

Age: mean ± standard deviation. Height tertiles: <160.1cm, 160.1-165.8cm, >165.8cm.

Table 2. Odds ratios (ORs) and 95% CI for atherosclerosis by height tertiles

	Shorter Hyperuricemia			Intermediate Hyperuricemia			Taller Hyperuricemia		
	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p
Atherosclerosis (CIMT ≥ 1.1 mm)									
No. at risk	352	105		306	122		314	138	
No. of cases (percentages)	98 (27.8)	39 (37.1)		75 (24.5)	31 (25.4)		53 (16.9)	16 (11.6)	
Age-adjusted OR	1.00	1.61 (0.99-2.63)	0.055	1.00	1.07 (0.65-1.77)	0.796	1.00	0.64 (0.35-1.18)	0.150
Multivariable OR	1.00	1.48 (0.88-2.48)	0.141	1.00	1.00 (0.59-1.70)	0.997	1.00	0.58 (0.31-1.11)	0.102
Multivariable OR*	1.00	1.09 (0.62-1.92)	0.765	1.00	0.76 (0.43-1.33)	0.333	1.00	0.49 (0.25-0.95)	0.036

Multivariable OR: adjusted further for age and body mass index, smoking, alcohol intake, systolic blood pressure, antihypertensive medication, diabetes, antihyperlipidemic medication, serum triglycerides, serum HDL cholesterol, and serum aspartate aminotransferase (AST). Multivariable OR*: adjusted further for serum creatinine. Height tertiles:<160.1cm, 160.1-165.8cm, >165.8cm.

Table 3. Odds ratios (ORs) and 95% CI for atherosclerosis by height tertiles for non-drinking men.

	Shorter Hyperuricemia			Intermediate Hyperuricemia			Taller Hyperuricemia		
	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p
Atherosclerosis (CIMT ≥ 1.1 mm)									
No. at risk	213	52		152	47		141	55	
No. of cases (percentages)	59 (27.7)	22 (42.3)		42 (27.6)	16 (34.0)		22 (15.6)	8 (14.5)	
Age-adjusted OR	1.00	2.13 (1.09-4.16)	0.027	1.00	1.30 (0.63-2.70)	0.477	1.00	0.90 (0.37-2.18)	0.814
Multivariable OR	1.00	2.12 (1.04-4.33)	0.040	1.00	1.31 (0.58-2.94)	0.514	1.00	0.86 (0.32-2.36)	0.772
Multivariable OR*	1.00	1.32 (0.60-2.88)	0.489	1.00	0.98 (0.41-2.32)	0.960	1.00	0.75 (0.26-2.13)	0.585

Multivariable OR: adjusted further for age and body mass index, smoking, alcohol intake, systolic blood pressure, antihypertensive medication, diabetes, antihyperlipidemic medication, serum triglycerides, serum HDL cholesterol, and serum aspartate aminotransferase (AST). Multivariable OR*: adjusted further for serum creatinine. Height tertiles: <160.1cm, 160.1-165.8cm, >165.8cm.

Table 4. Odds ratios (ORs) and 95% CI for atherosclerosis by height tertiles for drinking men.

	Shorter Hyperuricemia			Intermediate Hyperuricemia			Taller Hyperuricemia		
	(-)	(+)	p	(-)	(+)	p	(-)	(+)	p
Atherosclerosis (CIMT ≥ 1.1 mm)									
No. at risk	139	53		154	75		173	83	
No. of cases(percentages)	39 (28.1)	17 (32.1)		33 (21.4)	15 (20.0)		31 (17.9)	8 (9.6)	
Age-adjusted OR	1.00	1.12 (0.54-2.33)	0.766	1.00	0.94 (0.47-1.91)	0.868	1.00	0.49 (0.21-1.16)	0.104
Age-and-serum creatinine adjsuted OR	1.00	1.09 (0.48-2.46)	0.438	1.00	0.74 (0.35-1.57)	0.438	1.00	0.39 (0.16-0.98)	0.046
Multivariable OR*	1.00	1.04 (0.44-2.49)	0.928	1.00	0.54 (0.24-1.29)	0.142	1.00	0.35 (0.13-0.92)	0.034

Multivariable OR*: adjusted further for age and body mass index, smoking, alcohol intake, systolic blood pressure, antihypertensive medication, diabetes, antihyperlipidemic medication, serum triglycerides, serum HDL cholesterol, and serum aspartate aminotransferase (AST), and serum creatinine. Height tertiles: <160.1cm, 160.1-165.8cm, >165.8cm.

Discussion

The main findings of the present study were that hyperuricemia is associated with carotid atherosclerosis for Japanese men, and that body height, drinking status and serum creatinine are important determining factors for those associations.

A previous sex-combined study with 181 participants who had undergone transesophageal echocardiography reported that uric acid is independently and positively associated with subclinical thoracic atherosclerosis [1]. On the other hand, the Atherosclerosis Risk in Communities Study (ARIC Study) reported that uric acid itself may not be a risk factor for atherosclerosis [2]. In fact, two other studies hypothesized that uric acid may provide an antioxidant defense in humans, so that it may protect against oxidative stress in atherosclerosis [18, 19]. Finally, we reported previously that hyperuricemia is positively associated with subclinical atherosclerosis defined as mean carotid intima-media thickness (CIMT≥1.1mm) but inversely associated with subclinical atherosclerosis defined as maximum carotid intima-media thickness (CIMT≥1.1mm). Mean CIMT was calculated as the mean of right and left CIMT measurements not including carotid plaques. Maximum CIMT was defined as the greatest CIMT measurement on either side [20]. This study thus indicates that hyperuricemia per se might have a beneficial effect on atherosclerosis prevention whereas a background of hyperuricemia might mean a risk of atherosclerosis.

In our study, hyperuricemia was positively associated with carotid atherosclerosis for non-drinking shorter men, but this association no longer existed after further adjusted for serum creatinine. And after the same adjustment, hyperuricemia proved to be inversely associated with carotid atherosclerosis for drinking taller men.

The Circulatory Risk in Community Study (CIRCS) found a significantly inverse association between height and risk for both ischemic and hemorrhagic stroke [4], while another study reported that chronic kidney disease (CKD) was a significant risk of ischemic stroke for non-drinking but not for drinking men [10]. Since serum creatinine is reportedly not only associated with renal function but also with hyperuricemia [21], and carotid atherosclerosis is a known risk factor for ischemic stroke [3], hyperuricemia might be associated with carotid atherosclerosis for shorter non-drinking men and indicate the presence of renal dysfunction. This mechanism could explain the fact that, in our study, a significant association between hyperuricemia and carotid atherosclerosis was observed for shorter non-drinking men, but that this association was no longer observed after further adjustment for serum creatinine.

On the other hand, in our current study we also found significant inverse association for taller drinking men between hyperuricemia and carotid atherosclerosis after adjustment for serum creatinine. At the same time, a previous study of ours demonstrated height is positively associated with hyperuricemia and that this association is independent from classical cardiovascular risk factors including serum creatinine [6]. The study presented here indicates that for taller, but not for shorter, participants the main cause of hyperuricemia might be independent from classical cardiovascular risk factors such as renal dysfunction. We therefore believe the mechanism underlying this association is that the taller participants are characterized by a higher activity of purine metabolism than the shorter subjects.

Birth weight and height correlate strongly with adult height [22], and low birth weight is known to be associated with altered renal shape, reduced renal volume, and fewer nephrons [23], so that shorter stature may increase the chance of kidney malfunction occurring later in life [24]. Serum creatinine was found to be associated not only with renal function but also with hyperuricemia [21]. In addition, because alcohol consumption may activate purine metabolism, hyperuricemia may be partly the result of alcohol consumption [8]. Light to moderate alcohol consumption, on the other hand, was reported to have a beneficial effect on atherosclerosis [9]. Hyperuricemia in alcohol consumers may thus partly reflect this beneficial effect on atherosclerosis. This explains why our current study found a significant inverse association between hyperuricemia and carotid atherosclerosis only after further adjustment for serum creatinine, which reduces the effect of renal dysfunction. Uric acid used to be considered a major antioxidant in human plasma with possible beneficial anti-atherosclerotic effects [25]. However, one study demonstrated that uric acid levels were independently positively associated with subclinical thoracic atherosclerosis [1]. These contradictory findings may be partly explained by the mechanisms identified in our study. The report by the ARIC Study that uric acid itself may not be a risk factor for carotid atherosclerosis [2] also appears to support the existence of such mechanisms.

Certain potential limitations of this study warrant consideration. Because we did not have access to creatinine clearance data, and estimated GFR is not an effective tool for evaluating kidney function for a comparison of associations with various body heights [6], we could not perform an analysis adjusted for exact and detailed renal function. However, our analysis showed serum creatinine is one of

the most determinant factors for the association between hyperuricemia and carotid atherosclerosis both shorter non-drinking and taller drinking men. Since the method recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative (JCKDI) [26] does not take the influence of height and weight into account, whereas Horio's method [27] does, estimated GFR is not an effective tool for evaluating kidney function in terms of its association with various body heights. However, we also found that serum creatinine was a significant determinant of CKD as a risk factor for hyperuricemia as ascertained by either JCKDI or Horio [6]. Although a similar analysis for never-drinkers was not feasible because data for this group were not available, we discovered a significantly positive association between hyperuricemia and carotid atherosclerosis for non-drinking men. While the association between hyperuricemia and risk of carotid atherosclerosis was shown to be significant for taller drinking men in our study, a previous study reported a difference in associations with atherosclerosis between light to moderate and heavy drinkers [9]. Further investigations with a larger number of participants would be necessary to enable us to stratify alcohol status in more detail. We could not access the data for diuretic medication use even though they may have affected the serum uric acid level. However, our study population consisted of general participants without a history of cardiovascular disease, so that they were less likely to use diuretic medication. Furthermore, significant associations were also observed even after further adjustment for systolic blood pressure and liver function (AST).Finally, because this study was cross-sectional, we could not determine any causal relationships.

In conclusion, we were able to establish that hyperuricemia (serum uric acid>7.0mg/dL) is associated with carotid atherosclerosis for Japanese men. Moreover, body height, drinking status and serum creatinine levels were found to be important determining factors for those associations.

References

1. Gür M, Sahin DY, Elbasan Z, et al. Uric acid and high sensitive C-reactive protein are associated with subclinical thoracic aortic atherosclerosis. *J Cardiol* 61:144-148, 2013
2. Iribarren C, Folsom AR, Eckfeldt JH, et al. Correlates of uric acid and its association with asymptomatic carotid atherosclerosis: the ARIC study. Atherosclerosis Risk in Communities. *Ann Epidemiol* 6:331-340, 1996
3. Kitamura A, Iso H, Imano H, et al. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke* 35:2788-2794, 2004
4. Shimizu Y, Imano H, Ohira T, et al. Adult height and body mass index in relation to risk of total stroke and its subtypes: the Circulatory Risk in Communities Study (CIRCS). *J Stroke Cerebrovasc* Dis 23:667-674,2014
5. Honjo K, Iso H, Inoue M, et al. Adult height and risk of cardiovascular disease among middle aged men and women in Japan. *Eur J Epidemiol* 26:13-21, 2011
6. Shimizu Y, Nakazato M, Sekita T, et al. Relationships of adult body height and BMI status to hyperuricemia in general Japanese male population: The Nagasaki Islands Study. *Acta Medica Nagasakiensia* 58:57-62, 2013
7. Nasto LA, Fusco A, Colangelo D, et al. Clinical predictors of vertebral osteoporotic fractures in post-menopausal women: a cross-sectional analysis. *Eur Rev Med Pharmacol Sci* 16:1227-1234, 2012
8. Faller J, Fox IH. Ethanol-induced hyperuricemia: evidence for increased urate production by activation of adenine nucleotide turnover. *N Engl J Med* 307:1598-1602, 1982
9. Xie X, Ma YT, Yang YN, et al. Alcohol consumption and carotid atherosclerosis in China: the Cardiovascular Risk Survey. *Eur J Prev Cardiol* 19:314-321, 2012
10. Shimizu Y, Maeda K, Imano H, et al. Chronic kidney disease and drinking status in relation to risks of stroke and its subtypes: the Circulatory Risk in Communities Study (CIRCS). *Stroke* 42:2531-2537, 2011
11. Shimizu Y, Nakazato M, Sekita T, et al. Free thyroxine (FT4) and anemia in relation to drinking status of Japanese men: the Nagasaki Islands Study. *Endocr J* 60:1029-1034, 2013
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 36:S67-S74, 2013
13. Yamamoto T. Definition and classification of hyperuricemia. *Nihon Rinsho* 66:636-640, 2008 (in Japanese)
14. Hara T, Takamura N, Akashi S, et al. Evaluation of clinical markers of atherosclerosis in young and elderly Japanese adults. *Clin Chem Lab Med* 44:824-829, 2006
15. Kawamori R, Yamasaki Y, Matsushima H, et al. Prevalence of carotid atherosclerosis in diabetic patients. Ultrasound high-resolution B-mode imaging on carotid arteries. *Diabetes Care* 15:1290-1294, 1992
16. Nakamura K, Sakurai M, Miura K, et al. Alcohol intake and the risk of hyperuricaemia: a 6-year prospective study in Japanese men. *Nutr Metab Cardiovasc Dis* 22:989-996, 2012
17. Suzuki K, Konta T, Kubo K, et al. The association between serum uric acid and renal damage in a community-based population: the Takahata study. *Clin Exp Nephrol* 17:541-548, 2013
18. Glantzounis GK, Tsimoyiannis EC, Kappas AM, et al. Uric acid andoxidative stress. *Curr Pharm Des* 11:4145-4151, 2005
19. Stocker R, Keaney JFJr. Role of oxidative modifications in atherosclerosis. *Physiol Rev* 84:1381-1478, 2004
20. Shimizu Y, Sato S, Koyamatsu J, et al. Subclinical carotid atherosclerosis and hyperuricemia in relation to renal impairment in a rural Japanese population: The Nagasaki Islands study. *Atherosclerosis* 233:525-529, 2014
21. Yang J, Liu Z, Zhang C, et al. The prevalence of hyperuricemia and its correlates in an inland Chinese adult population, urban and rural of Jinan. *Rheumatol Int* 33:1511-1517, 2013
22. Sørensen HT, Sabroe S, Rothman KJ, et al. Birth weight and length as predictors for adult height. *Am J Epidemiol* 149:726–729, 1999
23. Hughson M, Farris AB 3rd, Douglas-Denton R, et al. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int* 63:2113–2122, 2003.
24. Eriksson JG, Forsén TJ, Kajantie E, et al. Childhood growth and hypertension in later life. *Hypertension* 49:1415–1421, 2007
25. Puddu P, Puddu GM, Cravero E, et al. Relationships among hyperuricemia, endothelial dysfunction and cardiovascular disease: molecular mechanisms and clinical implications. *J Cardiol* 59:235-242, 2012
26. Imai E, Equation for estimating GFR from creatinine in Japan. *Nihon Rinsho.* 66:1725-1729, 2008 (in Japanese).
27. Horio M, Orita Y, Manabe S, et al. Formula and nomogram for predicting creatinine clearance from serum creatinine concentration. *Clin Exper Nephrol* 11:110-114, 1997