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Abstract

Inflammation and pulse wave velocity (PWV) are a promising risk factor and marker, respectively, for atherosclerosis in the primary prevention setting. Atherosclerosis is now generally accepted to be an inflammatory disorder of the arterial wall, and the high-sensitivity C-reactive protein (hs-CRP) level has been reported to be a strong predictor of cardiovascular events. Hs-CRP is associated with two factors related to inflammation: local production of CRP by atheromatous tissue or coronary artery smooth muscle cells, and adipose tissue as a potent source of inflammatory cytokines. Hs-CRP has been established as a cardiovascular risk factor in North America and Europe and a cut-off value has been recommended. However, Japanese have lower hs-CRP values compared with Westerners, partly because Japanese have a lower body mass index (BMI), which correlates positively to hs-CRP. Furthermore, lifestyle and genetic factors can affect hs-CRP values. Therefore, a cut-off value needs to be established by cohort studies for the Japanese population. Carotid-femoral PWV measured by applanation tonometry has been most commonly used, mainly in Europe. However, this method is critically dependent upon the accurate placing of transducers over the arteries, and the method is both time-consuming and complex. Recently, a novel device was developed in Japan which measures brachial-ankle PWV (baPWV) using a volume-rendering method. baPWV is a suitable screening method because of its technical simplicity and shorter measurement time. baPWV is associated not only with

conventional cardiovascular risk factors but also with new risk factors, such as inflammation, γ-glutamyltransferase, chronic kidney disease, and psychosocial factors. Furthermore, a suitable cut-off value has yet to be established.

Introduction

Cardiovascular diseases are a leading cause of death in developed countries. Their prevention is therefore important and measures need to be taken from an early stage of atherosclerosis.

Atherosclerosis is now generally accepted to be an inflammatory disorder of the arterial wall [1], and the high-sensitivity C-reactive protein (hs-CRP) level is a strong predictor of cardiovascular events [2-4]. The research on hs-CRP as a cardiovascular risk factor has been mainly performed in North America and Europe. It has been reported that the hs-CRP level of Japanese is an order of magnitude smaller compared with that of Westerners [5,6], though conventional cardiovascular risk factors such as blood pressure, blood glucose, and low-density lipoprotein cholesterol, are similarly distributed. Thus, there is a need to investigate the significance and role of inflammation and especially hs-CRP, as a risk factor, in the development of atherosclerosis in the Japanese population.

Pulse wave velocity (PWV) is an indicator of arterial stiffness [7], and a higher PWV value has been associated with the development of atherosclerotic disease [8,9]. Carotid-femoral PWV

(cfPWV) has been most commonly measured by applanation tonometry, mainly in Europe. However, this method is critically dependent upon the accurate placing of the transducers over the arteries, and the technique is both time-consuming and complex [10]. Recently, a novel device was developed in Japan which measures brachial-ankle PWV (baPWV) by a volume-rendering method. This instrument determines baPWV by simultaneous oscillometric measurement of pulse waves in all four extremities. This new method is more appropriate for screening a large population than previous methods because of its technical simplicity and shorter measurement time [11]. Thus, the significance and role of baPWV as an early marker of atherosclerosis should also be investigated in the Japanese population.

Inflammation and hs-CRP

Though several inflammatory markers are known, such as P-selectin, interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), soluble intercellular adhesion molecule-1, and fibrinogen, hs-CRP has emerged as the most powerful inflammatory predictor of future cardiovascular risk [12,13]. Moreover, because the hs-CRP test is relatively cheap and easy to perform in serum, it can be used in primary prevention.

There are two possible mechanisms of hs-CRP elevation that may be relevant to the prevention of atherosclerotic diseases: local production of CRP by atheromatous tissue or coronary artery smooth muscle cells [14], and adipose tissue as a potent source of inflammatory cytokines, including TNF and IL-6, which induce hepatic production of CRP [15].

Early studies in Europe and the US reported that the hs-CRP level is associated with body mass index (BMI) and waist circumference [16,17]. However, Japanese have lower BMI compared with Westerners, and also, as previously mentioned, have lower hs-CRP levels. We therefore explored the relationships between fatness and visceral obesity parameters (by anthropometry, bioelectrical impedance analysis, and abdominal computed tomography) and hs-CRP in the Japanese population [5]. We found that the association with hs-CRP was stronger for parameters of visceral obesity (waist circumference, waist-to-hip ratio, and visceral adipose tissue accumulation) than for other parameters of obesity after adjustment for age, gender, and smoking.

Several lifestyle factors are related to variation in the level of hs-CRP. Smoking increases

the IL-6 level [18] and is associated with hs-CRP elevation [2,19]. Moreover, the hs-CRP level may be lowered by moderate drinking [20] and by physical activity, independently of weight loss [21].

Genetic factors may also affect the hs-CRP level. The IL-6 −174G/C polymorphism, which may have functional effects, may affect the hs-CRP level [22,23], but the data are controversial [24]. The C allele of the IL-6 −174G/C polymorphism is common among Caucasians but extremely rare among East Asians. However, the G allele of the IL-6 −634C/G polymorphism, which may also have functional effects, is common among East Asians [25,26]. We reported that the hs-CRP level differed significantly among IL-6 −634C/G genotype groups in nonsmokers (*P* for trend = 0.007), whereas no significant difference was found in current smokers, and comparison between −634CC and C/G + G/G groups revealed a significant interaction between smoking and the IL-6 −634C/G genotype (*P* = 0.007) [19]. These findings suggest that the impact of the −634G allele on hs-CRP elevation is greater in nonsmokers than in current smokers. Moreover, other inflammation-related polymorphisms, such as TNF-alpha and CRP itself, have

been reported as modifying the hs-CRP level [27,28].

In North America and Europe, concentrations of hs-CRP of <1 mg/L, 1–3 mg/L, and >3 mg/L are considered as conferring low, intermediate, and high risk, respectively [29]. However, the distribution of hs-CRP levels among Japanese is probably an order of magnitude smaller than in Westerners (Table 1). In particular, Saito et al. reported the hs-CRP concentrations of the general Japanese population [30] subject to external quality control for hs-CRP measurement using a latex particle-enhanced immunoassay (N Latex CRPII; Dade Behring, Tokyo, Japan) [31]. The hs-CRP concentrations in our previous studies were measured using the same method (latex particle-enhanced immunoassay; N Latex CRPII) at a commercial laboratory (intra-assay coefficient of variation, 2.0%) [5,32]. Therefore, a specific cut-off point for hs-CRP in Japanese is needed, although other cut-off values for traditional risk factors, such as blood pressure, blood glucose, and lipids, are almost the same as in Westerners. On the basis of studies of the relationship between hs-CRP and the metabolic syndrome, including our previous study [33], Oda et al. have indicated that the optimal cut-off point for hs-CRP might be 0.65 mg/dL in Japan [34].

However, the cut-off point for hs-CRP should be determined by prospective studies of cardiovascular events. Therefore, further prospective studies are needed to clarify which cut-off point should be used in the Japanese population.

Atherosclerosis is now generally accepted to be an inflammatory disorder of the arterial wall, and many have suspected that an infectious agent, such as *Cytomegalovirus* or *Chlamydia pneumoniae*, is responsible for chronic inflammation in atheroma [35]. Although a recent meta-analysis found no significant association between *Helicobacter pylori* seropositivity and coronary heart disease [36], several Japanese studies revealed a positive association [37-39]. Furthermore, we have found a significant association between *H. pylori* seropositivity and baPWV elevation, and a combination of hs-CRP elevation and *H. pylori* seropositivity shows a stronger association with baPWV elevation [40]. Because Japanese have a higher prevalence of *H. pylori* seropositivity compared with other developed countries [41], there is a particular need for the influence of chronic *H. pylori* infection on atherosclerosis to be elucidated in the Japanese population.

baPWV as an early atherosclerosis marker

We had previously reviewed and briefly reported the relationships between baPWV and conventional cardiovascular risk factors [42]. We have since surveyed large population-based studies to investigate the relationship of baPWV with various risk factors.

Inflammation also has a possible role in baPWV elevation. Table 2 shows the adjusted baPWV values of 3412 men and 854 women according to quartiles of hs-CRP. We observed a significant, progressive increase in baPWV across the quartiles of hs-CRP in male subjects after controlling for age, BMI, systolic blood pressure, heart rate, total cholesterol, log triglycerides, high-density lipoprotein cholesterol, fasting glucose, uric acid, white blood cells, estimated glomerular filtration rate (GFR), smoking, alcohol, exercise, past history of hypertension, hyperlipidemia, and diabetes. In female subjects, the relationship of quartile hs-CRP with baPWV had marginal significance after adjustment for the variables mentioned above and postmenopausal status [32]. β_2-Microglobulin (β2m) is related to inflammatory diseases, but there have been few

reports of a relationship between β2m and atherosclerosis. When adjusted mean baPWV values were compared with the quartiles of β2m, significant differences in baPWV were observed across the quartiles ($P = 0.037$). β2m is a marker of GFR, which is a strong confounder in analyses of the association between β2m and arterial stiffness, and our analyses were adjusted for estimated GFR. We speculate, therefore, that the inflammatory factor β2m is related to arterial stiffness [43].

Serum γ-glutamyltransferase (GGT) is a potential marker of cardiovascular disease [44]. In multiple regression analysis of male subjects, the serum GGT level was significantly associated with baPWV after adjustment for conventional cardiovascular risk factors, alcohol consumption, alanine aminotransferase, and hs-CRP. GGT is involved in the antioxidant system, and this may cause its association with atherosclerosis independently of alcohol and liver function [45].

Psychosocial factors also affect cardiovascular diseases [46]. We have examined the relationships of two theoretical stress models, the demand-control model (DCM) and the effort-reward imbalance (ERI) model, with baPWV. In women, high job strain from the joint effects of low job control and high job demands (DCM) conferred a higher risk of baPWV

elevation. However, high job strain in men and a high level of ERI in both genders were not related to a high value of baPWV [47]. Because several studies have reported that high occupational stress evaluated by the ERI model was related to an imbalance between the coagulation and fibrinolysis systems [48-50], occupational stress, especially a high-stress ERI model, may have a greater effect on cardiovascular events. Women may be more sensitive to the high stress of DCM compared with the ERI model [51]. This may explain the significant result in women but not in men. We have also examined the relationships of educational level and employment grade with baPWV. In men, educational level was significantly associated with the baPWV value after adjusting for cardiovascular risk factors (*P* for trend <0.0001). With regard to employment grade, only low-level non-manual workers had a significantly lower baPWV value compared with manual workers in a fully adjusted model. In women, however, neither educational level nor employment grade was associated with the baPWV value [52]. It has been speculated that analyses of the socioeconomic gradient in women's health in Japan may be better performed using household-based measures of socioeconomic status, because wage differences

between men and women are large and there is a strong dependence on family responsibility in welfare provision, geared around the high-earning male breadwinner [53].

Chronic kidney disease is associated with an increased risk of cardiovascular disease. Recently, the Japanese Society of Nephrology [54] proposed the use of estimated GFR (eGFR), using the Modification of Diet in Renal Disease equation for Japanese patients. Multiple regression analysis of data on 647 outpatients revealed that baPWV correlated negatively with eGFR, independently of traditional risk factors ($P < 0.0001$) [55]. Thus, chronic kidney disease involves not only cardiovascular events but also early atherosclerosis.

A broadly acceptable cut-off value for baPWV has not been established. In 2007, the Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology recommended the use of PWV measurement to stratify total cardiovascular risk, and the cut-off value of cfPWV has been given as <1.2 m/s [56]. There is an opinion that a cut-off value 1800 cm/s for baPWV should be recommended because baPWV is roughly 1.5 times the magnitude of cfPWV [57]. It has also been reported that receiver

operating characteristic curve analysis suggests that 1800 cm/s is the best cut-off value of baPWV for the identification of increased intima-media thickness in hypertensive patients [58]. However, these cut-off values are for the clinical setting, so a cut-off value for primary prevention is required. Thus, the cut-off value needs to be established according to its association with cardiovascular events in previous population-based cohort studies.

Conclusion

Inflammation and PWV are a promising risk factor and marker, respectively, for atherosclerosis in the secondary prevention setting. In particular, an hs-CRP-based global risk classification system has been established in North America and European countries and a cut-off value has been recommended. However, Japanese have lower hs-CRP values compared with Westerners because Japanese have lower BMI, which correlates to hs-CRP. Furthermore, lifestyle and genetic factors can affect hs-CRP values. There is therefore a need to establish a cut-off value for hs-CRP in population cohort studies in Japanese.

baPWV was developed in Japan as a suitable measure for use in the secondary prevention setting because of its technical simplicity and shorter measurement time. baPWV is associated not only with conventional cardiovascular risk factors but also with newer risk factors, such as inflammation, GGT, chronic kidney disease, and psychosocial factors. However, a suitable cut-off value for baPWV has yet to be established.

Acknowledgments

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Table 1. Comparison of hs-CRP levels and obesity parameters

Study	Country	Sex	Age (y)*	N	BMI (kg/m^2)**	hs-CRP (mg/dL)†
Yudkin 1999 [59]	UK	Both	59.0 ± 10.9	107	25.9 ± 4.5	0.135 (0.057–0.218)
Hak 1999 [16]	Netherlands	Female	50.9 ± 2.3	186	24.9 ± 4.0	0.068 (0.033–0.144)
Lemieux 2001 [17]	Canada	Male	43.3 ± 7.9	159	30.3 ± 3.9	0.221 ± 0.196
Yamada 2001 [6]	Japan	Both	55.8 ± 11.5	5903	22.9 ± 3.6	0.012 (0.003–0.030)
Forouhi 2001 [60]	UK	Male	40–55	28	26.1 ± 0.7	0.092 (0.034–0.161)
		Female	40–55	29	24.9 ± 0.7	0.070 (0.041–0.170)
Chambers 2001 [61]	UK	Male	49.4 ± 6.5	507	26.7 ± 4.0	0.147 ± 0.162
Saijo 2004 [5]	Japan	Male	40.4 ± 10.7	52	22.9 ± 4.3	0.052 (0.023–0.090)
		Female	32.3 ± 10.3	67	20.1 ± 2.3	0.010 (0.005–0.024)
Saijo 2005 [32]	Japan	Male	48.4 ± 6.8	3412	23.8 ± 2.9	0.045 (0.023–0.089)
		Female	46.8 ± 7.2	854	21.8 ± 3.4	0.025 (0.023–0.052)
Saito 2007 [30]	Japan	Male	64.9 ± 10.2	5213	23.5 ± 3.0	0.060 (0.030–0.131)
		Female	62.9 ± 10.6	7071	23.1 ± 3.3	0.045 (0.022–0.094)

*Mean ± SD or range

**Mean ± SD

†Mean ± SD or median (interquartile range)

Table 2. Adjusted baPWV values by gender according to quartiles of hs-CRP

			(hs-CRP range (mg/dL))	Mean PWV[a]	95% CI		
Men	Quartile	1	(<0.004–0.023)	1358	1349	to	1367
		2	(0.024–0.045)	1362	1353	to	1371
		3	(0.046–0.089)	1374	1366	to	1383
		4	(0.090–9.400)	1381	1372	to	1390
	P value (P for trend)			P < 0.01 (<0.001)			
Women	Quartile	1	(<0.004–0.012)	1241	1225	to	1256
		2	(0.013–0.025)	1248	1233	to	1263
		3	(0.026–0.052)	1247	1232	to	1262
		4	(0.053–3.34)	1266	1250	to	1282
	P value (P for trend)			P = 0.12 (0.055)			

[a]Adjusted for age, BMI, systolic blood pressure, heart rate, total cholesterol, HDL-cholesterol, fasting blood glucose, log triglycerides, uric acid, estimated GFR, smoking status, alcohol consumption, frequency of exercise, hypertension, hyperlipidemia, and diabetes

(From reference 32)