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Longitudinal changes of the serum calcium levels and accelerated progression of arterial stiffness with age

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ABSTRACT

Background and aims: The progression of arterial stiffness is accelerated by aging, although the underlying mechanisms have not yet been clarified. This prospective observational study was conducted to clarify whether longitudinal changes in the serum calcium/phosphate levels are associated with the accelerated progression of arterial stiffness with age.
Methods: In a cohort of employees at a construction company (1507 middle-aged Japanese men), the serum calcium/phosphate levels and brachial-ankle pulse wave velocity (baPWV) were measured at the start and at the end of a 3-year study period.
Results: A general linear model multivariate analysis revealed a significant interaction of the 2 factors {age and longitudinal changes of the serum calcium levels (delCa) during the follow-up period} on the longitudinal changes of the baPWV during the study period (delPWV). The delCa was significantly correlated with the delPWV even after adjustments for covariates in subjects aged ≥48 years. The delPWV in subjects aged ≥48 years with the delCa in the upper tertile (69 ± 137 cm/s) was significantly larger than that in the other groups even after adjustments for covariates (e.g., del PWV in subjects aged <48 years with the delCa in the lower tertile = 1 ± 94 cm/s) ($p < 0.01$).
Conclusions: The association between the arterial stiffness and serum calcium levels differed with age. Pathophysiological abnormalities related to increased serum calcium levels appeared to be associated with accelerated progression of arterial stiffness with age.

1. Introduction

It is thought that abnormal bone metabolism may have a significant link with atherosclerotic vascular damage [1–6]. Atherosclerotic vascular damage is generally classified into two phenotypes: atherosclerosis and arteriosclerosis. Arteriosclerosis is associated with increase of the arterial stiffness [7,8]. Several prospective studies have identified not only the pulse wave velocity (PWV), a marker of arterial stiffness, but also the serum calcium (Ca)/phosphate (P) levels, markers of bone metabolism, as predictors of future cardiovascular events [9–14]. It is believed that with age, pathophysiological abnormalities related to bone metabolism, such as osteoporosis or ectopic calcification, and also pathophysiological abnormalities related to atherosclerotic vascular damage, become more and more significant [1–3,15–18]. A recent cross-sectional study reported the existence of a significant relationship between the PWV and the serum Ca levels [4]. Based on the above background, we sought to determine whether abnormal Ca/P metabolism is associated with accelerated progression of arterial stiffness with advancing age.

Measurement of the brachial-ankle pulse wave velocity (baPWV) is sufficiently simple as to allow repeated measurements in large numbers of study subjects [19–21]. The baPWV reflects the stiffness of large-to middle-sized arteries, but also shows a close correlation with the carotid-femoral PWV, a marker of aortic stiffness [22]. In the present prospective study, we measured the baPWV and serum Ca/P levels at the start and at the end of the 3-

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year study period, and examined whether longitudinal changes in the serum Ca/P levels were associated with accelerated progression of arterial stiffness with age.

2. Materials and methods

2.1. Subjects

This prospective study was conducted in a cohort of Japanese employees at the company headquarters of a single large construction company [19–21]. The subjects were instructed to fast overnight prior to the health evaluations carried out the following morning. The annual health checkups were as mandated by the Occupational Health and Safety Law in Japan. Before the employees visited the health care center of this company for the annual health checkups, additional measurements {i.e., baPWV and radial augmentation index (rAI) measurements and measurement of the serum Ca and P levels} were carried out in all the employees in the years 2010 and 2013 (Start date: June to August 2010; End date: June to August 2013) (Fig. 1). These additional measurements were conducted under the condition that the provision/non-provision of consent for participation in the study protocol was voluntary and free of any obligation, and that the privacy of each participant would be kept confidential. Informed consent was obtained from all of the study participants prior to their participation in this study. The study was conducted with the approval of the Ethics Guidelines Committee of Tokyo Medical University.

All the participants were provided feedback on the results of the annual health evaluations. In accordance with the guidelines of the Japanese Societies of Atherosclerosis, Diabetes Mellitus, and Hypertension [23–25], subjects with positive atherosclerotic risk factors were advised to visit the healthcare center of the construction company, where they were recommended medication(s) and/or given advice by health professionals concerning therapeutic lifestyle modifications.

Subjects who met the following criteria either at initial (2010) or at the 3 years later examination (2013) were excluded from the study: 1) unreliable brachial-ankle PWV values {e.g., atrial fibrillation or ankle-brachial systolic blood pressure index <0.95 (the accuracy of the ankle pressure waveform is diminished)} [26]; 2) receiving medication for heart disease or stroke; 4) more than moderate renal dysfunction as assessed by glomerular filtration rate estimated by serum creatinine levels (eGFR) values of <60 mL/min/1.73 m^2; 5) standard deviation (SD) of the radial AI ≥6%, calculated on the basis of 10 radial pressure waveform records [27].

In this cohort, the number of female subjects was small (about 400 women), and gender differences of the baPWV have been reported [28] (In the present study, the baPWV values were significantly different between the men (mean = 1296 cm/s) and women (mean = 1231 cm/s), even after adjustments for age and some risk factors for cardiovascular disease). Then, the present study was analyzed in the male subjects. A total of 2105 male subjects working at the headquarters of the company were enrolled in 2010. Among these, 1717 male subjects were successfully followed up until 2011, whereas the remaining 388 subjects were lost to follow-up because of their failure to visit for the completion of tests, or for other reasons such as moving from the company headquarters to branch offices, changing jobs or retirement. Among the remaining 1717 subjects, 132 were excluded because of the presence of one of the following: atrial fibrillation (n = 5), ankle-brachial systolic blood pressure index values < 0.95 (n = 21), an SD of the radial rAI of ≥6% (n = 71), or cardiovascular disease (n = 35). In addition, 78 subjects with eGFRcr values of <60 mL/min/1.73 m^2 body surface area at the baseline examination were also excluded. The data of the remaining 1507 subjects were included in the analysis.

2.2. Measurements

The baPWV and rAI were measured on the same day as the annual health checkup. Therefore, the subjects were instructed to fast overnight, and to abstain from alcohol, smoking, and intake of caffeine and antioxidant vitamins for at least 12 h prior to the measurements.

2.3. Brachial-ankle pulse wave velocity

The baPWV was measured using a volume-plethysmographic apparatus (Form/ABI; Colin Co. Ltd., Komaki, Japan), as previously described [19–21]. In brief, occlusion cuffs, connected to both plethysmographic and oscillometric sensors, were attached to both the upper arms and ankles of the subjects lying in the supine position. The brachial and post-tibial arterial pressures were measured using the oscillometric sensors. The measurements were conducted after the subjects had rested for at least 5 min in the supine position, in a temperature-controlled room (24–26 °C) designated exclusively for this purpose. The distance between the sampling points of the baPWV was calculated automatically according to the height of the subject. The path length from the

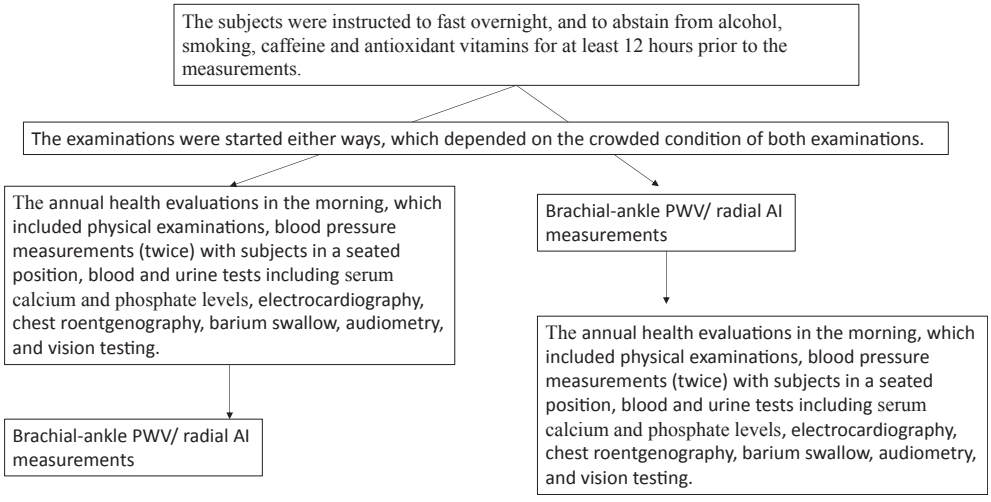

Fig. 1. A flow-chart of the measurements.