Short Communication

Interventional Cardiology

Association between arterial stiffness and bone mineral density

Abstract

Cardiovascular Disease (CVD) and osteoporosis are major public health problems that share common pathophysiological mechanisms besides aging. Although a global increase in life expectancy is a huge achievement driven by improvements in public health care, many societies across the world are not prepared for an aging society. Especially in elderly people, so-called multimorbidity, prevalence of which ranges from 55%-98% worldwide, is a problematic issue that needs to be solved. For this reason, acting on aging biology itself rather than modifying a single disease-specific process is highly recommended. In a recent study, we examined the relationship between Bone Mineral Density (BMD) and multiple cardiovascular measurements in Japanese general population without overt CVD and has demonstrated the partial relationship of osteoporotic state and enhanced arterial stiffness, as evaluated by Cardio-Ankle Vascular Index (CAVI).

Keywords: Arterial stiffness • Aging biology • Health care • Osteoporosis • Apoprotein

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Received date: 18-Nov-2024, Manuscript No. FMIC-24-152753;
Editor assigned: 20-Nov-2024, PreQC No. FMIC-24-152753 (PQ);
Reviewed date: 04-Dec-2024, QC No. FMIC-24-152753;
Revised date: 11-Dec-2024, Manuscript No. FMIC-24-152753 (R);
Published date: 18-Dec-2024, DOI: 10.37532/1755-5310.2024.16(S25).644

Description

CVD and osteoporosis are frequently seen as comorbidities, therefore preventive strategy and early detection are important [1,2]. In clinical settings, there have been large-scale clinical trials showing links between osteoporosis and CVD. In terms of heart failure, the European Prospective Investigation into Cancer (EPIC)-Norfolk Prospective study from the United Kingdom and the Cardiovascular Health study conducted in the United States have shown that the history of osteoporosis and low BMD was an independent predictor for future occurrence of heart failure [3,4]. And the EPIC-Norfolk Prospective study, the same study from UK, has shown the correlation between osteoporosis and future stroke risk [5]. Similarly, several studies investigated the correlations between osteoporosis and artery diseases, namely atherosclerosis. In animal models, both osteoprotegerin-deficient mice and apoprotein E-deficient mice have a greater ability to develop early vascular calcification, osteoporosis and increased risk of CVD [6]. In humans, two studies have shown the links between BMD and atherosclerosis measured by carotid Intima-Media Thickness (IMT) [7,8]. However, the correlation between BMD and arteriosclerosis such as arterial stiffness, usually measured by Pulse Wave Velocity (PWV) or CAVI, is under controversial debate. In the recent study by Mizuno et al., the relationship between BMD and multiple cardiovascular parameters was explored to investigate a possible association between the osteoporotic state and arterial stiffness in the Japanese general population [2].

The study population was 1,242 consecutive participants who underwent cardiovascular health check-ups at the University of Tokyo Hospital. After excluding participants with coronary artery disease, peripheral arterial disease, atrial fibrillation/atrial flutter, decreased left ventricular systolic function and pacemaker implantation,

1,169 men and women were analyzed. The calcaneus BMD was measured by quantitative ultrasound. Cardiovascular functions were evaluated with CAVI, Left Ventricular Global Longitudinal Strain (LVGLS), peak early diastolic transmitral velocity (E) / peak early diastolic mitral annular velocity (e') (E/e') and carotid IMT measurements. In univariate analysis, BMD was associated with CAVI, E/e' and IMT along with other cardiovascular risk factors, whereas no association was identified between BMD and LVGLS. In multivariate analysis, after adjustment for pertinent confounding variables, only CAVI remained associated with low BMD (Estimated coefficient=0.0050, p=0.004), although the direction of association was opposite and smaller in size compared to univariate analysis (Table 1). This can be explained that the observed association between BMD and CAVI in univariate analysis was due to confounding through the association between age and BMD or CAVI, but still does not completely deny the clinical significance of the correlation between CAVI and BMD. The correlation between osteoporotic state and cardiovascular parameters was also evaluated. Figure 1, shows the correlations between the cardiovascular parameters and BMD in a categorized manner, namely normal, osteopenia and osteoporosis. Variables other than LVGLS had significant correlations with osteoporotic state (CAVI, p<0.001; mean E/e', p<0.001; max IMT, p<0.001).

There is growing evidence that the coincidental occurrence of both diseases may be related to common pathophysiological mechanisms regardless of age [9]. Indeed, bone formation and vascular calcification share underlying biological mechanisms, mainly through inflammation and the RANK (Receptor Activator Of Nuclear Factor-KappaB (NFκB))/RANKL (RANK ligand)/OPG (Osteoprotegerin) system [10]. In this process, the RANK/RANKL/OPG system that belongs to TNF family is postulated to be important inducers of Vascular Smooth Muscle Cell (VSMC) calcification. The binding of RANKL to the RANK receptor promotes differentiation of preosteoclasts into mature osteoclasts through the activation of the NFκB intracellular signaling pathway, a process that is also important in bone resorption in osteoporosis. It should be also noted that angiotensin II, which is a well-known promoter of atherosclerosis and arterial stiffness, has been reported to activate osteoclasts leading to osteoporosis through the RANK/RANKL pathway [11,12]. These pathophysiological mechanisms could be a plausible explanation for the accumulating clinical trials that showed the association between low BMD and cardiovascular diseases.

In 2001, Framingham's study showed that patients with low BMD had more severe abdominal aortic calcification after adjusting for age and cardiovascular risk factors [13]. It has been observed that the association between osteoporosis and vascular calcification is also detected in coronary and peripheral arteries [14]. These findings support the results of the recent study by Mizuno et al., showing that low BMD is associated with increased risk of arterial stiffness, with the concept that calcification of the aorta and peripheral arteries foster arterial stiffness and central blood pressure augmentation, which can enhance CAVI and ultimately develop cardiac dysfunction, that could have been evaluated by LVGLS or E/e' if the participants of the recent study were in the advanced stage of CVDs [2].

Table 1: Correlation between bone mineral density and cardiovascular parameters in multivariate analysis.

Parameters model	B	Lower 95% CI	Upper 95% CI	p value
Model 1	0.0037	0.0002	0.0072	0.041*
Model 2	0.0046	0.0012	0.0080	0.009*
CAVI Model 3	0.0046	0.0012	0.0080	0.009*
Model 4	0.0050	0.0016	0.0084	0.004*
Model 1	-0.0049	-0.0159	0.0061	0.382
LVGLS Model 2	-0.0067	-0.0175	0.0041	0.225
Model 3	-0.0073	-0.0180	0.0035	0.185
Model 4	-0.0067	-0.0175	0.0041	0.221
Model 1	-0.0033	-0.0136	0.0070	0.529
mean E/e' Model 2	-0.0045	-0.0146	0.0056	0.379
Model 3	-0.0035	-0.0135	0.0065	0.493
Model 4	-0.0036	-0.0136	0.0065	0.487
Model 1	0.0004	-0.0008	0.0015	0.499
max IMT Model 2	0.0003	-0.0008	0.0015	0.593
Model 3	0.0004	-0.0007	0.0016	0.463
Model 4	0.0004	-0.0007	0.0015	0.502

Note: * Increased value; Model 1: Adjusted for age and sex; Model 2: Adjusted for Model 1 plus BMI, diabetes, hyperlipidemia, hypertension, current smoking and alcohol intake; Model 3: Adjusted for Model 2 plus albumin, eGFR, HDL-cholesterol, uric acid, serum iron, BNP; Model 4: Adjusted for Model 3 plus lipoprotein (a) and TyG index.

Abbreviations: B indicates regression coefficient; 95% CI: 95% Confidence Interval; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; HDL-Cholesterol: High-Density Lipoprotein-Cholesterol; TyG: Triglyceride-Glucose; BNP: Brain Natriuretic Peptide; CAVI:Cardio-Ankle Vascular Index; LVGLS: Left Ventricular Global Longitudinal Strain; e': Early Diastolic Mitral Annular Velocity; E: Early Diastolic Transmitral Flow Velocity; max IMT: Maximal Intima-Media Thickness.

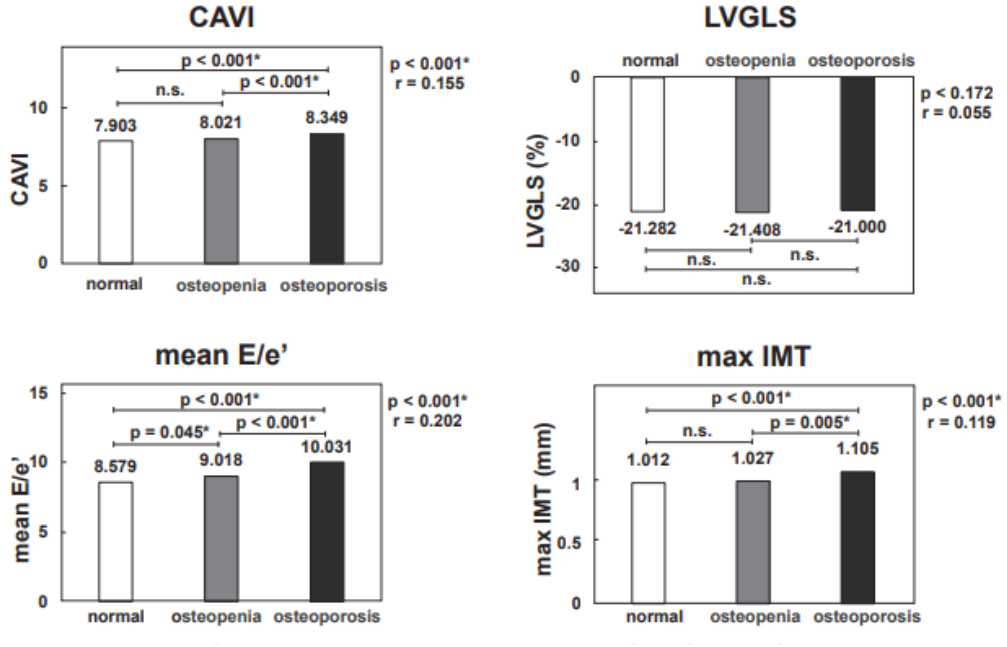

Figure 1: Correlation between bone mineral density and cardiovascular parameters.

Conclusion

Although the study is in accordance with the controversial debate and could not reach a solid conclusion showing a correlation between BMD and CAVI, the results give us an indication that increased arterial stiffness is likely to be comorbid with osteoporosis in the Japanese general population. During treatment, clinicians should pay attention to arterial stiffness in patients with low BMD and *vice versa*.

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