Getting Osteoporotic Fracture Risk Into Vascular Structure and Function

— Do You Know Your FRAX® Score? —

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With increasing lifespans, we have to consider the multiple factors required in caring or treating the elderly population. In fact, they can have multiple comorbidities (e.g., diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, or anemia), and the number of comorbidities have been shown to affect the prognosis of heart failure.¹ Epidemiologic and experimental studies have shown the potential cross-talk between osteoporosis and cardiovascular diseases.² Old story...calcium ions dissolving from bone deposits inside the vascular walls. Nowadays, we know that many factors such as age, chronic kidney disease, smoking, vitamin D deficiency, low body weight, or reduction of physical activity weaken the bone structure as well as progress in cardiovascular diseases.³ In addition, we know that loop diuretics decrease bone mineral density (BMD), whereas thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, β -blockers or statins increase it.^{4,5} Moreover, osteoporosis and cardiovascular diseases may share common molecular mechanisms by stimulating systemic inflammation.⁶ The renin-angiotensin II-aldosterone system stimulates the urinary excretion of calcium and magnesium, and the resultant activation of parathyroid hormone leads to bone loss and fracture.⁷

The Fracture Risk Assessment tool (FRAX®) was developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield, United Kingdom, and is modified according to geographic variations (<https://www.shef.ac.uk/FRAX/>).^{8,9} FRAX® estimates the risk of major or a hip osteoporotic fracture within the next 10 years. It is easy to calculate the degree of fracture risk by incorporating 12 factors listed on the freely available website (**Table**). In this issue of the Journal, Kajikawa and colleagues¹⁰ examine the association between FRAX® score and vascular function and structure. They enrolled 414 subjects aged 40–89 years and with multiple comorbidities (e.g., 73% hypertension; 70% dyslipidemia; 31% diabetes mellitus) and a history of cardiovascular disease (21% coronary artery disease; 11% stroke). In addition, 38% of the subjects had experienced a fracture. In the analyses, the authors found that flow-

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mediated or nitroglycerin-induced vasodilation negatively correlated with the FRAX® score in both sexes, whereas the brachial intima-media thickness positively correlated with the FRAX® score, regardless of menopause in women. When the subjects are divided into 2 groups based on the median FRAX® score, the high scoring group exhibited decreases in diastolic blood pressure, and flow-mediated, or nitroglycerin-induced vasodilation. More importantly, the FRAX® score remained an independent determinant of brachial artery intima-media thickness, and flow-mediated, or nitroglycerin-induced vasodilation in 4 models of multivariate analyses. The authors suggest that osteoporosis may be a non-negligible factor associated with atherosclerotic events.

Table. Risk Factors Adopted in FRAX® Model

No.	Risk factor
1	Age
2	Sex
3	Weight
4	Height
5	Personal history of fracture
6	Parental history of hip fracture
7	Current smoking
8	Glucocorticoid use equivalent to 5 mg/day prednisolone for 3 months or longer
9	Rheumatoid arthritis
10	Secondary osteoporosis associated with type 1 diabetes mellitus, adult osteogenesis imperfecta, untreated long-standing hyperthyroidism, hypergonadism, premature menopause, chronic malnutrition or malabsorption, and chronic liver disease
11	Alcohol intake 3 or more units/day
12	Femoral neck bone mineral density

FRAX, Fracture Risk Assessment tool.

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Their findings are reasonable for explaining the association between the 2 different disorders (osteoporosis vs. atherosclerosis) because most of the risk factors adopted in the FRAX® model are also well-known risk factors for subclinical atherosclerosis in asymptomatic individuals.¹¹ The FRAX® model was created from a series of meta-analyses of prospective cohort studies of approximately 45,000 individuals. It is important to note that FRAX® applies the algorithm from “population survey” into “individual future risk”. Clinical risk factors are selected on the basis of intuitive linkage to fracture risk, independent of BMD.⁹ Diabetes mellitus is known to increase the risk of bone fracture as well as atherosclerosis, but it is not adopted in the FRAX® model.¹² Kajikawa and colleagues used the FRAX® model without incorporating BMD. The predictive ability of FRAX® without BMD was validated as equivalent with it in the Japanese version of the FRAX® model.¹³ Although this study includes minor percentages of subjects taking bisphosphonates (1.4%), activated vitamin D₃ (1.9%), and/or calcium carbonate (0.7%), it might be interesting to conduct a future study on whether there is a relationship between subjects who take medicines for osteoporosis and alterations in vascular structure and function. The present authors also showed the association of FRAX® score with brachial-ankle pulse wave velocity, which is superior to flow-mediated vasodilation for predicting future cardiovascular events.¹⁴ This suggests additional study to examine the predictive value of FRAX® score on future “cardiovascular events” as well as “osteoporotic fracture risk”. Unfortunately, the present study did not demonstrate mechanistic insights by which molecules

link to osteoporosis and atherosclerosis; however, the accumulating evidence supports their observation that a number of molecules associated with bone metabolism can affect the progression of atherosclerosis through modulating vascular calcification, and endothelial and smooth muscle cellular function.¹⁵ The **Figure** illustrates the association between osteoporosis and atherosclerosis with aging.

In conclusion, the study by Kajikawa and colleagues provide valuable clues to better understanding of the relationship between atherosclerosis and osteoporosis using a computer calculation. Shall we check our FRAX® scores tonight?

Conflicts of Interest

None.

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