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Original Article

Association of muscle health impairment and atherosclerosis with major osteoporotic fracture risk in Taiwanese Vegetarians

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Abstract

Objectives: Despite the beneficial effects of "vegetarian style" diet on atherosclerosis, it is also proven potentially detrimental to bone health. The influence of muscle health or atherosclerosis on major osteoporotic fracture (MOF) risk in vegetarians has rarely been explored. This prospective study aimed to investigate an association of MOF risk with muscle health and atherosclerosis in vegetarians. **Materials and Methods:** We conducted a questionnaire survey with the Mini-Nutritional Assessment (MNA) on 39 vegetarians. The 10-year probability of MOF was determined using the Taiwanese Fracture Risk Assessment (FRAX®) calculator. Appendicular skeletal muscle (ASM) mass and bone mineral density were measured with dual-energy X-ray absorptiometry. Physical performance was evaluated using the 6-min walk test (6MWT). Common carotid artery intima–media thickness (ccIMT) was determined using sonography. Serum levels of parathyroid hormone (PTH), Vitamin D, adiponectin, and leptin were measured. **Results:** Eleven (28.2%) of 39 vegetarians had a moderate-high risk of MOF, defined by FRAX-calculated risk ≥10%. These subjects had lower ASM ($P < 0.005$) and 6MWT distances ($P < 0.01$) but greater ccIMT than those with low risk. The MOF risk was negatively correlated with ASM ($r = -0.51$, $P < 0.001$) and 6MWT distances ($r = -0.62$, $P < 0.001$) but positively correlated with ccIMT ($r = 0.56$, $P < 0.001$). Linear regression analysis revealed that MOF risk scores were negatively associated with ASM and 6MWT distance while positively associated with ccIMT. There was no significant association of MOF risk with MNA scores, serum levels of PTH, Vitamin D, adiponectin, or leptin. **Conclusion:** Decreased ASM mass, reduced physical performance, and atherosclerosis are significantly associated with MOF risk in vegetarians.

Keywords: *Atherosclerosis, Muscle health, Nutrition, Osteoporotic fracture risk, Vegetarian diet*

Introduction

Osteoporosis (OP) is a prevalent chronic condition and common morbidity in the general population. According to the National Nutrition and Health Survey in Taiwan, 41.2% of women and 22.6% of men aged 50 years and older have OP [1]. OP is associated with progressive structural deterioration of bone mineral density (BMD), compromised bone strength, and increased susceptibility to fracture. Fractures, in turn, may increase morbidity and mortality [2] and incur significant clinical, social, and financial costs to patients, families, and the health-care system [3]. Therefore, OP and its associated fractures constitute a major public health issue [4].

Since OP is asymptomatic and progressive before bone fractures occur, it is imperative to identify risk factors associated with low bone mass and bone fragility to reduce fracture rates and mortality [2]. The Fracture Risk Assessment (FRAX) tool, a risk algorithm introduced in 2008 in the UK, is widely used to predict the 10-year risk of hip fracture and major osteoporotic fracture (MOF) with or without femur neck BMD measurement [5,6]. The incidence

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of hip fracture in Taiwan is the highest in the world [4]; up to 15% of women and 12.5% of men had increased MOF risk detected using the Taiwanese FRAX calculator, launched in 2010 [7].

Dietary pattern (DP) is another significant modifiable factor behind bone health [8-10]. A vegan diet excludes all animal products, focusing solely on plant-based foods. Lacto-ovo vegetarians consume dairy and eggs but avoid meat, fish, and poultry. Partial vegetarians, or flexitarians, eat a mostly plant-based diet with occasional meat and animal products, whereas nonvegetarians include a variety of plant and animal foods in their diet. These DPs vary significantly in terms of nutrient profiles and health impacts [11]. All subjects in this study were lacto-ovo vegetarians. Plant-based diet patterns have become increasingly popular and well-accepted among senile individuals, environmentalists, and Buddhists. Although a meta-analysis revealed that vegetarians had 6% lower BMD at the lumbar spine and femoral neck than omnivores [10,12], more research is needed to elucidate the relationship between DPs and bone health in Taiwan [13].

Reduced muscle mass and strength among the aging population have become a noticeable public health concern [14]. Growing evidence suggests a link between muscle mass and skeletal health, including the risk of osteoporotic fractures [15,16]. Age-related decline in muscle mass, strength, and function can lead to sarcopenia, which is associated with reduced physical capability, lower life quality, and even increased mortality [15,17]. A registry-based cohort study revealed that prior loss of total body lean mass, but not total body fat mass, was associated with an increased risk of fractures [18]. Cawthon *et al*. observed that low muscle mass was linked to a high risk of hip and potentially other bone fractures in older males [19]. These findings suggest a connection between muscle impairment (low muscle mass or strength) and poor bone health.

Decreased overall protein intake or insufficient high-quality protein sources may impact muscle health. Venderley and Campbell reported that muscle creatine stores were significantly lower in vegetarians than in nonvegetarians [20]. Campbell *et al*. also demonstrated that the lacto-ovo-vegetarians receiving resistance exercise training for 12 weeks resulted in fat-free and whole-body muscle mass declines compared with their omnivorous counterparts [21]. These observations suggest the potential effect of a vegetarian diet on muscle health.

Atherosclerosis is a chronic inflammatory process characterized by the buildup of atheromatous plaque in the arteries [22] and is associated with an increased risk of cardiovascular disease (CVD). Traditional risk factors for CVD in the general population include hypertension, dyslipidemia, and smoking [23]. Dietary modifications have been found to significantly reduce CVD risk by improving lipid profile and insulin resistance, among other beneficial effects [24,25]. A systematic review has also indicated that a vegetarian diet is associated with lower fasting glucose, higher high-density lipoprotein cholesterol levels, and reduced CVD risk [26]. Besides, increasing biological and epidemiological evidence suggests links among atherosclerosis, sarcopenia, and OP [27,28], which may share overlapping clinical risk factors. Previous studies examining an association between CVD and fracture risks were mainly performed on omnivorous subjects [29], and the association is worth investigating in populations having different dietary habits.

In this pilot study, we constructed a multiple linear regression model using clinical and demographic variables, such as atherosclerosis and muscle health, to search for the major risk factors for osteoporotic fracture in Taiwanese vegetarian subjects.

Materials and methods

Study population

In this cross-sectional, prospective study conducted at a single center, 39 adult vegetarian volunteers were enrolled at Taichung Tzu Chi Hospital, Taiwan. The inclusion criteria for this study were (1) age at study entry older than 30 years; (2) absence of mental disease, CVD, chronic kidney disease, metabolic bone disease, rheumatoid arthritis, or osteoarthritis; and (3) noninstitutionalized and functionally independent status. Subjects were excluded if they met any of the following criteria: (1) incomplete completion of the clinical examination or questionnaire; (2) withdrawal from the study despite the initial agreement; (3) taking medication known to affect the musculoskeletal system (e.g., corticosteroids, anti-osteoporotic drugs, androgens, or anti-androgen drugs). This study was approved by the Ethics Committee of Taichung Tzu Chi Hospital (No. REC 108-13), and each participant's written consent was obtained according to the Declaration of Helsinki.

Mini-Nutritional Assessment

Mini-Nutritional Assessment (MNA) is a validated structured questionnaire used to assess the nutritional status of community-dwelling elderly patients, identify those at risk of malnutrition, and detect lifestyle characteristics associated with nutritional risk [30]. The total score on the MNA is 14, with scores between 8 and 12 indicating a potential risk of malnutrition and scores ≤7 indicating malnutrition status.

Determination of bone mineral density by dual-energy X-ray absorptiometry

BMD of the lumbar spine (L1–L4) and bilateral femoral neck was measured using dual-energy X-ray absorptiometry. BMD was calculated as the bone mineral content divided by the projected bone area surface into g/cm^2 units. The least significant detectable difference was ± 0.010 g/cm^2 for the lumbar spine L1–L4 and ± 0.012 g/cm^2 for the femoral neck.

Measurement of 10-year risk of osteoporotic fracture (Fracture Risk Assessment® score)

The web-based FRAX® algorithm [5], specifically the Taiwan FRAX® calculator [7], was used to determine the 10-year probability of a MOF. This calculator considers several clinical risk factors and country-specific fracture and mortality data, including femoral neck BMD, prior fractures, parental hip fracture history, age, gender, body mass index, ethnicity, smoking, alcohol use, glucocorticoid use, rheumatoid arthritis, and secondary OP.

Measurement of appendicular skeletal muscle mass

The appendicular skeletal muscle (ASM) mass of all four limbs was measured using bioelectrical impedance analysis and then summing the results of lean soft tissue in both the right and left arms and legs.

Ultrasound vascular imaging of carotid arteries

Ultrasound vascular imaging for carotid arteries includes measurement of common carotid artery intima–media thickness (ccIMT) [31]. The final ccIMT was represented by the largest average ccIMT measured at the far wall of the common carotid arteries along a 10 mm section of the artery proximal to the carotid bifurcation and the proximal 15 mm-long segment of the internal and external carotid arteries.

Assessments of physical performance

The 6-min walking test (6MWT) was used to assess functional exercise capacity and correlate it with physical fitness [32]. This test measures the distance (in meters) a subject can walk quickly on a flat, hard surface within 6 min. The Borg Category Ratio-10 Scale (Borg CR-10) Scale of Perceived Exertion was used in conjunction with the 6MWT to allow individuals to rate their level of exertion during exercise subjectively. After the 6MWT, subjects were asked to rate their perceived exertion on a scale from 0 (extremely easy) to 10 (extremely difficult).

Statistical analysis

The results were presented as the mean ± standard deviation or median (interquartile range). We performed a Chi-squared test to examine the between-group difference of categorical variables. The independent Student's *t*-test was used for the between-group comparison of numerical variables. Nonparametric Spearman's rank correlation test was used to examine the relationships between MOF risk and other clinical features. A multiple linear regression model was implemented to predict the dependent variable (MOF) based on independent variables, including age, MNA, parathyroid hormone (PTH), Vitamin D (25-OH), 6MWT, ASM, ccIMT, leptin, and adiponectin. The coefficient of determination, R^2, was used to measure the goodness of fit in the multiple regression model and how well the data points fit a curve or line. Adjusted R^2 was also calculated, which adjusted for the number of data points in the model. A two-sided probability of <0.05 was considered significant.

Results

Comparison of demographic data, muscle health, and laboratory findings in vegetarians with different major osteoporotic fracture risks

Based on the results of 10-year FRAX-calculated probability of a MOF [5,6], 11 (28.2%) vegetarians had a moderate-high osteoporotic fracture risk, defined as a risk higher than 10%. As illustrated in Table 1, vegetarians with a moderate-high risk of MOF were older and had significantly lower ASM and 6MWT than those with low MOF risk. Besides, they had greater ccIMT than those with low MOF risk (median 0.92 mm vs. 0.72 mm, $P = 0.051$). There were no significant differences in female proportion, MNA, and serum levels of PTH, Vitamin D (25-OH), adiponectin, or leptin between vegetarians with moderate-high and low risk of MOF.

Correlation of major osteoporotic fracture risk score with nutritional status, muscle health, carotid atherosclerosis, and serum levels of parathyroid hormone, Vitamin D (25-OH), adiponectin, or leptin

As shown in Table 2, there was an inverse correlation between MOF risk and ASM mass ($r = -0.51$, $P < 0.001$) or 6-min walking distance ($r = -0.62$, $P < 0.001$) but a positive correlation between MOF risk and ccIMT ($r = 0.56$, $P < 0.001$). Otherwise, MOF risk was not significantly correlated with any other parameter.

Linear regression analyses for predicting the Fracture Risk Assessment-calculated probability of major osteoporotic fracture

Prior to developing the multiple regression model, we assessed for multicollinearity by calculating the Variance Inflation Factor (VIF) for each predictor. All VIF values were below 10, indicating no significant multicollinearity among the variables. The linear logistic regression analysis was then implemented to identify the potential markers for predicting an increased risk of MOF. The coefficient of determination (R^2) was >0.5, indicating a good preliminary model to represent the problem. As illustrated in Table 3, age, ASM, 6MWT, ccIMT, and serum PTH levels were significant predictors of an elevated MOF risk. Among these significant predictors, the degree of carotid atherosclerosis, reflected by ccIMT, had the highest coefficient and influenced MOF risk positively.

Discussion

Vegetarian-style diets can significantly affect atherosclerosis and bone health [13,26,33]. Among postmenopausal Buddhists, the long-term vegan practice was associated with a higher probability of exceeding the lumbar fracture threshold and a lower hip BMD level after controlling for other variables [13]. In the present study, we were the first to reveal lower ASM mass and physical performance (6MWT distance) but greater ccIMT in vegetarians with moderate-high MOF risk than those with low risk. Accordingly, the MOF risk scores were negatively correlated with ASM mass or 6MWT but positively correlated with ccIMT. Linear regression analysis further showed ASM mass and 6MWT as negative predictors and ccIMT as a positive predictor for elevated risk of MOF. These observations suggest that muscle health impairment and atherosclerosis are significantly associated with MOF risk in vegetarians in Taiwan.

Age is a parameter expected to influence MOF risk because it is integral to the definition of FRAX. Poor nutritional status was significantly associated with a higher risk of fractures, and early MNA screening and management of nutritional status helps to reduce fracture events, especially in older people. However, there was no significant correlation between MNA scores and MOF risk in our study; this may be related to small sample size. Previous research also revealed that vegans had higher serum PTH and lower 25(OH)-D levels than omnivores [34]. Our results revealed nonsignificant higher PTH levels and lower 25(OH)-D levels in vegetarians with moderate-high MOF risk than those with low risk. There was an inverse correlation between serum PTH levels and serum 25-hydroxyvitamin D levels ($r_s = -0.28$). The low biopotency

Table 1: Demographic data, muscle health, and laboratory findings in all participants and vegetarians with different risks of major osteoporotic fracture[a]

	Total participants (*n*=39)	Vegetarians with moderate-high risk (*n*=11)	Vegetarians with low risk (*n*=28)
Age, years	63.9±12.7	74.5±4.11***	59.7±12.4
Female, *n* (%)	27 (69.2)	10 (90.9)	17 (60.7)
BMI (kg/m)	23.5±2.83	23.5±2.83	24.3±4.41
MNA	13.0±1.00	13.0±1.00	12.9±1.26
ASM (k)	5.36±0.69**	5.36±0.69**	6.34±0.89
6MWT (m)	370±136*	370±136*	513±71.3
ccIMT (mm)	0.92±0.28	0.92±0.28	0.72±0.20
PTH (pg/mL)	116±179	116±179	59.7±26.3
Vitamin D (ng/mL)	14.0±5.49	14.0±5.49	17.9±7.88
Adiponectin (ng/m)	5160±1650	5160±1650	4530±1940
Leptin (ng/m)	10.8±7.04	10.80±7.04	8.13±6.91

*P<0.01, **P<0.005, ***P<0.001, versus vegetarians with low risk of osteoporotic fracture, as determined by the Student's t-test or the Mann–Whitney U-test. [a]Continuous value is presented as the mean±SD, and binomial values presented as the n (%). BMI: Body mass index, MNA: Mini-Nutritional Assessment, PTH: Parathyroid hormone, 6MWT: Six-minute walking test, ASM: Appendicular skeletal muscle mass, ccIMT: Common carotid intima–media thickness

Table 2: The correlation between major osteoporotic fracture risk scores and nutritional status, muscle mass, physical capacity, carotid atherosclerosis, serum levels of parathyroid hormone, Vitamin D, leptin, or adiponectin

Variables	Correlation coefficients and *P* values	
	Spearman *r*	*P*
MNA	0.0419	0.800
ASM	−0.512	<0.001
6MWT (m)	−0.619	<0.001
ccIMT (mm)	0.557	<0.001
PTH levels (pg/mL)	0.315	0.051
Vitamin D levels (ng/mL)	−0.271	0.095
Leptin levels (ng/mL)	−0.0537	0.7453
Adiponectin (ng/mL)	0.239	0.143

P-values were determined by nonparametric Spearman's rank correlation test. MNA: Mini-Nutritional Assessment, ASM: Appendicular skeletal muscle mass, 6MWT: Six-minute walking test, ccIMT: Common carotid intima–media thickness, PTH: Parathyroid hormone

of Vitamin D in the vegan diet could explain the low Vitamin D status [34], which may drive subclinical calcium deficiency and stimulate PTH release.

In the present study, low muscle mass in ASM was significantly associated with moderate-high MOF risk, consistent with previous findings that reduced total body lean muscle mass was associated with osteoporotic fracture risk [17,18]. Lower limb ASM strength, partly reflected by the 6MWT distance, was inversely correlated with MOF risk, resonating with a recent report that a decline in muscle strength and performance could predict osteoporotic fracture risk [35]. In the assessment of muscle strength and endurance, tools such as the Biodex and Cybex systems provide precise and reliable measurements. Similarly, another study focused on the reliability of concentric isokinetic strength assessments of the knee and hip using the Biodex System 4 in healthy children, exploring the relationship between these measurements and functional strength tests [36]. These studies highlight the potential of such systems in detailed muscle function evaluation. In our study, while we did not use these specific systems, we employed 6MWT as a practical measure of physical performance, reflecting aspects of muscle endurance and functionality. Future research could benefit from incorporating tools such as Biodex or Cybex for a more comprehensive assessment of muscle strength and endurance in relation to osteoporotic fracture risk. Improved fitness and physical function, as determined by 6MWT, could help the prevention of falls and fractures [37]. Besides, an inverse correlation between MOF risk and 6MWT distance indicates that better motor performance is associated with reduced occurrence of bone fracture. Maintaining skeletal movement and strength through exercises or physiotherapy is the key component of anti-fracture care [37,38].

CVD and OP are considered common age-related but independent disorders. However, bone and vasculature are regulated by shared factors, and the process of vascular wall calcification resembles that of bone formation. Vegetarian diets help decrease serum total and low-density lipoprotein (LDL) cholesterol and lower blood pressure, contributing to a lower incidence of obesity, diabetes, hypertension, metabolic syndrome, ischemic heart disease, and CVD [25,26,39]. In our study, there was a positive association between the ccIMT in carotid sonography and the risk of MOF in the vegetarian volunteers. This is consistent with several large epidemiological studies showing a link between CVD and increased osteoporotic fracture risk [27,40]. Possible explanations for this association include shared lifestyle factors, changes in lipid metabolism, and falls [41-44]. Parhami *et al*. revealed that oxidized LDL, a pathogenic factor, could inhibit the osteoblast differentiation and increase OP risk [43]. Besides, vascular atherosclerosis could affect bone metabolism by reducing blood flow to the extremities and increasing bone loss and fracture risks [40]. Given a lack of atherogenic lipid profile in the present study, we could not explore the causal relationship between atherosclerosis and MOF risk in these vegetarian subjects.

Despite the potential clinical implications of this study, some limitations still need to be addressed. First, all subjects in this study are of Chinese ethnicity, and our findings may not be generalizable to other ethnic groups. Second, it should be noted that statins or other lipid-lowering medications may improve bone health [45,46], but we did not evaluate their

Table 3: Linear regression analyses for predicting the Fracture Risk Assessment-calculated probability of major osteoporotic fracture

	Beta coefficient (95% CI)	*t*	*P* (>|*t*|)
Intercept	17.0534 (−3.3987–37.5054)	1.705	0.09882
Age	0.1644 (0.0309–0.2978)	2.519	0.01755
MNA	−0.4404 (−1.4434–0.5627)	−0.898	0.37664
ASM	−1.9338 (−3.4401–−0.4275)	−2.626	0.01366
6MWT	−0.0174 (−0.0295–−0.0052)	−2.916	0.00677
ccIMT	6.7364 (0.4117–13.0611)	2.178	0.03765
PTH	0.0223 (0.0096–0.0350)	3.578	0.00124
Vitamin D (25-OH)	−0.0545 (−0.2129–0.1040)	−0.703	0.48751
Leptin	0.0001 (−0.0000–0.0003)	1.724	0.09528
Adiponectin	−0.0000 (−0.0000–0.0000)	−0.264	0.79357
Observations	39		
R^2	0.8352		
Adjusted R^2	0.7840		
F statistic	16.3260*** (df=9; 29)		

***P-value for the F statistics is < 0.001, MNA: Mini-Nutritional Assessment, PTH: Parathyroid Hormone, 6MWT: Six-minute walking test, ASM: Appendicular skeletal muscle mass, ccIMT: Common carotid intima–media thickness, CI: Confidence interval

impact on MOF risk in the enrolled vegetarians. Third, we acknowledged the importance of assessing various muscle groups and functional capabilities. Accordingly, we measured different muscle groups, including quadriceps, biceps brachii, triceps, and grip strength, and conducted functional assessments such as the Berg Balance Scale and 6MWT. However, it is important to note that our analysis did not specifically delve into the mechanical properties and overall functionality of these muscle groups. While these measurements were taken, due to the scope and focus of our study, a detailed analysis emphasizing the mechanical properties and functionality of muscle was not conducted. It is also important to note that our study did not include a specific questionnaire to assess the overall physical activity of participants.

In light of the observations regarding the nonsignificant correlation between PTH, Vitamin D levels, and MOF risk, we recognize the necessity of further investigation in this domain. In subsequent studies, we aim to delve deeper into this topic, considering the potential influences of these biochemical markers on osteoporotic fracture risk. It is also pertinent to consider that our study's findings might be influenced by the specific demographic of our cohort, which predominantly consists of vegetarians. This aspect could have a unique impact on the observed relationships between these biochemical markers and MOF risk. Our future research will aim to address these complexities to provide a more comprehensive understanding of the factors influencing osteoporotic fracture risk in different dietary groups. Although previous cross-sectional studies have reported the associations of adiponectin or leptin levels with BMD or MOF risk [47,48], the lack of statistical significance in the correlation or linear regression analysis herein could be due to the small sample size (n = 39). Future large-scale, multicenter studies are required to validate the associations of atherosclerosis with MOF risk in vegetarians. Our study's limitation also lies in not differentiating between white and red muscle types, which could be key in understanding OP and fracture risks; future research utilizing magnetic resonance imaging for detailed muscle analysis could address this gap. In addition, it is important to note that the nutrient profiles of vegan and vegetarian diets may vary greatly, and further detailed assessments of these diet patterns are needed.

Conclusion

Our study suggests that muscle health impairment and atherosclerosis are significantly associated with the risk of MOFs in Taiwanese vegetarians. Vegetarians with low skeletal muscle mass, impaired physical performance, and subclinical atherosclerosis may be at higher risk of MOF, which can be countered with interventions to improve muscle and vascular health through rehabilitation and optimal dietary practices. However, the FRAX tool may not fully capture all the relevant risk factors, and individualized clinical assessment is necessary to determine the optimal fracture prevention strategies for vegetarians.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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