Submitted: 03 January, 2026 Accepted: 12 March, 2026 Published: 30 July, 2026 DOI:10.22514/jomh.2026.058

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Baseline systolic blood pressure and longitudinal increase in HbA1c levels as predictors of bone mineral density in older men: a 4-year prospective study

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Abstract

Background: Bone mineral density (BMD) is a key determinant of fracture risk and functional decline in older adults. Age-related metabolic and vascular dysregulation may contribute to skeletal vulnerability; however, their predictive value for subsequent BMD levels in older men remains unclear. This study aimed to examine whether baseline metabolic indicators and their 4-year changes can predict BMD measured at follow-up in community-dwelling older men. **Methods**: In this prospective predictive analysis, 86 men aged 65 years and older underwent assessments of physical characteristics and metabolic syndrome-related indicators at baseline and after 4 years. The BMD of the distal forearm was measured at follow-up using dual-energy X-ray absorptiometry. Multiple linear regression analyses were performed to identify baseline and longitudinal metabolic predictors of follow-up BMD. **Results**: In the baseline predictor model, higher baseline systolic blood pressure was independently associated with lower BMD at follow-up. In the change-inclusive model, a 4-year increase in hemoglobin A1c (HbA1c) was independently associated with lower BMD at follow-up, whereas baseline HbA1c levels were not predictive. Other metabolic indicators did not show significant associations with follow-up BMD. **Conclusions**: Baseline systolic blood pressure and longitudinal increases in HbA1c levels were independent predictors of lower BMD measured at follow-up in community-dwelling older men. These findings suggest that commonly assessed metabolic indicators may provide useful predictive information for identifying older men at risk of low BMD, highlighting the importance of vascular and metabolic health in skeletal aging.

Keywords

Aging; Bone mineral density; Metabolic indicators; HbA1c levels; Hypertension

1. Introduction

Japan is experiencing one of the most rapidly aging populations in the world. According to the Ministry of Health, Labour and Welfare of Japan, individuals aged 65 years and older currently comprise nearly 30% of the total population, and this proportion is projected to increase to 39% by 2070 [1]. In aging societies, preventing the transition into disability and long-term care dependency is essential for extending healthy life expectancy. Among the major causes leading to the need for long-term care, fractures and falls account for approximately 16.1% [2], emphasizing the importance of maintaining skeletal integrity in older adults.

Bone mineral density (BMD) represents a fundamental physiological determinant of bone strength and fracture susceptibility. Numerous studies have demonstrated that individuals with lower BMD have a substantially increased risk of osteoporotic fractures [3]. Importantly, BMD measured at a single time point has been shown to predict future fracture risk over several years [3], reflecting the cumulative effects of age-related changes in bone remodeling and material properties rather than short-term fluctuations [4, 5]. From a physiological perspective, identifying determinants of lower BMD levels later in life is therefore critical for understanding skeletal vulnerability in aging populations.

Although osteoporosis is more prevalent in women, the prevalence of osteoporosis increases progressively with age in men as well [6]. Moreover, osteoporotic fractures in men are associated with higher mortality, delayed functional recovery [7], and greater loss of independence compared with women [8, 9]. These sex-specific differences underscore the importance of early identification of skeletal risk in aging men, particularly before clinically overt osteoporosis develops.

Obesity and metabolic syndrome are common age-related conditions that exert complex effects on bone metabolism. Several studies have reported a positive association between

body mass index (BMI) and BMD [10, 11], which has often been attributed to increased mechanical loading on the skeleton in heavier individuals [12]. However, this apparent protective effect of higher body weight may be offset by adverse metabolic influences. In individuals with severe obesity, increases in BMI may exceed gains in BMD [13], and excessive adiposity has been associated with impaired bone quality and increased fracture risk [14]. These findings suggest that metabolic burden, rather than body mass alone, plays a critical role in skeletal health during aging.

Age-related metabolic dysregulation is characterized by progressive impairments in glucose metabolism, insulin sensitivity, and lipid handling, accompanied by chronic low-grade inflammation. Experimental and clinical studies indicate that chronic hyperglycemia adversely affects bone physiology through multiple mechanisms, including accumulation of advanced glycation end-products within bone collagen, suppression of osteoblast differentiation and function, and alterations in bone material properties [15, 16]. These changes may not necessarily result in rapid bone loss detectable over short intervals, but instead contribute to a gradual decline in bone quality and reduced BMD later in life.

In parallel, metabolic disorders have been shown to accelerate age-related declines in skeletal muscle mass and strength, leading to sarcopenia and functional impairment [17, 18]. Because bone and muscle form an integrated musculoskeletal unit, deterioration in metabolic health may simultaneously compromise both tissues, increasing the risk of falls and fractures. From an aging physiology standpoint, metabolic indicators may therefore serve as early systemic markers of musculoskeletal vulnerability rather than as isolated risk factors for a single tissue [19].

Despite accumulating evidence linking metabolic abnormalities to musculoskeletal deterioration, few longitudinal studies have investigated whether metabolic syndrome-related indicators and their temporal changes can predict subsequent BMD levels in older men. This gap is partly attributable to the relatively low reported prevalence of osteoporosis in men (approximately 1.4%) [6], which has limited research attention to male populations. However, from a preventive and predictive perspective, identifying metabolic predictors of lower BMD before clinically apparent osteoporosis develops is essential for early intervention.

Accordingly, the present study was designed as a prospective predictive analysis focusing on BMD levels measured at follow-up, rather than on longitudinal changes in BMD [20]. We hypothesized that baseline metabolic syndrome indicators and their 4-year changes reflect cumulative physiological stress related to aging and are associated with lower BMD levels in later life. To test this hypothesis, we examined the predictive relationship between metabolic indicators and distal forearm BMD measured at follow-up in community-dwelling men aged 65 years and older.

2. Materials and methods

2.1 Subjects

Participants were recruited through flyers distributed along with announcements for special medical examinations sponsored by Mihara (M) City and Osakikamijima (O) Town in Hiroshima Prefecture. Individuals who expressed interest were invited to participate on the day of the examination. After a full explanation of the study using written information sheets, written informed consent was obtained from all participants. Baseline assessments were conducted in 2016 in M City and in 2019 in O Town, with follow-up assessments performed four years later (2020 in M City and 2023 in O Town). Additionally, participants who were receiving pharmacological treatment for diabetes mellitus (n = 5), dyslipidemia (n = 5), or chronic kidney disease (n = 2) at baseline were excluded to minimize their potential influence on bone metabolism and metabolic indicators. Furthermore, the exclusion criteria included a history of metabolic bone diseases, rheumatoid arthritis, or the use of medications known to significantly affect bone density, such as long-term glucocorticoids or anti-osteoporosis therapy; however, no participants met these specific criteria in the current study. Consequently, a total of 12 participants were excluded, and 86 participants were included in the final analysis. Among all examinees, 86 community-dwelling men aged 65 years and older who had complete data on metabolic syndrome indicators at both baseline and the 4-year follow-up, as well as bone mineral density (BMD) measurements at follow-up, were included in the present analysis. The physical and mental condition of each participant was assessed before and during the measurements, and the examination was discontinued immediately if any discomfort was reported.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Prefectural University of Hiroshima (approval no. 20MH017). A flow diagram of participant inclusion is presented in Fig. 1. To evaluate potential selection bias, physical characteristics, metabolic indicators, and physical performance measures (grip strength and Five-Times-Sit-to-Stand Test) at the 4-year follow-up were compared between participants included in the analysis and those excluded due to missing baseline data; the results are summarized in Table 1. The characteristics of the study population (n = 86), including follow-up physical performance data, are summarized in Table 2.

2.2 Examination procedure

Between 2016 and 2023, all participants underwent two health examinations: at baseline and after a 4-year follow-up period. At both time points, physical characteristics and blood-based metabolic indicators were assessed. Bone mineral density was measured only at the follow-up examination (2020 and 2023).

2.2.1 Measurement of metabolic syndrome indicators

Height (cm) and body weight (kg) were measured using standardized procedures, and body mass index (BMI; kg/m^2) was calculated. Metabolic syndrome-related indicators included triglycerides (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), low-density lipoprotein (LDL)

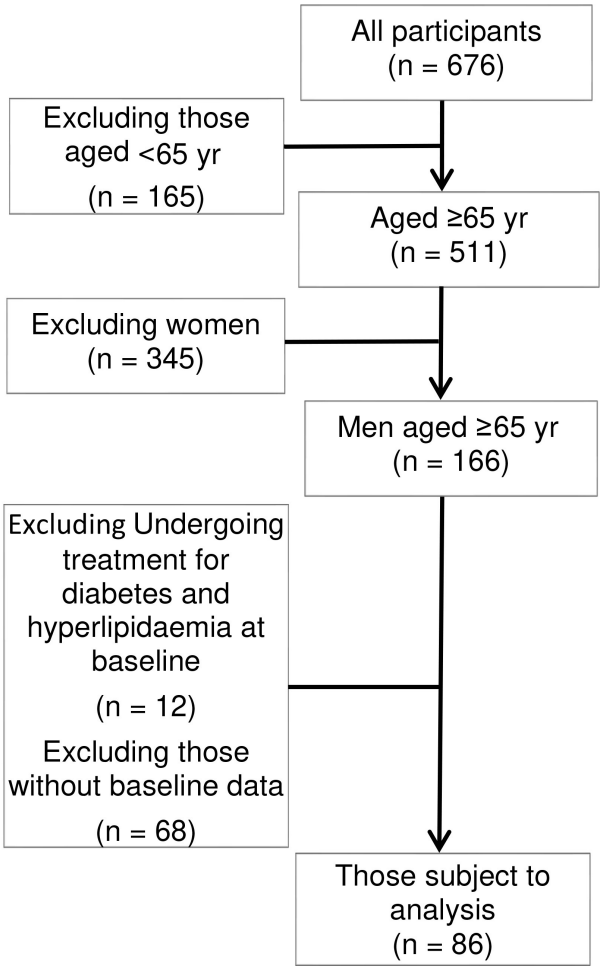

FIGURE 1. Flowchart of the participant recruitment and selection process.

TABLE 1. Comparison of physical characteristics and metabolic indicators at the 4-year follow-up between included and excluded participants.

	Subjects for analysis (n = 86)		Subjects excluded from analysis (n = 68)		*p*-value	Effect size	
	Mean	(SD)	Mean	(SD)		Cohen's *d* value	95% CI
Age (yr)	76	(6.3)	73.7	(6.9)	0.025	0.40	0.05–0.76
Height (cm)	163.9	(6.4)	163.6	(5.7)	0.728	0.56	−0.26–0.37
Weight (kg)	62.3	(8.8)	60.7	(7.7)	0.263	0.18	−0.14–0.50
Body Mass Index (kg/m^2)	23.2	(2.9)	22.7	(2.7)	0.327	0.16	−0.16–0.48
Triglycerides (mg/dL)	112.4	(58.9)	116.2	(64.8)	0.699	−0.06	−0.38–0.26
HDL cholesterol (mg/dL)	63.6	(13.9)	62.2	(16.8)	0.574	0.09	−0.23–0.41
LDL cholesterol (mg/dL)	119.7	(27.8)	125.4	(32.9)	0.248	−0.19	−0.51–0.13
HbA1c (%)	5.8	(0.6)	5.8	(0.5)	0.985	0.00	−0.31–0.32
Systolic blood pressure (mmHg)	134.4	(15.5)	132.2	(19.0)	0.449	0.12	−0.19–0.44
Diastolic blood pressure (mmHg)	76.1	(8.8)	77.7	(13.3)	0.370	−0.15	−0.16–0.17
Grip strength (kg)	31.5	(7.4)	30.9	(6.2)	0.624	0.08	−0.26–0.44
Five-Times-Sit-to-Stand Test (s)	9.2	(3.8)	9.1	(3.1)	0.971	0.01	−0.31–0.32
Bone mineral density (g/cm^2)	0.711	(0.07)	0.689	(0.08)	0.071	0.30	−0.03–0.61

SD: Standard deviation; CI: Confidence Interval; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Hemoglobin A1c.

TABLE 2. Physical characteristics and metabolic syndrome indicators of the study participants.

	Baseline		4 Years Later		*p*-value	Effect size	
	Mean	(SD)	Mean	(SD)		Cohen's *d* value	95% CI
Age (yr)	71.8	(6.4)	76.0	(6.3)	<0.001	—	
Height (cm)	164.7	(6.2)	163.9	(6.4)	<0.001	1.00	0.74–1.26
Weight (kg)	62.6	(8.4)	62.3	(8.8)	0.076	0.19	−0.02–0.41
Body Mass Index (kg/m^2)	23.1	(2.7)	23.2	(2.9)	0.632	−0.06	−0.27–0.15
Triglycerides (mg/dL)	112.2	(48.1)	112.4	(58.9)	0.980	0.00	−0.21–0.21
HDL cholesterol (mg/dL)	59.6	(14.2)	63.6	(13.9)	<0.001	−0.52	−0.74–−0.29
LDL cholesterol (mg/dL)	122.9	(28.7)	119.7	(27.8)	0.167	0.15	−0.06–0.36
HbA1c (%)	5.6	(0.5)	5.8	(0.6)	<0.001	−0.47	−0.69–−0.24
Systolic blood pressure (mmHg)	127.3	(15.1)	134.4	(15.5)	<0.001	−0.41	−0.63–−0.19
Diastolic blood pressure (mmHg)	76.1	(10.0)	76.1	(8.8)	0.908	−0.01	−0.22–0.20
Grip strength (kg)	—		31.5	(7.4)	—	—	
Five-Times-Sit-to-Stand Test (s)	—		9.2	(3.8)	—	—	
Bone mineral density (g/cm^2)	—		0.711	(0.07)	—	—	

SD: Standard deviation; CI: Confidence Interval; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Hemoglobin A1c.

cholesterol (mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and hemoglobin A1c (HbA1c, %). Triglycerides were measured using Determiner-C-TG, HDL cholesterol using MetaboLead HDL-C, and LDL cholesterol using MetaboLead LDL-C. Blood analyses were performed using BioMajesty JCA-BM8060 and JCA-BM9130 automated analyzers (JEOL Ltd., Tokyo, Japan). Four-year changes in metabolic indicators were calculated as the difference between follow-up and baseline values (follow-up minus baseline) and were used as explanatory variables in the predictive analyses.

2.2.2 Physical function assessment

To assess physical function and muscle strength as potential confounding factors at the follow-up period, grip strength and the Five-Times-Sit-to-Stand Test (5STS) were performed only at the 4-year follow-up. Grip strength was measured using a digital handheld dynamometer (T.K.K.5401, Takei Scientific Instruments Co., Ltd., Niigata, Japan). Participants performed two trials with each hand, and the maximum value (kg) was recorded. The 5STS, a measure of lower-extremity muscle strength and dynamic balance, required participants to stand up and sit down five times as quickly as possible from a standard chair without using their arms. The time taken to complete the five cycles was measured in seconds using a stopwatch.

2.2.3 Measurement of bone mineral density

Bone mineral density (g/cm^2) of the distal forearm was measured at follow-up using a dual-energy X-ray absorptiometry system (ALPHYS A, FUJIFILM Corporation, Tokyo, Japan). Measurements were performed on the left forearm; however, if the participant was left-handed or had a metallic implant in the left forearm, the right forearm was assessed instead.

Throughout the study period, the densitometer was calibrated 27 times. Calibration results showed a mean value of 1.001 g/cm^2 with a standard deviation of 0.009 g/cm^2 and a coefficient of variation of 0.97%, all of which were within the manufacturer's acceptable ranges, indicating high measurement reliability.

2.3 Statistical analysis

Sample size estimation was conducted using G*Power (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, NRW, Germany) based on the reported association between grip strength and forearm BMD. According to the findings of Bevier *et al.* [21], assuming a correlation coefficient of 0.47, a two-sided α level of 0.05, and statistical power of 0.80, the minimum required sample size was calculated to be 33 participants [22, 23]. The present study included 86 participants, exceeding this requirement.

Descriptive statistics were calculated as means and standard deviations. The normality of baseline metabolic indicators and their 4-year changes was assessed using histograms and the Kolmogorov-Smirnov test ($p > 0.05$). Differences in baseline characteristics between included and excluded participants were evaluated using Student's *t*-tests. Changes in physical and metabolic characteristics between baseline and follow-up were also examined using paired *t*-tests.

To identify metabolic predictors of bone mineral density at follow-up, multiple linear regression analyses were performed with follow-up BMD (g/cm^2) as the dependent variable.

Three predictive models were constructed:

Baseline predictor model:

Follow-up BMD was regressed on age at follow-up, baseline BMI, and baseline metabolic syndrome indicators.

Change-inclusive predictor model:

Follow-up BMD was regressed on baseline age, baseline BMI, baseline metabolic indicators, and the 4-year changes in these indicators.

Sensitivity analysis models:

To ensure the robustness of our findings against residual confounding by physical status, additional multivariate models were constructed by incorporating grip strength or the 5-time sit-to-stand (5STS) test time, measured at follow-up, into the change-inclusive model.

These models were designed to evaluate whether baseline metabolic status, subsequent metabolic changes, and physical performance were independently associated with BMD levels measured at follow-up. A p-value < 0.05 was considered statistically significant for all analyses. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Japan) [24].

3. Results

Table 1 shows the comparison between participants included in and excluded from the analysis at the 4-year follow-up. There were no significant differences in most physical and metabolic indicators between the two groups, including body mass index, blood pressure, HbA1c, and bone mineral density (all $p > 0.05$). Although the included group was slightly older than the excluded group (76.0 *vs.* 73.7 years, $p = 0.025$), the small to moderate effect sizes suggest that the analyzed sample is generally representative of the study population at follow-up.

The results of the multiple linear regression analyses examining metabolic predictors of bone mineral density (BMD) measured at follow-up are presented in Tables 3 and 4.

Table 3 summarizes the baseline predictor model, in which follow-up BMD (g/cm^2) was set as the dependent variable and baseline body mass index (BMI), age at follow-up, and baseline metabolic syndrome indicators were included as independent variables. In this model, baseline systolic blood pressure was significantly and independently associated with lower follow-up BMD (standardized $\beta = -0.0011$, $p = 0.021$). No other baseline metabolic indicators showed statistically significant associations with BMD in this model.

Table 4 presents the change-inclusive predictor model, which incorporated baseline age, baseline BMI, baseline metabolic indicators, and their 4-year changes as independent variables. In this model, an increase in HbA1c over the 4-year period was independently associated with lower BMD at follow-up (standardized $\beta = -0.0462$, $p = 0.0499$), after adjustment for baseline metabolic status. Changes in other metabolic indicators were not significantly associated with follow-up BMD.

Taken together, these findings indicate that baseline systolic blood pressure and an increase in HbA1c levels over four years are independent predictors of lower BMD levels in community-dwelling older men, whereas baseline HbA1c values alone were not predictive of BMD measured at follow-up.

Table 5 shows the results of the sensitivity analysis incorporating grip strength at follow-up into the change-inclusive model. When grip strength was added to the model, the association between the 4-year change in HbA1c and follow-up BMD was no longer significant ($\beta = -0.015$, $p = 0.60$). Grip strength itself did not show a significant independent association with BMD in this multivariate model ($\beta = 0.0007$, $p = 0.56$).

In the sensitivity analysis incorporating the Five-Times-Sit-to-Stand (5STS) test as a covariate (Table 6), the association between the 4-year change in HbA1c and follow-up BMD did

TABLE 3. Baseline metabolic indicators as predictors of bone mineral density at follow-up in older men.

Baseline indicator	β	95% CI	p-value	R^2
Age (yr)	−0.0024	−0.0046–−0.0002	0.036	
Body Mass Index (kg/m^2)	0.0020	−0.0034–0.0073	0.467	0.074
Triglycerides (mg/dL)	0.0001	−0.0002–0.0004	0.435	
Age (yr)	−0.0025	−0.0047–−0.0002	0.030	
Body Mass Index (kg/m^2)	0.0019	−0.0037–0.0075	0.511	0.069
HDL cholesterol (mg/dL)	−0.0002	−0.0013–0.0008	0.663	
Age (yr)	−0.0022	−0.0044–0.0000	0.053	
Body Mass Index (kg/m^2)	0.0022	−0.0030–0.0074	0.407	0.089
LDL cholesterol (mg/dL)	0.0003	−0.0001–0.0008	0.164	
Age (yr)	−0.0024	−0.0046–−0.0002	0.032	
Body Mass Index (kg/m^2)	0.0026	−0.0027–0.0079	0.336	0.072
HbA1c (%)	−0.0092	−0.0376–0.0192	0.520	
Age (yr)	−0.0025	−0.0046–−0.0004	0.022	
Body Mass Index (kg/m^2)	0.0035	−0.0017–0.0087	0.188	0.126
Systolic blood pressure (mmHg)	−0.0011	−0.0020–−0.0002	0.021	
Age (yr)	−0.0025	−0.0048–−0.0002	0.033	
Body Mass Index (kg/m^2)	0.0025	−0.0029–0.0080	0.357	0.069
Diastolic blood pressure (mmHg)	−0.0003	−0.0018–0.0012	0.716	

CI: Confidence Interval; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Hemoglobin A1c.

TABLE 4. Four-year changes in metabolic indicators as predictors of bone mineral density at follow-up.

Indicator	β	95% CI	p-value	R^2
Age at baseline (yr)	−0.0016	−0.0045–1.709 × 10^{-5}	0.052	0.078
BMI at baseline (kg/m^2)	0.0002	−0.0039–0.0071	0.560	
Triglycerides at baseline (mg/dL)	0.0002	−0.0002–0.0005	0.357	
4-year change in triglycerides (mg/dL)	0.0001	−0.0002–0.0004	0.565	
Age at baseline (yr)	−0.0025	−0.0047–−0.0003	0.030	0.071
BMI at baseline (kg/m^2)	0.0023	−0.0037–0.0083	0.451	
HDL-cho at baseline (mg/dL)	−0.0001	−0.0013–0.0010	0.816	
4-year change in HDL-cho (mg/dL)	0.0004	−0.0016–0.0024	0.687	
Age at baseline (yr)	−0.0020	−0.0042–0.0002	0.079	0.097
BMI at baseline (kg/m^2)	0.0024	−0.0029–0.0076	0.365	
LDL-cho at baseline (mg/dL)	0.0005	−0.0001–0.0010	0.105	
4-year change in LDL-cho (mg/dL)	0.0003	−0.0004–0.0010	0.391	
Age at baseline (yr)	−0.0024	−0.0045–−0.0002	0.032	0.115
BMI at baseline (kg/m^2)	0.0023	−0.0030–0.0075	0.398	
HbA1c at baseline (%)	−0.0116	−0.0395–0.0165	0.414	
4-year change in HbA1c (%)	−0.0462	−0.0925–−4.218 × 10^{-5}	0.050	
Age at baseline (yr)	−0.0026	−0.0048–−0.0004	0.019	0.130
BMI at baseline (kg/m^2)	0.0037	−0.0016–0.0089	0.169	
Systolic blood pressure at baseline (mmHg)	−0.0009	−0.0020–0.0001	0.086	
4-year change in systolic blood pressure (mmHg)	0.0003	−0.0007–0.0013	0.574	
Age at baseline (yr)	−0.0027	−0.0050–−0.0003	0.025	0.082
BMI at baseline (kg/m^2)	0.0030	−0.0025–0.0085	0.281	
Diastolic blood pressure at baseline (mmHg)	0.0002	−0.0016–0.0019	0.849	
4-year change in diastolic blood pressure (mmHg)	0.0011	−0.0009–0.0032	0.279	

CI: Confidence Interval; BMI: Body mass index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Hemoglobin A1c.

TABLE 5. Multiple linear regression analysis of 4-year changes in metabolic indicators and grip strength as predictors of bone mineral density.

Indicator	β	95% CI	p-value	R^2
Age at baseline (yr)	−0.0021	−0.0050–0.0008	0.150	0.128
BMI at baseline (kg/m^2)	0.0040	−0.0033–0.0112	0.275	
Triglycerides at baseline (mg/dL)	0.0001	−0.0002–0.0005	0.459	
4-year change in triglycerides (mg/dL)	0.0000	−0.0004–0.0003	0.838	
Grip strength after 4-year (kg)	0.0008	−0.0018–0.0034	0.565	
Age at baseline (yr)	−0.0020	−0.0048–0.0009	0.168	0.122
BMI at baseline (kg/m^2)	0.0047	−0.0027–0.0120	0.210	
HDL-cho at baseline (mg/dL)	0.0005	−0.0009–0.0019	0.492	
4-year change in HDL-cho (mg/dL)	0.0002	−0.0022–0.0026	0.845	
Grip strength after 4-year (kg)	0.0012	−0.0015–0.0038	0.379	
Age at baseline (yr)	−0.0017	−0.0046–0.0012	0.250	0.134
BMI at baseline (kg/m^2)	0.0048	−0.0024–0.0120	0.185	
LDL-cho at baseline (mg/dL)	0.0003	−0.0003–0.0010	0.320	

TABLE 5. Continued.

Indicator	β	95% CI	p-value	R^2
4-year change in LDL-cho (mg/dL)	0.0003	−0.0004–0.0011	0.389	
Grip strength after 4-year (kg)	0.0009	−0.0017–0.0034	0.501	
Age at baseline (yr)	−0.0023	−0.0051–0.0005	0.100	
BMI at baseline (kg/m^2)	0.0054	−0.0018–0.0126	0.137	
HbA1c at baseline (%)	−0.0236	−0.0578–0.0106	0.172	0.150
4-year change in HbA1c (%)	−0.0157	−0.0756–0.0443	0.602	
Grip strength after 4-year (kg)	0.0007	−0.0019–0.0034	0.581	
Age at baseline (yr)	−0.0022	−0.0049–0.0005	0.113	
BMI at baseline (kg/m^2)	0.0054	−0.0015–0.0123	0.120	
Systolic blood pressure at baseline (mmHg)	−0.0010	−0.0023–0.0003	0.137	0.190
4-year change in systolic blood pressure (mmHg)	0.0005	−0.0008–0.0019	0.458	
Grip strength after 4-year (kg)	0.0014	−0.0011–0.0039	0.258	
Age at baseline (yr)	−0.0023	−0.0053–0.0006	0.114	
BMI at baseline (kg/m^2)	0.0043	−0.0028–0.0114	0.227	
Diastolic blood pressure at baseline (mmHg)	0.0005	−0.0018–0.0028	0.654	0.150
4-year change in diastolic blood pressure (mmHg)	0.0020	−0.0008–0.0048	0.150	
Grip strength after 4 years (kg)	0.0012	−0.0013–0.0038	0.346	

CI: Confidence Interval; BMI: Body mass index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Hemoglobin A1c.

TABLE 6. Multiple linear regression analysis of 4-year changes in metabolic indicators and physical performance (Five-Times-Sit-to-Stand Test).

Indicator	β	95% CI	p-value	R^2
Age at baseline (yr)	−0.0029	−0.0055–−0.0004	0.024	
BMI at baseline (kg/m^2)	0.0020	−0.0035–0.0075	0.468	
Triglycerides at baseline (mg/dL)	0.0002	−0.0001–0.0005	0.273	0.093
4-year change in triglycerides (mg/dL)	0.0001	−0.0002–0.0004	0.477	
Five-Times-Sit-To-Stand Test after 4-year (s)	0.0026	−0.0018–0.0070	0.245	
Age at baseline (yr)	−0.0032	−0.0058–−0.0006	0.018	
BMI at baseline (kg/m^2)	0.0025	−0.0035–0.0085	0.412	
HDL-cho at baseline (mg/dL)	−0.0002	−0.0014–0.0009	0.677	0.083
4-year change in HDL-cho (mg/dL)	0.0003	−0.0017–0.0023	0.779	
Five-Times-Sit-To-Stand Test after 4-year (s)	0.0023	−0.0022–0.0067	0.313	
Age at baseline (yr)	−0.0027	−0.0052–−0.0001	0.041	
BMI at baseline (kg/m^2)	0.0029	−0.0024–0.0082	0.284	
LDL-cho at baseline (mg/dL)	0.0005	−0.0001–0.0010	0.095	0.110
4-year change in LDL-cho (mg/dL)	0.0003	−0.0004–0.0010	0.400	
Five-Times-Sit-To-Stand Test after 4-year (s)	0.0023	−0.0020–0.0066	0.288	
Age at baseline (yr)	−0.0029	−0.0054–−0.0004	0.025	
BMI at baseline (kg/m^2)	0.0025	−0.0028–0.0079	0.345	
HbA1c at baseline (%)	−0.0090	−0.0378–0.0199	0.538	0.122
4-year change in HbA1c (%)	−0.0455	−0.0918–0.0009	0.055	
Five-Times-Sit-To-Stand Test after 4-year (s)	0.0017	−0.0026–0.0061	0.431	

TABLE 6. Continued.

Indicator	β	95% CI	p-value	R^2
Age at baseline (yr)	−0.0031	−0.0056–−0.0006	0.016	
BMI at baseline (kg/m^2)	0.0040	−0.0014–0.0093	0.144	
Systolic blood pressure at baseline (mmHg)	−0.0009	−0.0020–0.0001	0.086	0.136
4-year change in systolic blood pressure (mmHg)	0.0002	−0.0008–0.0012	0.655	
Five-Times-Sit-To-Stand Test after 4-year (s)	0.0016	−0.0026–0.0059	0.449	
Age at baseline (yr)	−0.0032	−0.0059–−0.0006	0.016	
BMI at baseline (kg/m^2)	0.0034	−0.0022–0.0089	0.230	
Diastolic blood pressure at baseline (mmHg)	0.0002	−0.0015–0.0019	0.815	0.092
4-year change in diastolic blood pressure (mmHg)	0.0011	−0.0010–0.0031	0.292	
Five-Times-Sit-To-Stand Test after 4-year (s)	0.0020	−0.0023–0.0064	0.355	

CI: Confidence Interval; BMI: Body mass index; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; HbA1c: Hemoglobin A1c.

not reach statistical significance but remained near the threshold (β = −0.0455, p = 0.055), indicating a sustained trend. The 5STS test time itself was not significantly associated with BMD in this model (β = 0.0017, p = 0.431).

4. Discussion

In this prospective predictive analysis of community-dwelling older men, baseline systolic blood pressure and 4-year increases in HbA1c were identified as independent predictors of lower bone mineral density (BMD) measured at follow-up. These findings suggest that vascular and metabolic burden accumulated during aging may contribute to skeletal vulnerability later in life, even when metabolic indicators remain within subclinical ranges.

With respect to blood pressure, baseline systolic blood pressure was independently associated with lower BMD at follow-up. Yang *et al.* [25] reported that femoral neck BMD in individuals aged 50 years and older was lower in those with a history of hypertension than in normotensive individuals. Consistent with this observation, the present study demonstrated a predictive association between baseline systolic blood pressure and subsequent BMD levels. From a physiological perspective, hypertension is accompanied by chronic inflammation and vascular dysfunction, which may influence bone remodeling. Pramusita *et al.* [5] found that Tumor Necrosis Factor-alpha (TNF-α), which is known to exacerbate inflammation, was increased in hypertensive patients and that bone resorption is accelerated due to an increase in osteoclasts, which are bone-resorbing cells, as TNF-α increases Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), which is involved in osteoclastogenesis. These inflammatory and osteoclastogenic pathways may represent a mechanism linking vascular aging to skeletal health [5].

Regarding glucose metabolism, 4-year increases in HbA1c, but not baseline HbA1c levels, were independently associated with lower BMD at follow-up. While previous studies have shown that overt diabetes and poorly controlled hyperglycemia (HbA1c >7.0%) are associated with increased fracture risk [26, 27], no consensus has been reached regarding the direct relationship between subclinical glucose levels and BMD [28, 29]. The significance of the present study lies in its focus on longitudinal changes in HbA1c levels rather than static baseline status. These findings demonstrate that even a numerical increase in HbA1c over time—predominantly within a range below the diagnostic criteria for diabetes—is associated with lower BMD measured at follow-up.

Several biological mechanisms may explain this association. Previous studies have shown that advanced glycation end-products (AGEs) accumulate under chronic hyperglycemic conditions, promoting bone resorption and suppressing bone formation, ultimately leading to reduced bone mass [30, 31]. Ferron *et al.* [32] demonstrated in osteoblast-specific insulin receptor knockout mice that impaired insulin signaling reduced osteoblast number and bone formation, resulting in decreased BMD. In addition, increased intracellular sorbitol accumulation in patients with type 2 diabetes has been reported to enhance osteoclast-mediated bone resorption [33]. Together, these findings support the hypothesis that longitudinal increases in HbA1c reflect cumulative metabolic stress that adversely affects bone remodeling through both osteoblast and osteoclast pathways [34, 35]. Notably, the association between increases in HbA1c and BMD lost significance when grip strength was included in the model (Table 5). This result suggests a potential overlap or complex interplay between muscle strength, glucose metabolism, and bone health in this population [27, 36]. This likely reflects the “bone-muscle unit” concept, where bone and muscle act as a single functional unit regulated by biochemical crosstalk [37]. Chronic subclinical hyperglycemia may simultaneously impair both bone quality and muscle protein synthesis, leading to concurrent declines in both systems [38, 39]. Furthermore, it is noteworthy that while the adjustment for grip strength attenuated the association, the association between HbA1c change and BMD remained nearly significant after adjusting for the 5-time sit-to-stand (5STS) test (Table 6, p = 0.055). This discrepancy

between physical performance measures is informative; while grip strength is a robust surrogate for overall muscle mass and general metabolic health [40], the 5STS test specifically assesses dynamic lower-limb strength and balance [41]. The persistent trend observed in the 5STS model suggests that the impact of longitudinal HbA1c elevation on bone density is not merely a byproduct of impaired physical mobility. Rather, it underscores a distinct metabolic pathway—potentially involving AGE accumulation—through which glucose dysregulation independently compromises BMD [42, 43].

Although baseline systolic blood pressure and 4-year increases in HbA1c levels were significantly associated with follow-up BMD, the regression coefficients were relatively small, indicating that their direct effects on BMD were modest. Nevertheless, the coefficients of determination (R^2 = 0.12–0.13) suggest a moderate explanatory capacity of the predictive models. This finding is consistent with the multifactorial nature of skeletal aging, in which bone health is influenced by complex interactions among metabolic, vascular, and musculoskeletal systems [44].

Several limitations should be considered. The physical characteristics of the participants were similar to those reported in age-matched Japanese populations [45], supporting the external validity of the findings with respect to anthropometric measures. However, participants were volunteers and may have been more health-conscious than the general population. Second, although we excluded individuals receiving treatment for major metabolic diseases such as diabetes and dyslipidemia, other potential confounding factors—including smoking status, alcohol consumption, dietary intake (*e.g.*, calcium and vitamin D), and the use of other medications—were not assessed. The lack of these data represents a source of residual confounding. Furthermore, baseline BMD was not measured, preventing evaluation of longitudinal changes in BMD. Accordingly, the findings should be interpreted as identifying predictors of lower BMD levels at follow-up, rather than the rate of BMD decline. Despite these limitations, this 4-year longitudinal study in older men demonstrated that baseline systolic blood pressure and longitudinal increase in HbA1c levels are meaningful predictors of subsequent BMD levels.

5. Conclusions

In this prospective predictive analysis of community-dwelling older men, baseline systolic blood pressure and 4-year increases in HbA1c were identified as independent predictors of lower bone mineral density measured at follow-up. These findings indicate that vascular burden present at baseline and subsequent increases in HbA1c levels are associated with skeletal vulnerability later in life.

Importantly, baseline HbA1c levels alone were not predictive of bone mineral density, suggesting that longitudinal increases in HbA1c, rather than static hyperglycemia, may be more relevant to bone health during aging. From a predictive perspective, commonly assessed metabolic indicators may provide useful information for identifying older men at risk of low BMD before the onset of clinically overt osteoporosis.

Although causal relationships cannot be inferred, the present findings highlight the potential value of maintaining vascular and metabolic health as part of strategies aimed at preserving skeletal integrity in aging men.

AVAILABILITY OF DATA AND MATERIALS

The obtained data cannot be shared publicly because the datasets have ethical or legal restrictions for public deposition owing to the inclusion of sensitive information from human participants. Based on regulations regarding ethical guidelines in Japan, the ethical review board of the Faculty of Health and Welfare, Prefectural University of Hiroshima imposed restrictions on the data collected in this study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

TI—conceived the original idea for the study, performed analyses of the data, and drafted the manuscript; measured the metabolic indicator. RT, NH and AO—performed the survey, and analyzed the measured data, and visualized the data. SA, HI and YO—contributed to the interpretation of data, provided critical comments and revised the manuscript. RM, KK, YC and AO—commented on the results from the metabolic indicators and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from all subjects involved in the study. All participants in the present study consented to the publication of their results before they responded to the survey. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Prefectural University of Hiroshima (approval no. 20MH017 and 01 October 2020).

ACKNOWLEDGMENT

We would like to express our deepest gratitude to the residents of Mihara City and Osaki Kamishima Town for their cooperation with this research.

FUNDING

This work was supported by JSPS KAKENHI, Grant Numbers: JP 21K11007 and JP 24K14175.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Tadayuki Iida, Nichika Higa, Ruriko Miyashita, Satomi Aoi, Hiromi Ikeda, Reina Taguchi, Keiko Kanagawa, Yoko Okuyama, Yu Chikashita, Atsuhiko Ota. Baseline systolic blood pressure and longitudinal increase in HbA1c levels as predictors of bone mineral density in older men: a 4-year prospective study. Journal of Men's Health. 2026; 22(7): 46-56. doi: 10.22514/jomh.2026.058.