Assessment of Subclinical Manifestations of Atherosclerosis of Coronary and Peripheral Arteries and Bone Strength Parameters in Women

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Aim. To study associations between calcification of the coronary arteries (CA), the state of the peripheral vascular wall and bone strength indices.

Material and methods. In a cross-sectional study were included 200 women at the age 45-69 y.o. who were observed on an outpatient basis and signed informed consent. A survey was conducted on the presence of cardiovascular risk factors and the risk of fractures. The intima-media thickness (IMT), the presence and number of atherosclerotic plaques (AP) were studied using duplex scanning. Pulse wave velocity (PWV), augmentation index (AI) were measured by applanation tonometry. The presence of calcium deposits in coronary vessels was determined by multispiral computed tomography (MSCT) using the Agatston index. The bone mineral density (BMD) of the spine, hip neck (HN) and proximal hip (PH) was measured using double energy x-ray absorptiometry. The marker of bone resorption C-terminal telopeptide of type-1 collagen (CTx) was determined in blood serum by the β-crosslaps method.

Results. There was a positive correlation between the parameters of vascular stiffness, subclinical atherosclerosis of peripheral vessels and CA calcification: AI and calcium index ($r=0.25$, $p<0.05$), IMT and calcium index ($r=0.23$, $p<0.05$), presence of AP and calcium index ($r=0.26$, $p<0.05$). The PWV increased as the calcium index increased, but the correlation remained at the trend level. Women with low bone mass had higher PWV ($p<0.05$), AI ($p<0.01$), IMT ($p<0.02$), CTx level ($p<0.001$) and a higher number of AP than those with normal BMD. CTx was inversely correlated with PWV and calcium index ($p<0.05$). Based on multivariate linear regression analysis (adjusted for age, menopause duration, low body weight, smoking factor and total cholesterol) the independent nature of the relationship between the Agatstone index and BMD in all the measured parts of the skeleton, between AI and BMD of HN, and between IMT and BMD of HN was confirmed. The relationship between the marker of bone resorption CTx and BMD of the spine and PH remained highly reliable.

Conclusion. The correlation of stiffness indices and subclinical atherosclerosis of peripheral arteries, which is a predictor of high risk of cardiovascular events, allows to suggest an important role of changes in the peripheral vascular wall in increasing cardiovascular risk. A decrease in BMD and an increase in the marker of bone resorption, associated with an increase in indices of vascular stiffness and subclinical atherosclerosis and, especially, CA calcification, allows us to think about the common mechanisms of development and progression of atherosclerosis and osteoporosis. Therefore, early examination of women with a high cardiovascular risk, assessed by the SCORE scale, after 45 years and before menopause to detect vascular rigidity and the presence of subclinical atherosclerosis, and performing x-ray densitometry for individuals with changes in these indices will allow stratify the risks of atherosclerosis and osteoporosis complications and recommend preventive use of drugs that reduce vascular rigidity and increase BMD.

Key words: bone mineral density, osteoporosis, subclinical atherosclerosis, coronary arteries calcification, Agatston index, pulse wave velocity, augmentation index.

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Introduction

Cardiovascular diseases (CVD) and osteoporosis are age-related diseases and pose a serious threat to the health and quality of life of postmenopausal women. Currently, numerous clinical and experimental data have been accumulated, suggesting that a decrease in bone mineral density (BMD), impaired phosphorus-calcium metabolism and an increase in vascular stiffness, along with preclinical manifestations of systemic atherosclerosis are interrelated pathological processes that have some common pathogenetic mechanisms [1,2]. There is also a similarity in the course of these diseases: they can be asymptomatic for many years and often manifest clinically after menopause. However, preclinical changes in the vascular wall and bone loss can develop before menopause during the transition period, accompanied by a gradual decrease in estrogen levels [3,4]. For an objective assessment of the relationship between atherosclerosis and osteoporosis, the following surrogate markers of these diseases are often used: calcification of the aorta or coronary arteries, parameters of subclinical atherosclerosis, vascular stiffness and BMD [5,6]. The most accessible and widespread methods for diagnosing subclinical atherosclerosis are duplex scanning of the carotid arteries with an assessment of the intima-media thickness (IMT) and the severity of atherosclerotic plaques (AP), as well as multispiral computed tomography (MSCT) of coronary arteries with an assessment of the calcium index [7]. Pulse wave velocity (PWV) and augmentation index (AI) are the commonly measured parameters for the vascular stiffness assessment [8].

According to the clinical and epidemiological studies, a decrease in BMD increases the risk of premature death largely due to a negative effect on the prognosis of CVD associated with atherosclerosis rather than due to the development of pathological fractures. It was found that in patients with diagnosed osteoporosis, aortic calcification develops more often than in those with normal BMD [9,10]. In patients with chronic renal failure who do not require dialysis, a decrease in BMD was accompanied by an increase in calcium deposition in the coronary arteries, measured by MSCT [11]. The results of recent studies suggest that a decrease in BMD is an additional independent marker of a high risk of cardiovascular mortality in elderly patients [12].

Considering that the mechanisms of osteoporosis and atherosclerosis development are not completely clear, it was suggested that osteoporosis is partially associated with the progression of atherosclerosis [13,14]. In a recent study, concerning relationship between artery calcification and osteoporosis in the elderly, J. Zhu et al. have found that osteoporotic fracture and a pronounced decrease in BMD are closely associated with the occurrence of echogenic plaques in the carotid and coronary arteries [15]. Moreover, in a systematic review N. Veronese et al. [16] demonstrated that a history of fractures increases the risk of mortality from CVD (hazard ratio 1.78; 95% confidence interval 1.09-2.91). Similar results were obtained in other studies [17,18]. In a series of studies examining the associations between BMD and parameters of vascular rigidity, a negative association of BMD with PWV and AI was noted [6,19,20]. In prospective observational studies, it has been demonstrated that in women with progression of aortic calcification, there is a more intense loss of BMD, and the presence of calcifications in the aorta is a predictor of bone loss and the devel-

opment of fractures [21,22]. A similar association has been reported for coronary vascular calcification and bone loss [23,24].

The links revealed in the mechanisms of development of both diseases contribute to a better understanding of the pathogenesis of the diseases and the future development of unique pharmacological agents and therapeutic approaches that can simultaneously stop the manifestations of both diseases in elderly people.

The objective of this work is to assess the relationship between the coronary arteries calcification, the condition of the peripheral vascular wall and BMD in women.

Material and methods

This cross-sectional study was carried out on the basis of the Federal State Institution "National Medical Research Center for therapy and Preventive Medicine" of the Ministry of Healthcare of the Russian Federation. The study population comprised 200 women aged between 45 and 69 years, who were followed on an outpatient basis and signed an informed consent. The study protocol was approved by the local ethics committee.

For the analysis, individual thematic maps of patients were used. The maps reflected information about risk factors for CVD and osteoporosis, results of medical examinations, comorbidities and medications taken. Patients with the following diseases and conditions were not included in the study:

1) all clinical manifestations of atherosclerosis including the history of ischemic heart disease; previous cerebrovascular accidents; transient ischemic attacks; established atherosclerosis of peripheral arteries and hemodynamically significant lesions of the valvular apparatus of the heart;
2) the established diagnosis of second and third degree arterial hypertension (constant intake of antihypertensive therapy);
3) diseases causing secondary osteoporosis, including endocrine diseases (type I diabetes mellitus, primary hyperparathyroidism, thyrotoxicosis, Cushing's syndrome, Addison's disease, hyperprolactinemia), blood diseases (multiple myeloma, systemic mastocytosis, lymphoma, leukemia, pernicious anemia), inflammatory rheumatic diseases (ankylosing spondylitis, polymyositis/dermatomyositis, systemic lupus erythematosus), diseases of the gastrointestinal tract (malabsorption, Crohn's disease), chronic renal failure, various post-organ transplantation conditions;
4) cancers;
5) use of medications that affect bone metabolism (menopausal hormone therapy, glucocorticoids, immunosuppressants, osteoporosis treatment drugs);
6) use of medications that affect the parameters of vascular stiffness and BMD (statins, β-blockers, ACE inhibitors) and medications that affect only vascular stiffness (calcium antagonists, tableted antihyperglycemic drugs, magnesium preparations) on a regular basis for more than six months;
7) surgical interventions on the spine and hip joints, accompanied by the implantation of metal structures.

All women underwent physical examination, laboratory and non-laboratory tests on an outpatient basis. Anthropometric data (height, weight, waist and hip circumference) were measured and blood pressure (BP) was recorded. Total cholesterol (TC), alkaline phosphatase (ALP) and total calcium were measured using the Architectc8000 analyzer (Abbott, USA). C-terminal telopeptide of type-1 collagen (CTx) was studied in blood serum using enzyme-linked immunosorbent assay (β-crosslaps).

BMD was measured by dual energy X-ray absorptiometry using the Hologic apparatus (Delphi W) in the lumbar vertebrae (L1-L4), hip neck (HN) and proximal hip (PH). The results were evaluated both in absolute values (g/cm^2) and in terms of standard deviation (SD) from the peak of bone mass (T-score). The diagnosis of "osteopenia" was established according to the WHO criteria with T-score from -1 to -2.4 SD, "osteoporosis" – -2.5 SD and below. The IMT, presence and number of AP and the degree of stenosis of the carotid arteries were investigated using duplex scanning. Values greater than 0.9 mm were considered an increase in IMT. IMT more than 1.5 mm indicated the presence of AP. PWV and AI were assessed by applanation tonometry (SphygmoCor). PWV of 10 m/s or more was considered pathological. Negative AI was considered normal, while positive AI indicated increased rigidity. Coronary

calcium was quantified using MSCT method on the OptimaTMST660 (GE Healthcare) computer tomograph in a step-by-step mode with a slice thickness of 0.75 mm. To assess the degree of coronary arteries calcification, the Agatston calcium score was used, which is based on the estimation of the X-ray absorption coefficient and the area of calcification. The calcification degree analysis results are expressed by the calcium score value. The calcium score value of more than 100 units was considered increased.

Mathematical and statistical data processing was performed using the Statistica.12.0, SPSS Statistics 26.0 and Excel 2016 software packages. Mean values (M) and standard deviations (±SD) were calculated for quantitative variables. Qualitative variables were described by absolute and relative values. The reliability was evaluated using the nonparametric Mann-Whitney test and the Kruskal-Wallis test between two groups and between three or more groups, respectively. Rank correlation analysis was performed using the r-Spearman coefficient. Pearson's chi-square test was used to compare the frequencies of features and qualitative variables. In addition, linear and logistic regression analysis were used. Differences were considered significant at $p<0.05$.

Results

The average age of the patients was 56.9±6.4 years. The characteristics of the patients in the group as a whole are presented in table 1.

74 (37%) patients were overweight and 41 (20.5%) were obese. Arterial hypertension of the first degree was detected in 32 (16%) women who did not take antihypertensive drugs on a regular basis. 23 (12%) patients were smokers. 160 (80%) individuals had hypercholesterolemia.

Positive correlation was found between the parameters of vascular stiffness, subclinical atherosclerosis of peripheral vessels and coronary arteries calcification: AI and calcium score ($r=0.25$, $p<0.05$), IMT and calcium score ($r=0.23$, $p<0.05$), the presence of AP and calcium score ($r=0.26$, $p<0.05$). However, there was no correlation between PWV and calcium score.

In the general group, osteoporosis was detected in 52 patients (26%), osteopenia - in 91 (45.5%), normal BMD in 57 (28.5%). Patients with osteoporosis, despite their older age, had blood pressure levels comparable to that of women with normal BMD, and the TC level was higher in the presence of low BMD. Women with low bone mass had higher values of PWV ($p<0.05$), AI ($p<0.01$), IMT ($p<0.02$) and CTx levels ($p<0.001$), as well as a greater number of AP than those with normal BMD. Moreover, in patients with substantial decrease in BMD, i.e. with osteoporosis, significant differences in all indicators were observed, while in women with a slight decrease in BMD (osteopenia), these indicators tended to increase. In addition, low BMD, that corresponds to both osteopenia and osteoporosis, was associated with high calcium score ($p<0.03$) (Table 2).

Table 1. Clinical and instrumental characteristics of patients (n=200)

Parameters	M±SD
Age, years	56.9±6.4
BMI, kg/m²	26.4±4.7
Heart rate, bpm	65.6±9.2
SBP, mm Hg	124.7±13.4
DBP, mm Hg	75.9±8.4
SCORE, %	1.4±1.1
IMT of the right carotid artery, mm	0.92±0.3
IMT of the left carotid artery, mm	0.83±0.3
Largest IMT on the right or left, mm	0.85±0.3
AI, %	27.5±8.8
PWV, m/s	8.1±1.6
Calcium score	30.9±69.3
ALP, units/l	66.5±25.4
Calcium, mmol/l	2.4±0.1
TC, mmol/l	6.01±1.3
CTx, ng/ml	0.40±0.2
BMD L1-L4, g/cm²	0.89±0.15
T-score L1-L4, SD	-1.36±1.41
BMD HN, g/cm²	0.73±0.12
T-score HN, SD	-1.10±1.05
BMD PH, g/cm²	0.88±0.14
T-score PH, SD	-0.53±1.1

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, BMD – bone mineral density, IMT – intima-media thickness, AI – augmentation index, PWV – pulse wave velocity, ALP – alkaline phosphatase, TC – total cholesterol, CTx – C-terminal telopeptide of type-1 collagen, HN – hip neck, PH – proximal hip

Table 2. Comparative characteristics of the studied parameters depending on the state of the bone mass

Parameters	Norm	Osteopenia	Osteoporosis
Age, years	53.5±5.3	57.1±6.5***	60.6±5.2***
SBP, mm Hg	125.6±13.7	123.9±13.2	125.2±13.5
DBP, mm Hg	76.9±1.4	75.6±8.2	75.1±8.4
TC, mmol/l	5.8±1.6	6.02±0.9	6.3±1.5
CTx, ng/ml	0.35±0.17	0.44±0.26	0.46±0.19***
AI, %	26.4±8.5	26.9±9.5	30.8±7.4**
PWV, m/s	7.9±1.5	8.2±1.5	9.3±1.8*
IMT, mm	0.79±0.37	0.92±0.33	1.02±0.28*
Number of AP in coronary arteries, n	0.86±1.12	1.63±1.50	2.45±1.42*
Patients with AP in coronary arteries, %	44	69	87*
Calcium score	12.6±45.5	40.9±64.1*	73.75±85.7*

*p<0.05, **p<0.01, ***p<0.0001 compared to Norm

SBP – systolic blood pressure, DBP – diastolic blood pressure, TC – total cholesterol, CTx – C-terminal telopeptide of type-1 collagen, AI – augmentation index, PWV – pulse wave velocity, IMT – intima-media thickness, AP – atherosclerotic plaque

A negative correlation was found between: AI and BMD in all measured areas of the skeleton (p<0.05); IMT and BMD of HN (p<0.05); the presence of AP and BMD of PH and HN (p<0.05). The strongest positive relationship was noted between calcium index and BMD in all evaluated parts of the skeleton. Further, a negative correlation was found between the marker of bone resorption CTx and PWV and between the presence of AP and calcium index (Table 3).

The linear regression analysis, adjusted for age, the presence of menopause, low body weight, smoking and TC level also revealed a negative relationship with AP (p<0.05) and Agatston calcium score (p<0.02).

The distribution of women, depending on the presence and duration of postmenopause, was as follows: with a preserved menstrual cycle – 29 (14.5%), postmenopause less than 5 years – 53 (26.5%), from 5 to 10 years – 60 (30%), more than 10 years – 58 (29%). The average duration of the postmenopausal period was 7.4±6.4 years. The following increase in vascular stiffness indicators and subclinical atherosclerosis was associated with the onset of menopause and an increase in the duration of postmenopause: PWV (from 6.9 m/s to 9.1 m/s, p<0.05), AI (from 23.3% to 32, 1%, p<0.001), IMT (from 0.72 mm to 1.03 mm, p<0.05), AP number (from 0.53 to 2.6, p<0.05), calcium score (from 10.4 units to 50.8 units, p<0.05). At the same time, BMD decreased in all parts of the skeleton and the level of the bone resorption marker CTx tended to increase (Table 4).

It (is) should be noted that changes in the arterial wall occurred with a high frequency in women 45 years of age and older before menopause and in the first 5 years of postmenopause: AP were observed in 30% of the women, PWV ⩾10 m/s – in 42%, AI> 20% - in 58%.

Based on the results of multivariate linear regression analysis (adjusted for age, duration of menopause, low body weight, smoking factor and TC) the independent association between the Agatston calcium score and BMD in all measured parts of the skeleton, between AI and BMD HN, and between the IMT and BMD HN was confirmed. The relationship between the bone remodeling marker CTx and BMD L1-L4 and PH remained highly significant (Table 5). The inverse correlation of PWV and the presence of AP with bone mass was not confirmed in the regression analysis.

Table 3. Correlation relationship between the parameters of the state of the peripheral and coronary arteries vascular wall and bone tissue strength indicators

Parameters	AI	PWV	IMT	Presence of AP	Calcium score
BMD PH, g/cm²	-0,23*	-0,01	-0,06	-0,21*	-0,38**
BMD HN, g/cm²	-0,21*	-0,04	-0,22*	-0,24*	-0,37**
BMD L1-L4, g/cm²	-0,33**	-0,08	-0,06	-0,12	-0,51**
CTx, ng/ml	-	-0,20*	-0,14	-0,26**	-0,18*

*p<0,05,**p<0,01

BMD – bone mineral density, IMT – intima-media thickness, AI – augmentation index, PWV – pulse wave velocity, CTx – C-terminal telopeptide of type-1 collagen, HN – hip neck, PH – proximal hip, AP – atherosclerotic plaque

Table 4. The studied indicators depending on the presence and duration of menopause

Parameters	Before menopause	Postmenopause <5 years	Postmenopause 5-10 years	Postmenopause >10 years	p
The largest of two IMT	0.72±0.29	0.72±0.31	0.89±0.35	1.03±0.34	0.05
AI	23.3±8.5	27.7±10.2	28.1±7.0	32.1±7.8	0.001
PWV	6.9±0.9	7.5±0.9	7.9±1.6	9.1±1.9	0.05
Number of AP	0.53±0.42	0.84±0.65	1.36±0.97	2.6±1.35	0.05
Calcium score	10.4±8.8	26.6±17.9	35.5±10.7	50.8±25.3	0.05
CTx	0.35±0.21	0.42±0.20	0.47±0.18	0.41±0.27	0.06
BMD L1-L4	1.00±0.10	0.93±0.16	0.85±0.13	0.83±0.14	0.0001
T-score L1-L4	-0.43±0.92	-0.97±1.53	-1.72±1.15	-1.98±1.28	0.0001
BMD HN	0.77±0.09	0.76±0.14	0.70±0.10	0.69±0.09	0.01
T-score HN	-0.77±0.82	-0.75±1.26	-1.31±0.90	-1.49±0.84	0.02
BMD PH	0.91±0.10	0.88±0.16	0.86±0.12	0.83±0.11	0.03
T-score PH	-0.22±0.84	-0.19±1.32	-0.72±0.99	-0.91±0.92	0.03

IMT – intima-media thickness, AI – augmentation index, PWV – pulse wave velocity, AP – atherosclerotic plaque, CTx – C-terminal telopeptide of type-1 collagen, BMD – bone mineral density, HN – hip neck, PH – proximal hip

Table 5. Comparative significance of risk factors for a decrease in BMD (according to linear regression analysis)

Risk factors/ markers	BMD L1-L4		BMD HN		BMD PH	
	β	p	β	p	β	p
Constant	0.924	0.0001	0.952	0.0001	0.922	0.0001
Age	-0.005	0.001	-0.004	0.003	-0.003	0.033
Duration of postmenopause	-0.007	0.0001	-0.005	0.0001	-0.004	0.005
TC	-0.15	0.02	-0.18	>0.05	-0.13	>0.05
CTx	-0.11	0.02	-0.08	0.02	-0.13	0.003
BMI<18 kg/m²	0.008	0.0001	0.012	0.0001	0.015	0.001
Smoking	-0.04	>0.05	-0.08	>0.05	-0.06	>0.05
PWV	-0.008	>0.05	0.000	>0.05	0.006	>0.05
AI	0.000	>0.05	-0.002	0.02	-0.001	>0.05
IMT	0.039	>0.05	0.039	0.05	0.011	>0.05
AP	-0.024	>0.05	-0.019	>0.05	-0.014	>0.05
Calcium index	-0.001	0.0001	-0.001	0.017	0.000	0.047

β – regression coefficient, p – values indicate between-group differences, TC – total cholesterol, CTx – C-terminal telopeptide of type-1 collagen, BMI – body mass index, PWV – pulse wave velocity, AI – augmentation index, IMT – intima-media thickness, AP – atherosclerotic plaque, BMD – bone mineral density, HN – hip neck, PH – proximal hip

Discussion

In the present study, we demonstrated the associations between changes in the vascular wall of peripheral arteries, coronary arteries calcification and the state of bone mass and bone metabolism in women. The changes in the studied parameters were observed with the onset of menopause and during the postmenopausal period. The maximal changes in the indices of vascular stiffness (AI and PWV), subclinical atherosclerosis (IMT, number of AP, calcium index) and the lowest BMD were found in women with 10+ years of menopause. We obtained similar results in another study, which focused on the relationship between BMD, parameters of vascular stiffness and subclinical atherosclerosis of peripheral vessels in postmenopausal women [20]. It should be noted that an increase in vascular stiffness was reported in young people under 40, which was ac-

companied by an increase in the frequency of ischemic stroke in prospective observation [25]. When analyzing the relationship between the condition of the vascular wall and bone mass in women aged 45 years and older, the study demonstrated that the parameters of vascular stiffness (PWV and AI) and subclinical atherosclerosis (IMT and the presence of AP) of peripheral vessels were significantly higher in women with osteoporosis, compared to the patients with normal BMD. However, in the regression analysis, adjusted for a number of indicators, an independent association between the AI and IMT with the BMD was confirmed. The association of PWV and the presence of AP with BMD was not particularly stable, although in other studies the authors reported a significant and independent relationship between these indicators. In the Japanese 10-year population study, in women with low BMD arterial stiffness, represented by PWV, increased significantly and in women with osteoporosis (complicated by vertebral fractures) a significant increase in the carotid artery IMT was observed [26,27]. In a one-stage study of middle-aged and elderly men and women, low BMD was associated with a high frequency of detection of AP [17]. In postmenopausal women with low BMD and the presence of AP, the incidence of vertebral fractures was significantly higher than in women without AP, and these associations remained significant after adjusting for atherosclerosis risk factors [18].

The relationship between calcium score and BMD in all parts of the skeleton was more significant than with indicators of vascular stiffness and subclinical atherosclerosis of peripheral arteries, which was consistent with the studies of other authors. In the Song S.O. et al. study a strong relationship was shown between a decrease in spinal and PH BMD and an increase in calcium content in the coronary arteries according to the MSCT data [28]. In another study, it was demonstrated that in women with osteoporotic fractures, the incidence of calcification of the aorta and coronary arteries increased and their severity correlated with a decrease in BMD [29]. It has long been known that low BMD is a risk factor and a predictor of fracture. In recent large studies and various meta-analyses, BMD, along with fractures of the vertebra or hip, were considered as predictors of CVD and the related mortality [16,21].

`To date, there are few studies demonstrating the relationship between the indicators of bone metabolism and the state of the vascular wall. In the present study, the CTx bone resorption marker negatively correlated with PWV, the presence of AP in the carotid arteries and calcium deposits in the coronary arteries. However, when adjusted for age, the presence of menopause, low body weight, smoking and TC levels, the relationship with AP and the Agatston calcium score was present. When assessing the level of CTx in men with ischemic heart disease with different severity of atherosclerosis and the number of affected arteries, no correlation with cardiovascular events (myocardial infarction and stroke) was found [30].

Conclusion

Correlation of indicators of peripheral arteries stiffness and subclinical atherosclerosis, which is a predictor of high risk for cardiovascular events, suggests an important role of changes in the peripheral vascular wall in increasing cardiovascular risk. A decrease in BMD and an increase in the level of the bone resorption marker, associated with an increase in vascular stiffness and subclinical atherosclerosis and, especially, coronary arteries calcification, suggest the commonality of atherosclerosis and osteoporosis development and progression mechanisms. Therefore, when establishing an increased cardiovascular risk in premenopausal women 45 years of age and older using the SCORE scale at the outpatient stage, it is advisable to conduct examinations focused on identification of subclinical atherosclerosis, as well as determination of bone mass decrease (X-ray densitometry). The proposed algorithm of actions will allow to stratify the risks for complications of atherosclerosis and osteoporosis and recommend prophylactic administration of medications that reduce vascular rigidity and increase BMD.

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