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Impact of whole-body vibration exercise on physical performance and bone turnover in patients with monoclonal gammopathy of undetermined significance

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ABSTRACT

Objective: Monoclonal Gammopathy of Undetermined Significance (MGUS) is a risk factor for reduced physical performance, osteoporosis, and fractures due to compromised musculoskeletal metabolism. In this condition it is unknown whether whole-body vibration (WBV) exercise favorably alters physical performance and bone metabolism.

Methods: To evaluate the effect of three-months WBV exercise (30 min; 2x/week) including an optional three-month extension on physical performance, bone metabolism and bone mineral density. Endpoints included functional assessments, bone turnover markers and bone mineral density assessed by peripheral quantitative computed tomography of the tibia.

Results: Fifteen MGUS patients (median age 62.0, nine female) completed the first three months of which ten completed the three-month extension. Measures of physical functioning including chair rise test, timed up and go and 6-minute walk test improved ($p = 0.007$; $p = 0.009$; $p = 0.005$) after three and six months of WBV exercise. Total tibial bone mineral density remained unaltered ($p > 0.05$). WBV exercise tended to increase levels of sclerostin ($p = 0.093$) with a transient increase in osteoclast resorption markers (N-terminal telopeptide of collagen type 1, tartrate resistant acid phosphatase 5b) after three months while Dickkopf-1 ($p = 0.093$), procollagen I N-terminal propeptide ($p = 0.074$) and total alkaline phosphatase ($p = 0.016$) appeared to decline. No exercise-related adverse events were reported.

Conclusion: WBV exercise in MGUS patients improves indicators of physical performance. Observed trends in bone turnover markers and changes in distal tibial bone mineral density may indicate a regulatory effect of WBV exercise on bone metabolism and warrants further evaluation by large scale studies.

1. Introduction

Monoclonal gammopathy of undetermined significance (MGUS) and the clinically more advanced smoldering myeloma are confirmed precursors of symptomatic multiple myeloma (MM) [1]. Both conditions are characterized by increased production of complete or incomplete monoclonal immunoglobulins and an increased plasma cell fraction in the bone marrow. Clinical symptoms such as hypercalcemia, renal insufficiency, anemia or osteolytic lesions indicate the progression to symptomatic MM [2].

There is growing evidence that compromised structure, quality and metabolism of bone along with an increased fracture risk already occur in MGUS patients [3–6], while reductions in bone mineral density are not unequivocally confirmed [7]. Accordingly, a comparative high-resolution peripheral quantitative computed tomography analysis revealed that MGUS patients exhibit altered trabecular microarchitecture,

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reduced trabecular and cortical thickness with increased endocortical area and cortically reduced volumetric bone mineral density [8]. Data of this investigation showed impaired bone formation accompanied by increased serum levels of the osteoblast inhibitor Dickkopf-1 (DKK-1) in MGUS patients [8]. Finite element analysis confirmed increased cortical porosity and a lower apparent modulus indicating reduced bone strength in MGUS patients [9]. Tibial and radial assessments in a current high-resolution peripheral quantitative computed tomography study revealed predominantly trabecular abnormalities in this condition [10].

In case of progression to symptomatic MM, myeloma bone disease frequently occurs with lytic lesions and osteopenia due to increased resorptive osteoclast activity and suppressed osteoblast function [11]. Even though the underlying pathophysiology governing bone turnover in myeloma bone disease is not completely understood, established indicators include a high biologic activity of the receptor activator of nuclear factor-kappa B (RANK) pathway triggering osteoclast activity and recent data suggest a correlation between high levels of RANK ligand and an elevated RANK ligand and osteoprotegerin ratio with an increased risk of progression from MGUS to MM [12]. Concomitantly, increased expression of WNT signaling inhibitors such as secreted frizzled-related protein 3, sclerostin and DKK-1 is considered key to compromised bone formation and regeneration in myeloma bone disease. While only minor sclerostin expression is detected in primary MM cells from patients or MM cell lines, osteocytes seem to be the primary source for sclerostin in myeloma bone disease [11,13]. Conversely, substantially increased expression of DKK-1 by MM cells was demonstrated in MM patients and DKK-1 levels appear to correlate with the extent of bone disease [14,15]. In addition, DKK-1 apparently upregulates sclerostin expression by osteogenic precursors and osteocytes [16]. DKK-1 is therefore considered a MM cell-derived mediator of compromised bone remodeling in MM and potentially in MGUS [17].

Patients newly diagnosed with MM report reduced physical function and quality of life already before initiation of treatment [18]. Exercise interventions enhance physical fitness in patients with malignant disorders and multiple organizations have issued exercise recommendations for patients living with cancer [19,20]. However, results are inconclusive, particularly regarding direct associations of distinct treatment objectives with defined types of activity, intensity, duration and frequency [19,20]. Unfortunately, evidence confirming direct exercise-induced bone health is scarce [21–26]. Inconsistent findings may result from insufficient application of exercise training principles, particularly the principles of specificity, progression and overload [27,28]. In this regard, a recent review on exercise interventions in patients with MM reports inconclusive effectiveness because of weak methodology [29].

Whole-body vibration exercise (WBV) is an effective means of providing specific exercise intervention for patients not amenable to conventional neuromuscular exercise due to health issues, injury risk, time or motivational constraints and lacking exercise experience [30]. To ensure the quality of reporting WBV treatment trials biomechanical parameters such as frequency, peak-to-peak displacement or periodicity of the sessions have been defined [31,32]. Many findings confirm safety and feasibility as well as efficacy of low-magnitude high-frequency WBV for improving physical performance in healthy subjects as well as in adult patients with chronic diseases, chemotherapy-induced peripheral neuropathy as well as pediatric cancer patients [33–40]. More recently, favorable effects of WBV on quality of life, physical functioning, and fatigue were evidenced in patients with hematological malignancies [41,42]. Beyond the well-established neuromuscular adaption, further evidence implies positive responses of WBV on bone metabolism and bone mineral density in patients with osteoporosis [43,44]. Whether these alterations of bone structure and metabolism in osteoporotic patients are mainly caused by enhanced muscular function or rather a direct vibration-induced bone response through e.g. fluid-flow or sheer stress onto osteocytes warrants investigation.

Recent in-vitro studies suggest that mechanical stimulation ameliorates the inhibitory effect of the MM microenvironment on osteocyte growth and a previous animal model confirmed that low intensity vibration protects bone quantity and quality and mitigates progression in a murine model of MM [45,46]. In wistar rats mechanical vibration increases bone density dependent of the vibration stimulus frequencies [47]. Consequently, it can be speculated that WBV might be a promising stimulus to enhance physical performance and bone quality in patients with MM and its precursor condition MGUS, thereby improving quality of life, reducing fracture risk and potentially reinforcing resilience of the bone against osteolytic action. The aim of this study was the use of WBV exercise in patients with MGUS to investigate whether WBV improves physical performance of the lower extremities and elicits an adaptive response of bone turnover and consecutive adjustments of tibial bone structures.

2. Patients and methods

2.1. Study design and participants

To answer the research question a prospective, non-randomized, one-arm, single-center exploratory exercise intervention study was applied. The study duration for each participant lasted at least three months with an optional three months extension. All participants were recruited at regular follow-up consultations for their precursor condition. Key selection criteria were an age of ≥ 18 years with a pre-established diagnosis of MGUS or smoldering myeloma with no contraindications to WBV exercise (Supplement 1). For sample size calculation an average increase in bone density by vibration stimulation of 1% within three to six months was estimated. Based on study data on bone strength in tibia of postmenopausal women [48], we assumed a standard deviation of the relative change in bone density of 1.25%. Based on these assumptions, fifteen patients in a one-group design were calculated to be required to significantly represent the increase in bone density with 80% power on a 0.05 significance level. All participants provided written informed consent before any study-related procedures. The investigation was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University of Würzburg (No. 178/17) and registered with the German Clinical Trial Register (DRKS 00014792).

2.2. Assessments

A comprehensive evaluation including physical performance testing, bone density measurements by tibial peripheral quantitative computed tomography and laboratory analyses took place at baseline, after three and six months. Bone structure and quality of the left distal tibia was assessed with an XCT 2000 bone scanner (Stratec Medizintechnik, Pforzheim, Germany). A technician performed a 30 mm planar scout view of the talocrural joint (at a speed of 30 mm/s) and placed a reference line at the tibial endplate. Images were obtained at 4, 14 and 38% of distal tibial length. Voxel size was 0.5 mm, slice thickness was 2.5 mm. The readout parameters included: total volumetric bone mineral density (mg/cm^3, at 4% of distal tibial length), trabecular bone mineral density (mg/cm^3, at 4% of distal tibial length), cortical bone mineral density (mg/cm^3, at 14% of distal tibial length), cortical cross-sectional area (mm^2, at 14% of distal tibial length) and proportional cortical area (%, at 38% of distal tibial length).

A certified, automated clinical routine laboratory analyzer assessed the following blood variables: blood count, creatinine, calcium, immunoglobulin levels, light-chains (kappa and lambda) levels, M – Gradient of the specific immunoglobulins, alkaline phosphatase, N-terminal telopeptide of collagen type 1, osteocalcin, procollagen I N-terminal propeptide, tartrate resistant acid phosphatase 5b. DKK-1, sclerostin, bone-specific alkaline phosphatase, and myostatin were assessed by an external supplier (Immundiagnostik AG, Bensheim,

Germany).

Assessment of physical performance involved the 6-minute walk test, handgrip strength in a seated position and the elbow flexed at 90 degrees employing a dynamometer (DynEx1, Akern srl, Florence, Italy), the short physical performance battery including chair rise test, usual gait speed and static balance [49], timed up and go test and single-two leg jump performance (Leonardo, Novotec Medical, Pforzheim, Germany). Anthropometric evaluation comprised of body height and mass as well as the skeletal muscle index (skeletal muscle mass by height squared, kg/m^2) calculated from bioelectrical impedance analysis data (BIA 101 Anniversary, Akern srl, Florence, Italy) [50].

2.3. Intervention

The intervention lasted three months with an optional extension of another three months. The 30-min training sessions were guided and scheduled twice per week with two participants exercising at the same time. All WBV exercises were predefined and performed on the side-alternating vibration platform (Galileo, Novotec Medical GmbH, Pforzheim/ Germany). The progression of intensity included increasing WBV frequency, amplitude with progressive difficulty of specific types of exercises. Details are provided in the supplements (Supplement 2). Briefly, the parameters used in this investigation were as follows: (1) frequency: 7–30 Hz, (2) amplitude 1.5–3 mm, and (3) exercise duration ranging from 30 to 180 sec. Adverse events such as muscle weakness, pain and fatigue were closely monitored.

2.4. Statistical analysis

Descriptive statistical analysis included absolute frequencies and corresponding proportions, and median analyses. Due to the small sample size with non-normal distribution of data, pairwise comparisons were employed with Wilcoxon signed-rank test. *$P < 0.05$ and **$P < 0.01$ were considered as significant. If not indicated otherwise, analyses are based on a per-protocol analysis. All statistical analyses were performed with SPSS version 25 statistical software package (SPSS Inc. Chicago IL) and all graphs with GraphPad PRISM Version 8.

3. Results

Details on recruitment are provided in the consolidated standards of reporting trials scheme (Fig. 1). Fifteen participants (9 females) with a median age of 62.0 years (range 47–73) commenced the intervention program. Three patients were diagnosed with smoldering myeloma, twelve had MGUS. Baseline characteristics are summarized in Table 1. The adherence to training sessions of the fifteen participants in the first three months ranged from 83 to 100% (mean 96%). While fifteen participants completed only three months of exercise, ten volunteered to extend the intervention for three months. Adherence to training sessions of the ten participants in the extension period was on average 97% (range 96–100%). All participants also including those who quit the guided exercise sessions after three months attended both the three- and six-month assessment. The six-month outcome data of the five patients who stopped the exercise intervention after three months were inhomogeneous due to some patients continuing various individual exercise programs and others ceasing completely. Since the results cannot be interpreted reliably their data were excluded here. None of the participants cancelled their involvement prematurely and no intervention-associated adverse events were observed.

3.1. Physical performance

Key variables related to physical performance improved with the WBV exercise intervention. Specifically, median distance covered in the 6-minute walk test increased progressively from 555 m to 582 m ($p = 0.009$) and 661.5 m ($p = 0.005$) after three and six months, respectively (Table 2; Fig. 2). Chair rise test ($p = 0.006$ and $p = 0.007$) and timed up and go ($p = 0.002$ and $p = 0.009$) also improved after three and six months. Handgrip strength increased from 32.9 kg to 34.4 kg ($p = 0.3$) and 36.6 kg ($p = 0.032$) after three and six months. The short physical performance battery reflecting a comprehensive analysis of three individual tests (static balance; usual gait speed; chair rise test) also improved over time (data not shown).

3.2. Peripheral quantitative computed tomography measures

No statistical difference between time points was observed for total bone mineral density ($p = 0.221$ and $p = 0.441$ after three and six months; Table 3a). Trabecular and cortical bone mineral density also showed no significant changes over time (Table 3a). Cortical area decreased after six months in the ten subjects participating in the extension period ($p = 0.022$; Table 3a). An additional sub-group analysis revealed that in the more homogeneous cohort of female participants ($n = 9$) total bone mineral density continuously increased over time (Table 3b) with an increase of cortical bone mineral density after three months ($p = 0.038$).

3.3. Parameters of bone turnover and blood chemistry

Regarding bone turnover a decrease of total alkaline phosphatase was detected after three and six months of WBV (-15.2% and −13.8%; $p = 0.048$; $p = 0.016$, Table 4). Bone-specific alkaline phosphatase (−16.9% and −13.9%; $p = 0.088$; 0.721), procollagen I N-terminal propeptide (−8.4% and −13.2%; $p = 0.100$; $p = 0.074$) and osteocalcin (−11.4% and −11.9%; $p = 0.345$; $p = 0.407$) decreased not significantly over time. Tartrate resistant acid phosphatase 5b increased initially at three months and returned towards baseline levels at six months (40.7% and 15.1%; $p = 0.096$; $p = 0.953$). Levels of DKK-1 declined by 13.3% after six months of WBV ($p = 0.093$, Fig. 3) while DKK-1 levels reversed towards baseline levels in the participants quitting WBV exercise after three months (data not shown). In parallel, there was an increase in sclerostin levels by 2.6% over the six months timespan ($p = 0.093$, Fig. 3). Myostatin levels did not change over the course of the study ($p = 0.865$; $p = 0.445$ at three and six months). Further markers including calcium, creatinine, hemoglobin and M−protein levels revealed only minor changes over time with no consistent trend (Table 4).

4. Discussion

We hypothesized that WBV exercise improves physical performance and bone turnover in patients with MGUS. To the best of our knowledge, this is the first exploratory study to investigate the effects of WBV exercise on sclerostin, DKK-1 and on bone mineral density in patients with MGUS. Over the time course of three to six months, peripheral quantitative computed tomography data indicates overall favorable adaptions specifically in total bone mineral density and cortical bone mineral density for the females, along with a reversal of transiently increased levels of tartrate resistant acid phosphatase 5b and N-terminal telopeptide of collagen type 1. Overall trabecular bone mineral density evidenced by peripheral quantitative computed tomography in connection with three- and six-months WBV remained statistically unaltered over the time course. This finding appears to be in line with current literature, reporting no structural adaptations of the tibial bone detectable by peripheral quantitative computed tomography in connection with WBV after three, six months and even after twelve months in osteoporotic individuals [51,52]. However, the external WBV-induced load, i.e. amount of WBV sessions per week, session duration, and intensity in previous studies may have been insufficient to induce structural bone adaptation since the participants of these studies did not show any functional improvement [51,52]. The progressive increase of total bone mineral density of 3.3% (Table 3a) observed along with the

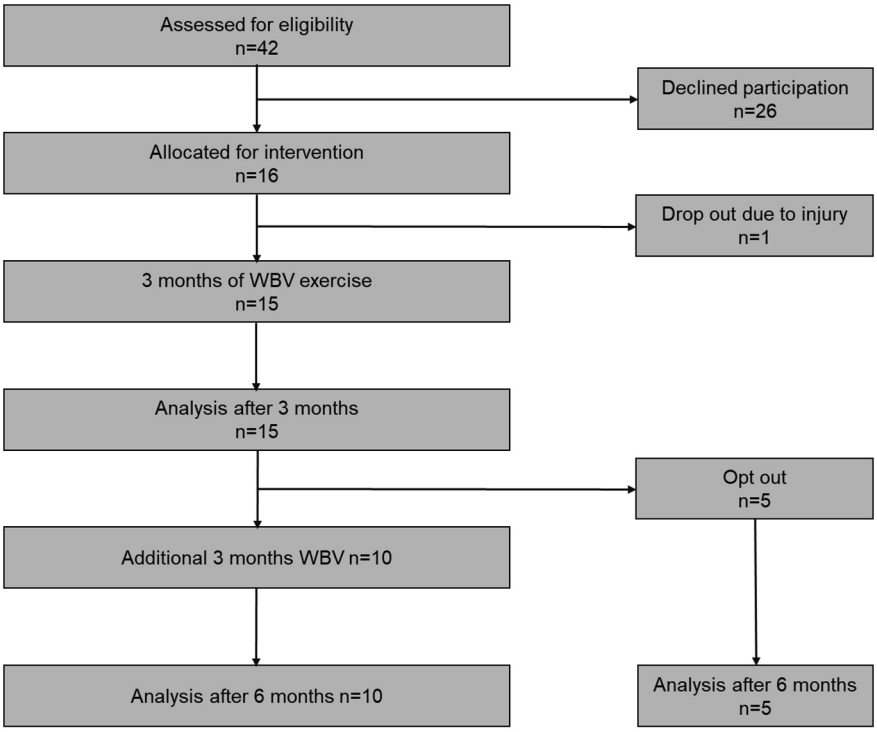

Fig. 1. Flow-chart of the patient recruitment process and follow-up.

Table 1
Baseline characteristics of the participants.

Variable	Median (interquartile range)	Minimum	Maximum
Age [y]	62.0 (13.0)	47.0	73.0
Height [cm]	165.0 (11.0)	158.0	180.0
Body mass [kg]	75.4 (17.1)	59.4	119.0
Bone mass index [kg/m^2]	26.4 (8.5)	23.0	37.0
Skeletal muscle index [kg/m^2]	9.3 (2.5)	6.5	11.3

Minimum: lowest value; Maximum: highest value.

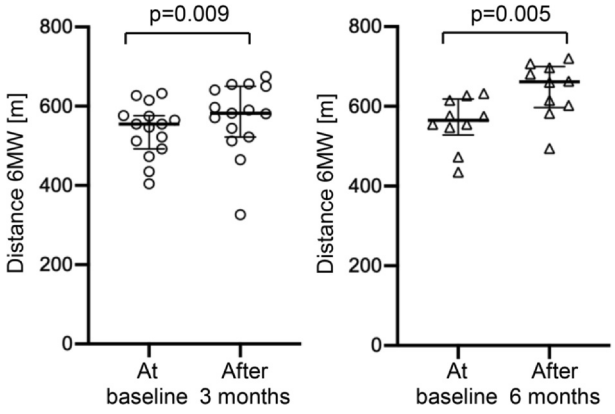

Fig. 2. Distance covered during the 6-minute walk test (median, interquartile range) at baseline and after three (circles) and six (triangles) months of WBV exercise for each participant.

significant functional improvements in our investigation may imply a beneficial bone and functional response of our patients to WBV. Further studies with larger sample size and greater exercise stimulus, i.e. more and/or longer sessions per week or increased exercise intensity are warranted to verify this conclusion. A progressive increase in total bone mineral density was observed in the more homogeneous subgroup of female participants, also during the extension period of the intervention. More specifically, in the females, the cortical bone mineral density after three months increased significantly along with a non-significant decrease of the trabecular bone mineral density. In summary, these data may indicate a sufficient mechanical load by the WBV exposure to induce adaptive responses in a generally smaller and thinner female compared to male tibia. Accordingly, further large-scale studies need to investigate the influence of WBV-induced load in male patients.

Analysis of bone biomarkers support the finding of a WBV-induced adaptive response of the bone, revealing an increase in both tartrate resistant acid phosphatase 5b as a marker for osteoclast number as well as an transient increase in N-terminal telopeptide of collagen type 1 indicating enhanced bone resorptive activity, potentially matching the decline in trabecular bone mineral density and cortical cross-sectional

Table 2
Parameters of physical assessment at baseline, three and six months of WBV (Median (interquartile range)).

Variable	Baseline	3 Months	Change in %	*p*-Value	Baseline	6 Months	Change in %	*p*-Value
Number of participants	15	15			10	10		
Handgrip Strength [kg]	32.9 (11.4)	34.4 (10.8)	4.6	0.300	33.9 (12.2)	36.6 (7.0)	8.0	0.032*
Gait Speed [m/s]	1.5 (0.2)	1.5 (0.2)	0	0.041*	1.5 (0.2)	1.5 (0.2)	0	0.483
Time in chair rise test [s]	8.7 (2.3)	6.8 (1.9)	−21.8	0.006**	8.6 2.7)	6.6 (2.5)	–23.3	0.007**
Time for timed up and go [s]	7.1 (1.3)	5.8 (1.5)	−18.3	0.002**	6.7 (1.0)	5.7 (0.7)	−14.9	0.009**
Distance in 6-minute walk [m]	555.0 (84.0)	582.0 (128)	4.8	0.009**	565 (89.5)	661.5 (1.3)	17.1	0.005**

Table 3a
Parameters of peripheral quantitative computed tomography at baseline, three and six months of WBV (Median (interquartile range)).

Variable	Baseline	3 Months	Change in %	*p*-Value	Baseline	6 Months	Change in %	*p*-Value
Number of participants	15	15			10	10		
Total bone mineral density [mg/cm^3]	428.9 (118.9)	443.0 (113.5)	3.3	0.221	423.1 (126.1)	444.1 (80.8)	5.0	0.441
Trabecular bone mineral density [mg/cm^3]	107.2 (40.0)	105.7 (49.6)	−1.4	0.279	119.0 (44.4)	110.6 (68.8)	−7.1	1.000
Cortical bone mineral density [mg/cm^3]	1151.1 (58.2)	1157.8 (57.2)	0.6	0.118	1154.9 (34.4)	1154.0 (28.1)	0	0.721
Cortical cross-sectional area [mm^2]	267.8 (101.9)	265.8 (101.5)	−0.8	0.950	273.4 (104.3)	269.3 (92.4)	−1.5	0.022*
Proportional cortical area [%]	35.2 (13.2)	35.5 (13.8)	0.9	0.112	35.0 (14.1)	33.6 (12.2)	−4	0.169

Table 3b
Parameters of peripheral quantitative computed tomography at baseline, three and six months of WBV for all female subjects (Median (interquartile range)).

Variable	Baseline	3 Months	Change in %	*p*-Value	Baseline	6 Months	Change in %	*p*-Value
Number of participants	9	9			5	5		
Total bone mineral density [mg/cm^3]	415.3 (83.2)	428.1 (91.8)	3.0	0.093	415.3$^{\#\#}$ (48.6)	444.1$^{\#\#}$ (59.2)	6.9	0.465$^{\#\#}$
Trabecular bone mineral density [mg/cm^3]	102.2$^{\#\#\#}$ (27.6)	98.7$^{\#\#\#}$ (33.2)	−3.4	0.063$^{\#\#\#}$	112.0$^{\#\#\#\#}$	99.2$^{\#\#\#\#}$ (92.6)	−11.4	0.109$^{\#\#\#\#}$
Cortical bone mineral density [mg/cm^3]	1151.1 (78.0)	1157.8 (80.4)	0.6	0.038*	1151.1 (33.5)	1172.3 (36.8)	1.8	0.138
Cortical cross-sectional area [mm^2]	218.8 (86.0)	218.8 (57.1)	0	0.326	218.8 (56.6)	213.5 (49)	−2.4	0.225
Proportional cortical area [%]	34.7 (8.5)	32.9 (12.88)	−5.2	0.110	34.7 (11.5)	32.8 (6.7)	−5.5	0.500

$^{\#}$n = 8;$^{\#\#}$n = 4;$^{\#\#\#}$n = 7;$^{\#\#\#\#}$n = 3.

area, with both markers returning towards baseline levels after six months. Conversely, alkaline phosphatase and bone alkaline phosphatase as well as osteocalcin and procollagen I N-terminal propeptide decreased after three months of WBV. In summary, the combination of reduced bone forming activity together with increased resorption actually would reflect a state of reduced WNT signaling in bone cells [53]. In line with this observation we detected an increase in sclerostin levels after three months. While literature regarding sclerostin expression with WBV intervention seems inconsistent with either decreased or unaltered levels, an increase has not been reported so far [51,54]. One explanation for the increased sclerostin expression might be the finding of an inverse decrease in DKK-1 levels, supposed to correlate with the extent of bone disease in MM patients [15].

Both Sclerostin and DKK-1 are secreted WNT antagonists. DKK-1 binds a larger region on the receptors' extracellular surface compared to sclerostin and blocks additional classes of WNT proteins [55]. Even though Sclerostin and DKK-1 are perceived as having somewhat redundant functions in WNT inhibition, the bone forming potential of DKK-1 inhibition appears limited [56] compared to the more effective sclerostin inhibition [57]. Furthermore, the sources of both factors are different in myeloma and its precursor conditions. While sclerostin is preferentially secreted by osteocytes, DKK-1 may preferentially stem from plasma cells in the bone marrow microenvironment [11,13,58]. Divergent developments of DKK-1 and sclerostin levels have been observed before and are commonly considered a consequence of compensatory regulation [55]. It has been demonstrated that sclerostin inhibition or deficiency of the SOST gene encoding sclerostin lead to a compensatory increase in DKK-1 [55], since DKK-1 is a direct transcriptional target of the beta-catenin downstream WNT signaling [59]. Accordingly, it is tempting to speculate that DKK-1 engenders an increase in sclerostin. There is data suggesting that DKK-1 may stimulate SOST mRNA and sclerostin protein expression in myeloma bone disease [16]. Vice versa an increase in sclerostin may trigger a decrease in DKK-1. WBV exercise may cause an increase in sclerostin, potentially liberated from apoptotic osteocytes. As a result, WBV may trigger an initial response of preferentially trabecular bone resorption and reduced formation by inhibiting osteoblastic WNT signaling. This may get along with a preferentially cortical adaption and condensation leading to increased cortical and total bone mineral density. WBV-induced increase in sclerostin may elicit an inhibiting effect on myeloma cells, reflected in the observed decrease in plasma cell-derived DKK-1, analogously to what has been reported for a successful MM treatment response [17].

The present work focused on investigating participants with the

Table 4
Blood chemistry at baseline, 3 and 6 months of WBV (Median (interquartile range)).

Variable	Baseline	3 Months	Change in %	*p*-Value	Baseline	6 Months	Change in %	*p*-Value
Number of participants	15	15			10	10		
Alkaline phosphatase [U/l]	79.00 (27.5)	67.00 (25.0)	−15.2	0.048*	79.50 (39.0)	68.50 (24.8)	−13.8	0.016*
Bone-specific alkaline phosphatase [U/l]	16.48 (9.0)	13.78 (8.6)	−16.9	0.088	16.18 (8.8)	13.93 (8.0)	−13.9	0.721
Osteocalcin [ng/ml]	13.10 (13.7)	11.60 (10.0)	−11.4	0.345	11.75 (16.7)	10.35 (6.1)	−11.9	0.407
Procollagen I N-terminal propeptide [µg/l]	45.50 (42.7)	41.70 (44.8)	−8.4	0.100	44.50 (41.1)	38.60 (21.3)	−13.2	0.074
Tartrate resistant acid phosphatase 5b [U/l]	1.62 (1.1)	2.28 (1.7)	40.7	0.096	1.72 1.24	1.98 (1.1)	15.1	0.953
DKK-1 [pmol/l]	55.19 (29.0)	51.28 (37.0)	−7.1	0.156	50.48 (33.9)	43.76 (31.4)	−13.3	0.093
Sclerostin [pmol/l]	42.70 (13.3)	45.46 (21.0)	6.5	0.125	45.28 (27.1)	46.46 (18.0)	2.6	0.093
Myostatin [ng/ml]	37.55 (12.0)	35.79 (6.8)	−4.7	0.865	36.40 (12.7)	38.07 (9.2)	4.6	0.445
Calcium [mmol/l]	2.31 (0.3)	2.32 (0.1)	0.9	0.330	2.29 (0.2)	2.22 (0.2)	−3.1	0.241
N-terminal telopeptide of collagen type 1 [nM BCE/l]	9.10 (6.4)	10.60 (3.1)	16.4	0.201	8.45 (7.0)	7.75 (6.4)	−8.3	0.919
M−gradient [g/l]	5.3 (5.7)	4.5 (6.5)	−15.1	0.507	4.1 (4.6)	4.8 (5.8)	17.1	0.178
Hemoglobin [g/dl]	13.8 (1.5)	13.7 (1.6)	0	0.527	13.7 (1.9)	13.3 (2.4)	−0.03	0.046*
Creatinine [mg/dl]	0.9 (0.3)	0.9 (0.4)	0	0.432	0.9 (0.4)	1.0 (0.4)	11	0.038*

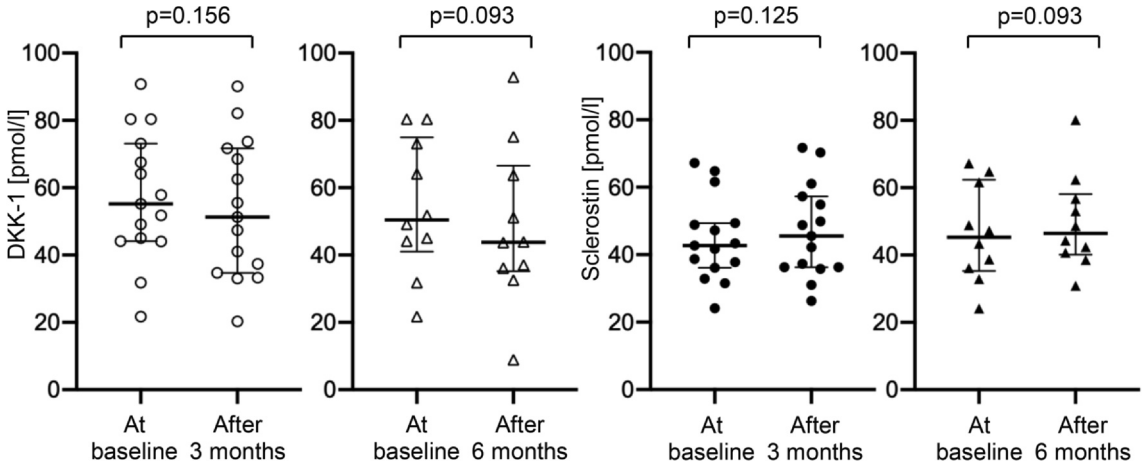

Fig. 3. Serum levels of DKK-1 and sclerostin (median, interquartile range) at baseline and after three and six months of WBV for each participant (circles, triangles).

precursor conditions MGUS and smoldering myeloma to avoid a potential MM treatment-associated bias and to reduce the risk of intervention-related adverse events. WBV as intervention was selected for this type of patients because i) available data confirms this type of exercise to be safe [33], ii) WBV is time efficient, iii) WBV allows employing established principles of exercise intervention in untrained elderly patients [27] and iv) evidence reveals that WBV vibration is a potent stimulus to induce favorable changes in bone metabolism and architecture [43]. There is clear evidence that exercise intervention and specifically WBV elicit improvements in neuro-muscular performance [35,41]. Accordingly, the comprehensive assessment of physical performance in the present investigation was an integral part of the outcome measures [60]. The plantar-induced vibration exercise (2x/week) improved functional tasks assessed by 6-minute walk test, chair rise test and timed up and go which largely depend on leg muscle strength and endurance. From this perspective it is not astonishing that handgrip strength exhibited only minor improvements [27]. Interestingly while endurance performance (6-minute walk test) improved progressively over six months, improvements in chair rise test and timed up and go associated with maximum power plateaued after three months. In general, improvements in muscle strength at the beginning of a period of strength training are considered to be more functional than morphological [61] and the present findings suggest that the extent of progression and overload could have been more pronounced during the second part of the intervention.

The strength of the current work is the first demonstration of the highly significant improvement of physical performance in patients with MGUS and a trend in favorable bone turnover markers in female participants after six months of WBV.

5. Conclusions

This prospective, non-randomized single-center exploratory study involving progressive WBV exercise (2x/week for three months) improves variables related to muscle strength and endurance and seems to induce favorable bone turnover in the MM precursor conditions MGUS and smoldering myeloma. Further studies are warranted to specify the effect of WBV on bone turnover, bone mineral density and bone structure in myeloma bone disease.

6. Limitations

The limitations of the present setup include the overall small number of participants, the lack of a control group and a relevant intra-cohort heterogeneity. However, the small number of participants allowed to accurately control duration and intensity and execution of each movement during WBV exposure. Individual motivational problems commonly associated with exercise intervention studies were overcome by providing an attractive and guided exercise intervention reflected by the high adherence to training sessions (96–100%). Motivational factors may have been apparent during enrollment. Even though the present exercise intervention did not require previous exercise experience nor athletic ambitions, 26 out of 42 patients (62%) declined to participate. However, all participating individuals adhered for at least three months and two-third even completed a voluntary three-month extension period. The five subjects who quite after three months did so because of time constraints commuting to the exercise facility twice weekly.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2020.100323.

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