

Original Article

A controlled trial comparing one-year biochemical bone metabolism outcome in postmenopausal frail osteopenic women under weekly alendronate treatment, with or without whole-body vibration intervention

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Abstract

Purpose: The influence of regular exercise on bone properties is not well defined. Frail subjects have limitations to perform exercise with skeletal impact. This study aims to analyze whole-body vibration treatment (WBV) as an enhancer of bisphosphonate effects in postmenopausal frail women with osteopenia/osteoporosis. **Methods:** Fifty-three postmenopausal sedentary osteopenic women were treated during 12 months with a drinkable alendronate (ALN) formulation. By randomization, 21 of them underwent a WBV (15-min sessions, 3 days per week) as an additional treatment. The serum C-terminal telopeptide of type I collagen (CTX) and total alkaline phosphatase (T-AP) were determined at 0, 6 and 12 months of ALN therapy. In subgroups of 19/13 women, peripheral quantitative computerized tomography (pQCT) was applied at the tibia mid shaft to determine the volumetric BMD of cortical bone (CtBMDv) and the polar strain-strength index (SSIp). **Results:** CTx levels fell significantly deeper in the WBV subgroup (-39.3% and -30.3%, respectively, $p < 0.01$), suggesting that in these women WBV promotes a greater effect of ALN on bone resorption inhibition. Basal CtBMDv and SSIp values were similar in both groups and were weakly (negatively) associated with basal CTx values. After treatment, the correlation between CtBMDv or SSIp values with CTx values were also weak and negative in the Sedentary subgroup but become positive and closer in the WBV subgroup. **Conclusions:** Vibration treatment enhanced the ALN-induced inhibition of bone resorption and may affect positively bone properties. Protracted treatments should show whether this trend is maintained as to effectively reduce the incidence of falls and skeletal fractures in frail subjects.

Keywords: Bone biochemical markers, Drinkable alendronate, Osteopenia, Osteoporosis, Peripheral quantitative computerized tomography, Whole-Body-Vibration

Introduction

The positive influence of regular exercise on bone properties has been described in several clinical studies in young and old healthy people^{1,2}. However, it is not yet well defined which loading type, dose, and schedule of intervention shows a higher impact on the skeleton³. Although some guidelines are available, there is no general agreement about regular exercise prescription to postmenopausal frail women with osteopenia or osteoporosis⁴⁻⁶.

Addition of exercise programs to long-term treatments of osteoporotic individuals with bone metabolism modulators

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Variable	Sedentary group (n=32) Mean \pm SD	WBV group (n=21) Mean \pm SD	p*
Age (years)	65 \pm 5.8	66.5 \pm 5.3	ns
Age at menarche	12.9 \pm 1.7	13.0 \pm 1.4	ns
Age since menopause initiation	45.5 \pm 5.8	42.9 \pm 7.2	ns
BMI	34.3 \pm 4.7	36.4 \pm 6.3	ns
T-AP (U/L) basal	218.4 \pm 48.5	204.1 \pm 48.5	ns
T-AP 6 months	188.5 \pm 39.1	171.9 \pm 39.3	ns
T-AP 12 months	183.1 \pm 38.8	166.9 \pm 40.4	ns
CTx (ng/ml) basal	0.89 \pm 0.07	0.84 \pm 0.14	ns
CTx 6 months	0.65 \pm 0.08	0.51 \pm 0.07	p<0.01
CTx 12 months	0.62 \pm 0.07	0.51 \pm 0.07	p<0.01
Weight (kg) basal	70.0 \pm 11.1	71.4 \pm 10.8	ns
Weight 6 months	70.0 \pm 11.1	68.7 \pm 10.1	ns
Weight 12 months	68.3 \pm 10.4	68.5 \pm 9.7	ns
Fat (%) basal	40.8 \pm 7.1	43.2 \pm 5.9	ns
Fat 6 months	40.8 \pm 7.1	42.3 \pm 5.7	ns
Fat 12 months	40.6 \pm 6.9	42.3 \pm 5.7	ns
Muscle (%) basal	21.8 \pm 3.4	22.1 \pm 4.5	ns
Muscle 6 months	21.8 \pm 3.4	22.7 \pm 3.6	ns
Muscle 12 months	22.5 \pm 1.8	22.7 \pm 3.7	ns
Visceral (%) basal	11.5 \pm 3.4	10.3 \pm 3.4	p<0.05
Visceral 6 months	11.5 \pm 3.4	9.1 \pm 2.8	p<0.05
Visceral 12 months	10.0 \pm 3.1	9.0 \pm 2.7	ns

The sample was divided into those keeping their life style (Sedentary group) and those accepting whole-body vibration interventions (WBV group). p of t-tests of non-related samples, comparing Sedentary vs. WBV groups are indicated.

ns = nonsignificant, BMI = Body Mass Index, T-AP = Serum Total Alkaline Phosphatase, CTx = Serum C-terminal telopeptide of type I collagen.

Table 1. Age, age at menarche, age since menopause, BMI, serum T-AP and CTx, weight, and impedance-assessed percentages of body fat, muscle and visceral masses of the 53 sedentary, osteopenic post-menopausal women studied, all of them receiving weekly alendronate during 12 months.

as bisphosphonates (BPs) may interact positively with their effects on bone material or structural properties. However, this “drug/loading” interaction may vary between different bone regions depending on differential patterns of drug accumulation, the variable influence of aging, and different comorbidities which may also vary largely between individuals.

Passive skeletal stimulation with WBV has been suggested in postmenopausal sedentary women with osteoporosis^{7,8}. This procedure would compensate for the lack of active physical activity by the passive induction of fast movements in legs, hips and spine. With the necessary caution, WBV is easy to apply even in women with poor stability and balance with high risk of falls⁸.

Contraindications derived from WBV-induced health problems or discomfort were seldom reported. Nevertheless, results have been controversial depending on the study design, type of individuals, and treatment, especially concerning the use of BPs^{9,10}. To note, WBV proved to increase bone formation in the tibia of growing mice compared to controls¹¹ while it was shown inactive in adult intact mice¹².

Among the different BPs indicated in postmenopausal osteoporosis, alendronate (ALN) is the most commonly used compound in many countries to rapidly reduce bone turnover. Liquid formulations show an intra-individual variance of absorption about 3-fold larger than that of

the solid forms¹³⁻¹⁵. Under BP treatment inhibition of bone resorption is coupled with a lower bone formation. Nevertheless, in most treated patients bone mass and strength were increased and fracture incidence was reduced, especially in osteoporotic women, suggesting a balance 'anabolic' effect^{16,17}. In patients with high baseline values of bone turnover markers, an average 40-60% reduction is usually observed after BP treatment. In patients who are unable or not willing to do regular exercise, a combination of ALN and WBV treatments may improve the anabolic outcome^{16,17}. Results might be optimized by avoiding any negative interaction between drug and physical impacts at the bone cellular level (i.e. drugs should target skeletal sites undergoing excessive catabolism without interfering with the load-induced remodeling).

The positive interaction of BP treatment with the effect of the directional mechanical stimulation of the skeleton has been supported by different models. The most compelling evidence was the BP-induced improvement of post-yield bone properties, toughness and strength of the mid shaft of rat femur¹⁸. Bisphosphonates increase both survival and density of osteocytes, which constitute the sensors and directional effectors for bone modeling within the bone mechanostat system¹⁸.

In order to test whether the combined effects of a liquid formulation of ALN and WBV are or not additive, we have treated a sample of frail postmenopausal sedentary osteopenic women with standard doses of ALN and WBV sessions as separate or combined therapies during one year. No control group treated with WBV alone was included in this type of test because of regulatory reasons.

In addition, to provide some insight on the "drug/loading" interaction on bone tissue and design indicators, a pQCT study of the calf was carried out in sub-group samples as available.

Subjects and methods

Fifty-three post-menopausal women, consecutively attended at our clinic in Zárate (province of Buenos Aires, Argentine), were recruited after giving a written consent. Inclusion criteria were: 1) For those of 45-50 years of age, 5 years or more since last menses or at least 2 years since last menses with plasmatic oestradiol levels <30 pg/mL and FSH >40 UI/L; 2) if they were 51 to 55 years old, one year or more since last menses with oestradiol levels <30 pg/mL and FSH >40 UI/L, and 3) for those of more than 56 years: at least one year since last menses. As general requirements, they had to show: 1) a protracted history of sedentary behavior (no sport, leisure or working physical practice other than ordinary in-house activities); 2) no osteopenic or osteoporotic values of hip or lumbar spine BMD (t-score below -2.00 for Argentinian population) in studies performed no more than one year earlier; 3) no treatment with any anti-resorptive therapy for osteoporosis in the last 3 months (excluding calcium and vitamin D supplements);

4) no contraindication for BP or WBV treatments (severe cardiovascular, respiratory, digestive, renal, hematological, endocrine, immunologic or neoplastic conditions, hypersensitivity to BPs, difficulties for taking liquids, bone fractures still under consolidation, inability to keep standing while taking medication of training at the platforms, epilepsy, acute thrombosis, risk factors for mandible osteonecrosis), and 5) no participation in other clinical trials within the 2 previous months. No osteotropic medications other than the study drug were allowed, except circumstantial medications like those for common cold, toothache, or minor trauma. Patients receiving sex-hormones, non-steroid anti-inflammatory drugs or thyroid hormones maintained the doses steady during the whole observational period. Table 1 shows the main population features.

After inclusion, all patients received 70 mg oral ALN per week in a drinkable form (*Gador SA, Buenos Aires; Xeolas, Dublin*). Calcium and Vitamin D supplements were allowed upon demand, aiming to enrich poor diets. The sample was further randomized to offer or not WBV training, 15-min sessions standing with slightly bent knees with 25 cm of amplitude position, 3 days per week, at the same dose (frequency 18 to 22 hz) during the whole observational year. Twenty one patients accepted this treatment (WBV group). The 5 women who did not accept plus the remaining ones (n=32 in total) continue with their common daily activities (Sedentary group). A WBV treatment was considered complete when compliance with at least of 80% of every session was registered. Any eventual gross change in physical activity was registered for every patient.

At baseline, BMD was assessed at lumbar spine and hip by DEXA (*Lunar system, GE Healthcare, Little Chalfont, UK*). Osteopenia was diagnosed when a t-score below -2 was shown at least in one of the assessed sites. Body composition (fat, muscle and visceral masses) was studied by bioelectrical impedance (*Omron-HBF 500 system*) according to manufacturer instructions (correlation with air displacement plethysmography in women, $r=0.85$, $p<0.01$, % error=18.3)¹⁹.

In a sub-set of 32 women, 19 from the Sedentary group and 13 from the WBV group, a pQCT (XCT 3000-Stratec, Pforzheim) analysis was done. The system was positioned at the tibia mid-shaft and operated according to manufacturer instructions, to assess cortical vBMD (CtBMDv, in mg/cm³) as a bone material indicator, and SSIP as an indicator of bone strength. The SSIP calculation considers bone tissue density (CtBMDv) and bone size (assessed as the cross-section moment of inertia) (CSMI) of cortical area of the scan. The CSMI is expected to reflect the directional skeletal influences of muscle forces mobilized by WBV^{13,20,21}. The CV measurements were below 1% for CtBMDv and below 3% for SSIP^{13,20,21}. A positive effect of the WBV input over those CV values was expected at the studied site.

Serum C-terminal telopeptide of type I collagen (CTX) were determined by ELISA-test (normal range for

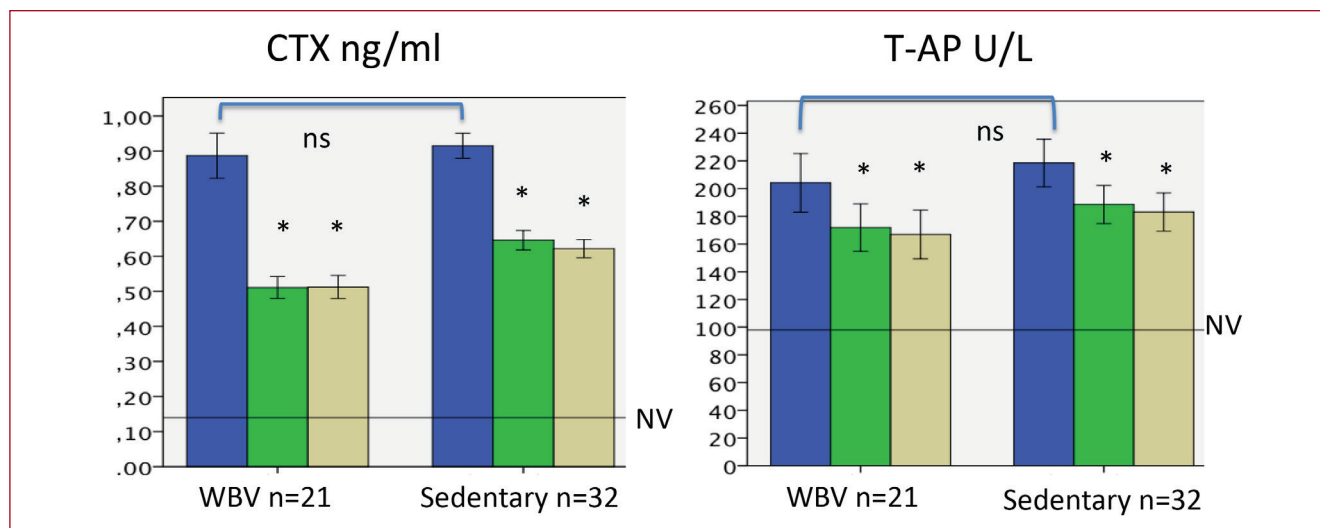


Figure 1. Variations in CTx and T-AP after 1 year of Alendronate (ALN) administration, 70mg weekly. Variations in CTx and T-AP at basal (blue), 6 months (green), and 12 months (beige) after ALN administration to the whole sample (n=53) of postmenopausal sedentary osteopenic women. WBV: women using whole-body vibration as an additional therapy; Sedentary, women not using WBV as an additional treatment. NV: CTx Normal Value 0.14-1.35; NV: T-AP Normal value 98-279 U/L, * $p < 0.01$ (t-test related samples comparing to basal).

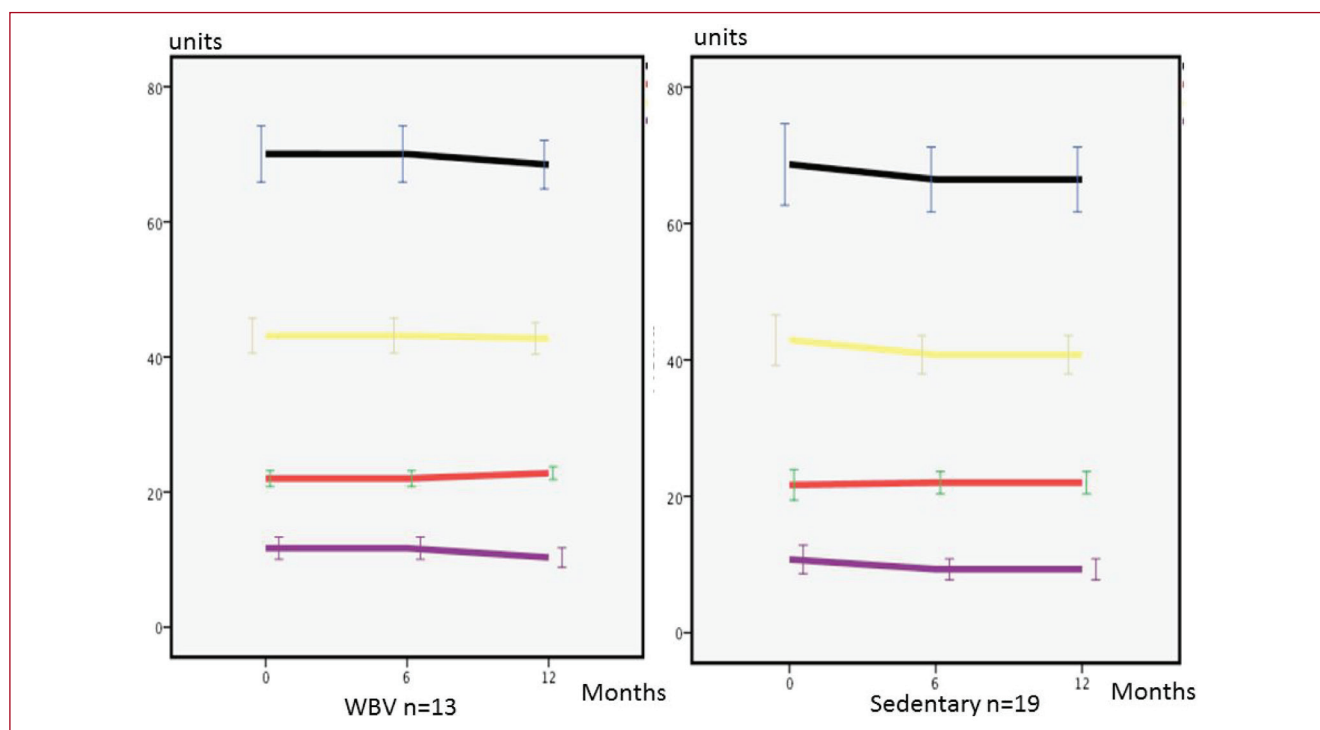


Figure 2. Variations in weight and in lipid, muscle and visceral masses in postmenopausal women receiving weekly alendronate (ALN) therapy during 12 months. Weight (kg, black), lipid (%), muscle (%), and visceral (%) contents as assessed by bioelectrical impedance in 32 whole bodies from postmenopausal sedentary and osteopenic women receiving weekly ALN therapy during 12 months and being subjected to pQCT analysis for bone properties. The sample was divided by randomization into women continuing with their daily style of life (Sedentary group, n=19) or accepting to undergo 3-weekly whole-body-vibration intervention (WBV group, n=13). $p > 0.05$ (t-test non-related samples comparing both groups of patients).

Group	n	Bone Biochemical Markers and correlations	Basal 0	Month 6	Month 12	% Variation 0-12 months
Sedentary	19	CTx (ng/mL)	0.89±0.1	0.63±0.1	0.61±0.1	-31.5 *
		Correlation with CtBMDv	0.464	0.462	0.394	-15.1
		Correlation with SSIp	0.443	0.246	0.110	-75.2
		T-AP (U/L)	221.5±47.7	191.1±39.7	183.9±39.7	-17.0 *
		Correlation with CtBMDv	0.311	0.241	0.296	-4.8
		Correlation with SSIp	0.392	0.315	0.334	-14.8
WBV	13	CTx (ng/mL)	0.84±0.1	0.49±0.1	0.48±0.1	-42.9 *
		Correlation with CtBMDv	0.232	0.392	0.424	+82.8
		Correlation with SSIp	0.363	0.350	0.387	+6.7
		T-AP (U/L)	206.7±53.6	171.9±45.0	167.8±44.1	-18.8 *
		Correlation with SSIp	-0.142	-0.078	-0.058	-59.2
		Correlation with CtBMDv	0.163	0.224	0.235	+44.2

While a group continue with their normal life style (Sedentary), the other underwent 3-weekly whole-body-vibration interventions (WBV group). Table shows means ±SD of plasma cross-laps of C-terminal telopeptide of type I collagen (CTx) and total alkaline phosphatase (T-AP). Pearson correlation coefficients between CTx or T-AP versus CtBMDv (volumetric cortical bone density) and SSIp (strain-stress index) (PQCT indicators of bone material and strength properties) are also shown. (*) p<0.05 calculated with t-test with dependent samples comparing basal data with those obtained at month 12.

Table 2. Bone biochemical markers variations (%) assessed in a sub-group of 32 postmenopausal sedentary and osteopenic women who underwent pQCT analysis after 6 and 12 months of weekly alendronate 70 mg.

postmenopausal women: 0.142-1.351 ng/mL) and total alkaline phosphatase (T-AP) by a kinetic method (DEA; normal range 98-279 U/L). All laboratory and image studies were performed blinded for the analyst at Maimonides University, Buenos Aires.

Safety was monitored during the 12-month follow-up. Adverse effects detection and reports were managed according to the regulatory norms of the country: The National Administration of Drugs, Foods, and Medical Devices in Argentina, Res. 5358-2012 (Regulatory Health Authority), including reporting severe or unexpected events to the Ministry of Health²².

Statistical analyses. SPSS 15 for Windows (SPSS Inc., Chicago) was used. Normality of distributions was determined using Kolmogorov-Smirnov tests. Comparisons between non-paired or paired groups were determined by Student T Test. Pearson and/or Spearman correlations coefficients were determined for two-tailed significant levels upon type of data. Fisher tests assessed the significance of the differences between correlation coefficients. Significance level was fixed at p<0.05.

Ethical aspects. This phase-IV study was approved by Maimonides University Ethical Committee and notified to ANMAT (Ministry of Health Regulatory Agency, file 19518-11-4), and the Join Commission of Health Research (CCIS) of the Province of Buenos Aires as specified by local norms.

Results

The mean changes in CTx and T-AP achieved after 12 months of weekly ALN treatment in the whole sample of 53 postmenopausal sedentary women are resumed in Figure 1. PQCT variations in CTx and T-AP in the sub-groups studied by pQCT (n=32) showed similar results (not shown) being this sub-sample representative of the study population.

There was a significant reduction in CTx and T-AP in both WBV and Sedentary patients, yet without achieving normal values. The WBV women showed a significantly stronger reduction of serum CTx compared with the Sedentary group (-39.3% vs -30.3%, p<0.01) (Table 1 and Figure 1).

No other inter-group difference was found concerning clinical features, with the only exception of higher amounts of basal and mid-time values of visceral tissues in Sedentary than WBV individuals. Nevertheless, both groups matched at the end of the study period (Table 1, Figure 2).

Table 2 shows the correlation coefficients between the CTx or T-AP and the CtBMDv or SSIp at 0, 6, and 12 months of ALN therapy. No significant differences in basal mid-shaft CtBMDv between WBV and Sedentary groups were found (Table 3). Being the CtBMDv a 'tissue' component in the SSIp formula, the differences in SSIp's are therefore suggested to come from the 'geometric' component of the index, i.e. the torsion (polar) CSMI of cortical bone area at the tibia mid-shaft (Tables 2 and 3).

pQCT variables, biochemical marker and correlations	Sedentary group n=19	WBV group n=13
SSip	1532.0 ± 380.2	1331.9 ± 271.4
CtBMDv (mg/cm ³)	1053.6 ± 40.4	1067.5 ± 38.3
SSip / CtBMDv	r= 0.62* p= 0.004	r= 0.81* p= 0.001
Δ%CTx / CTx	r= -0.16 p= 0.52	r= -0.63* p= 0.022
Δ%CTx / CtBMDv	r= -0.51* p= 0.02	r= -0.21 p= 0.5
Δ%CTx / SSip	r= 0.004 p= 0.98	r= 0.03 p= 0.92

While one group remained sedentary, other was subjected to 3-weekly whole-body-vibration intervention (WBV group). The percentages of C-terminal telopeptide of type I collagen variation after 12 months (Δ%CTx) were correlated with basal CTx absolute values, CtBMDv as a cortex material indicator, and SSip as a bone strength indicator. (*) Highly significant correlations, p<0.05.

Table 3. Volumetric bone cortical density (CtBMDv) and strain-stress index (SSip) absolute values assessed at tibia mid-shaft by pQCT and correlation (Spearman) in a sub-group of 32 post-menopausal sedentary osteopenic women treated during 12 months with weekly alendronate.

In the pQCT-analysed sub-groups, basal CtBMDv and SSip values were mutually correlated in both WBV and Sedentary women (Spearman test, r=0.63 and 0.81, p<0.01). Despite that CtBMDv is one of the factors involved in SSip calculation, the CtBMDv-vs-SSip correlations differed between groups. Correlations of CtBMDv or SSip data with basal CTx values were weak (Table 2). After 12 months of ALN treatment, the correlation between CtBMDv or SSip and CTx or T-AP tended to be even weaker in the sedentary group. In contrast, in the WBV group the correlation between Ctx and CtBMDv remained steady, and that with SSip improved. In the WBV group, the correlation between CtBMDv and T-AP was stronger, and that between SSip and T-AP weaker, at the end of the study than at baseline (Table 2). No severe adverse events could be attributed to either ALN or WBV therapies.

Discussion and conclusions

The Sedentary women studied were treated due to their low BMD (DEXA) because of their high fracture risk. Their basal CTx and T-AP values ranked over the normal range, suggesting that average 15 years after menopause their bone metabolism was adapted to daily life style and hormonal status. After one year of treatment, the outcome was as expected in these patients when followed in real practice. ALN administration was more effective in depressing bone resorption in the WBV-treated women than in the Sedentary group.

The underlying mechanism of this interaction is open to discussion. To note, as long as the overall body composition did not differ between groups in this study, these results suggest that the skeletal metabolism should have been

positively impacted by vibration therapy. In this study weekly administration of ALN during 12 months inhibited bone metabolism as expected, averaging about -30% in Sedentary group and -40% in the WBV group. The CV's of both turnover indicators rounded 6-7%, much less than those reported in similar studies using ALN tablets^{14,15,23-31}. Variations look greater in practice than under clinical-trial conditions. The relatively regular outcome in our study was sought by using a drinkable formulation containing already soluble ALN. The smaller variation observed with this type of treatment would have allowed achieving statistical significance of inter-group differences in CTx's¹⁵.

The observed effects on biochemical markers suggest that the selected pharmaceutical formulation of BP reduces the variation of its very low digestive absorption. The available tablets may randomly stick in the upper part of the digestive system, disaggregate slowly, and absorb poorly once the fasting period has been terminated. It is usually recommended to keep at least half an hour fasting after taking oral ALN, yet in practice the compliance with such instruction seems unpredictable²³. In addition, patients in practice may mix the tablets with water or other inadequate beverages. Accordingly, we chose to treat the whole sample with the newer liquid formulation in which the compound is totally soluble, runs quickly to the duodenum, and shows an intra-individual variance of absorption about 3-fold lower than the solid forms^{13,14,15}. In addition, most patients prefer to take the formulation without adding other liquids, thus warranting the lack of pharmaceutical adverse interactions during the upper digestive transit. We believe that by using this improved formulation in frail subjects the differences between groups were hereby more easily demonstrable,

perhaps partly explaining some uncertainties or lower statistical powers in other comparable trials^{25,26}.

The marked inhibition of bone resorption by the addition of WBV over the levels achieved by BP treatment is a clear evidence of both the efficacy of the product and the usefulness of simultaneous WBV therapy which looks desirable in clinical practice²⁶⁻²⁸. However, the clinical significance of such remarkable effect of WBV still remains to be clarified. The WBV impacts on the whole skeleton, but the way it was used here may likely mobilize predominantly the lower spine, hips and lower limbs' bones, as judged by the selected vibration schedule that strains and stresses the bones through muscle forces⁷⁻¹⁰. In these frail, sedentary women the WBV pattern applied in the study was restricted by safety considerations. Hence, just moderate frequency and repeated short periods of expositions were used. Nevertheless, one year of serial applications was regarded as a period long enough to promote bone changes⁷⁻¹⁰.

To note, the new customary physical input may promote an adaptation of the cross section shape and/or structure of any loaded long bone through a spatially-oriented, local modulation of either modeling or remodeling. In fact, high loads acting on bones may be anabolic to these both types of cellular-mediated mechanisms³. In this study, during ALN treatment, the WBV group showed a lower total bone turnover than the Sedentary group. Regrettably, the study design does not differentiate between changes induced by WBV and BP treatments. This constitutes an important limitation of this study due to regulatory reasons. Interestingly, in this study we can speculate that WBV would have enhanced bone resorption with respect to the Sedentary group, being ALN more potent at the active bone remodeling units as reflected by the observed differences in CTx depression between groups. However, the absence of a control group impeded to confirm this hypothesis^{29,30}. Indeed, the drug-induced inhibition and the WBV activation of bone metabolism may have not taken place simultaneously at the same skeletal sites. Hence the bone metabolic fraction which was not inhibited by the drug (ALN weekly schedule is far from achieving a metabolic saturation) may comprise different skeletal components. In other words, WBV might have prevented the ALN-induced inhibition of bone resorption only at the loaded sites, allowing ALN act predominantly at the bone remodeling units activated by disuse. This biomechanical interaction between WBV and ALN treatments was absent in the Sedentary women.

One possible mode of action of the "drug/loading" interaction may be suggested by the fact that, in the WBV sub-group analyzed by pQCT, the bone strength indicator at the tibia mid-shaft tended to associate progressively with the variation in CTx, a trend which was not observed in the Sedentary group. The moderate correlations observed after only one year of treatment suggest the convenience of testing the WBV-ALN association for longer periods, after which more concrete end-points as the incidence of new

skeletal fractures can be shown.

While others have described the relationship between the degrees of ALN-induced inhibition of bone resorption and prevention of new fractures¹⁶, this effect was not fully explained. Our one-year study does not show any adverse interaction between treatments, suggesting but not confirming that the deeper bone metabolism inhibition observed in the WBV group has really contributed to achieve a better bone quality. In fact, both ALN and WBV are used in practice. Moreover, the effects induced by BPs on bone resorption markers in clinical practice resemble those seen in patients treated under controlled conditions, even with less variation attributable to the formulation.

To note, exercise induces bone gain by enlarging bone size in young subjects³¹ but not so in postmenopausal women with osteopenia. The chance to improve bone quality after menopause is limited to re-arranging the bone internal structure in response to daily loadings³¹. A recent cross-over study applying WBV to young men shows that the stimuli affect bone resorption but not bone formation markers³². Although their participants and clinical conditions are quite different from ours, in our study WBV loading improved bone biochemical markers after very short inputs as those induced by following a single-day scheme. Conversely, in an *in vivo* model of OvX rats, it was shown that 12-weeks of WBV improved osseo-integration of hydroxy-apatite-titanium cylindrical implants by down-regulating osteoclastogenesis and up-regulating osteoblast performance, hence bone microstructural indicators were improved after protracted WBV use³³. In this line, there are evidences that long bone fragility in inactive rats cannot be prevented by ALN alone. Hence, BP therapy can be best suited with the physical input³⁴.

Regardless of the huge differences between animal and human osteopenic models, results of this study are rather in agreement with both, the deeper inhibition of bone resorption observed by adding WBV to a BP treatment, and the mild trend to improvement shown by the correlations between bone markers and CtBMD in this study. At any rate, regarding the extra metabolic effects of WBV as related to some re-arrangement of bone structure is an interesting hypothesis. In this study we analyzed these correlations in spite that CtBMDv is one of the factors involved in SSIp calculation, as showing that the achieved reduction of CTx tended to evolve negatively with the SSIp more specifically than with its CtBMDv component in the sedentary group. Furthermore, the evolution in time was positive and less marked in the CtBMDv component in the WBV than in the Sedentary individuals. Some speculations can be elaborated, indeed, but the present study cannot advance further and the findings should be analyzed in futures studies with different designs and technological approaches.

Some limitations of this study must be mentioned. Unfortunately, the one-year follow-up of a 'control' group of postmenopausal women treated with WBV only was not allowed in our country, as long as they certainly could have

some enhanced risk of fractures demanding alendronate.

In conclusion, results show that a 6-12-month WBV treatment added to customary ALN administration in postmenopausal sedentary women with osteopenia/osteoporosis would enhance the ALN-induced inhibition of CTx-assessed bone resorption. This effect may be unrelated to the basal values of indicators of bone mineral status or whole-bone strength. Rather, all the patients react proportionally in a similar way, which is a presumably positive outcome. In this study, patients undergoing WBV tended to improve the association between bone resorption inhibition and bone strength. Bone resorption fell significantly deeper in the WBV group, showing that WBV is safe in this population and enhances the inhibitory effect of ALN on bone resorption. The treatment-induction of bone metabolism to work for a better bone structure can be hypothesized, but protracted treatments will disclose whether this trend remains or not during enough time as to reduce the rate of new skeletal fractures.

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References

- Schoneau E, Neu CM, Beck B. Bone mineral Content per muscle cross-sectional area as an index of the functional muscle bone unit. *J Bone Miner Res* 2002; 17:1095-1101.
- Ferretti JL, Capozza RF, Cointy GR, Capiglionni R, Roldán EJA, Gimenez CR, Zanchetta JR. Densitometric and tomographic analyses of musculoskeletal interactions in humans. *J Musculoskel Neuron Interact* 2000; 1:31-34.
- Nikander R, Kannus P, Rantalainen T, Uusi-Rasi K, Heinonen A, Sievänen H (2010). Cross-sectional geometry of weight-bearing tibia in female athletes subjected to different exercise loadings. *Osteoporos Int* 2010; 21(10):1687-94.
- Chahal J, Lee R, Luo J. Loading dose of physical activity is related to muscle strength and bone density in middle-aged women. *Bone* 2014; 67:41-45.
- Bassey JE. Exercise for prevention of hip fracture. *Age & Aging* 2001; 30(Suppl 4):29-31.
- Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, Harbour RT, Caldwell LM, Cred G. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database of Systems reviews* 2011; Doi: 10.1002/14651858.CD000333.pub2
- Weber-Rajek M, Mieszkowski J, Niespodziński B, Ciechanowska K. Whole-body vibration exercise in postmenopausal osteoporosis. *Prz Menopauzalny* 2015; 14:41-47.
- Rittweger J. Vibration as an exercise modality: how it may work, and what its potential might be. *Eur J Appl Physiol* 2010; 108:877-904.
- Iwamoto J, Takeda T, Sato Y, Uzawa M. Effect of whole-body vibration exercise on lumbar bone mineral density, bone turnover, and chronic back pain in post-menopausal osteoporotic women treated with alendronate. *Aging Clin Exp Res* 2005; 17:157-163.
- Iwamoto J, Sato Y, Takeda T, Matsumoto H. Whole body vibration exercise improves body balance and walking velocity in postmenopausal osteoporotic women treated with alendronate: Galileo and Alendronate Intervention Trail (GAIT). *J Musculoskel Neuron Interact* 2012; 12:136-143.
- Xie L, Choi ES, Busa B, Donahue LR, Miller LM, Rubin CT, Judex S. Low-level mechanical vibrations can influence bone resorption and bone formation in the growing skeleton. *Bone* 2006; 39:1059-1066.
- Christiansen BA, Kotiya AA, Silva MJ. Constrained tibia vibration does not produce an anabolic bone response in adult mice. *Bone* 2009; 45:750-759.
- Braun MJ, Meta MD, Schneider P, Reiners C. Clinical evaluation of high-resolution new peripheral quantitative computerized tomography (pQCT) scanner for the bone densitometry at the lower limbs. *Phys Med Biol* 1998; 43:2279-2294.
- Bell KJ, Hayen A, Irwig L, Hochberg MC, Ensrud KE, Cummings SR, Bauer DC. The potential value of monitoring bone turnover markers among women on alendronate. *J Bone Miner Res* 2012; 27:195-201.
- Gómez Acotto C, Antonelli C, Flynn D, McDaid D, Roldán EJA. Upper gastrointestinal tract transit times of tablet and drinkable solution formulations of alendronate. A bioequivalence and a quantitative, randomized study using video-deglutition. *Calcif Tiss Int* 2012; 91:325-334.
- Roldán EJA, Ferretti JL (chairmen), Bellido T, Cannatta J, Blumel JE, Jee W. Round table: How do anti-osteoporotic agents avoids fractures? *Bone* 2000; 26:393-396.
- Morelli S, Scodelaro Bilbao P, Katz S, Roldán E, Boland R, Santillán GE. Protein Phosphatases: Possible bisphosphonate binding sites mediating stimulation of osteoblast proliferation. *Arch Biochem Biophys* 2011; 507(Issue 2):248-253.
- Capozza RF, Mondelo N, Reina PS, Nocciolino L, Meta M, Roldan EJ, Ferretti JL, Cointy GR. Mineralization- and remodeling-unrelated improvement of the post-yield properties of rat cortical bone by high doses of olpadronate. *J Musculoskel Neuron Interact* 2013; 13(2):185-94.
- Pribyl MI, Smith JD, Grimes GR. Accuracy of the Omron HBF-500 body composition monitor in male and female college students. *Int J Exerc Sci* 2011; 4:93-101.
- Roldán EJA, Bogado CE. Assessment of material, structural, and functional properties of the human skeleton by peripheral quantitative computerized tomography (pQCT) systems. *Curr Osteoporosis* 2009; Rep 7:37-41.
- Roldán EJA, Capiglionni R, Capozza RF, Cointy GR, Ferretti JL. Postmenopausal changes in the distribution of the volumetric BMD of cortical bone. A pQCT study of the human leg. *J Musculoskel Neuron Interact* 2001; 2:157-162.
- Machín MP, Arabetti, C. Entorno regulador de la investigación clínica argentina según la Administración Nacional de Medicamentos, Alimentos y Tecnología Médica. *Acta Médica del Centro* 2009; 3(1): 62-66.
- Brookhart MA, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM, Patrick AR, Mogun H, Solomon DH (2007) Gaps in treatment among users of osteoporosis medications: the dynamics of nono compliance. *Am J Med* 2007; 120:251-256.
- Cryer B, Binkley N, Simonelli C, Lewiecki EM, Lanza F, Chen E, Petruschke RA, Mullen C, de Papp AE. A randomized placebo-controlled, 6-month study of once-weekly alendronate oral solution for postmenopausal osteoporosis. *Am J Geriatr Pharmacother* 2005; 3:127-136.
- Coaccioli S, Celi G, Crapa ME, Masia F, Brandi ML. Alendronate soluble solution: a higher adherence rate in the treatment of osteoporosis.

- Clin Cases Miner Bone Metab 2014; 11:123-125.
26. Brandi ML, Black D (2013) A drinkable formulation of alendronate: potential to increase compliance and decrease upper GI irritation. Clin Cases Miner Bone Metab 2013; 10:187-190.
 27. Delmas PD. Clinical use of biochemical markers of bone remodeling in osteoporosis. Bone 1992; 13(Suppl):S17-S21.
 28. Adachi JD. The correlation of bone mineral density and biochemical markers to fracture risk. Calcif Tissue Int 1995; 59(Suppl 1): S16-S19.
 29. Frost, H. M. (1987). Bone "mass" and the "mechanostat": a proposal. Anat Rec 1987; 219(1):1-9.
 30. Frost HM. Bone's mechanostat: a 2003 update. Anat Rec A: Discov Mol Cell Evol Biol 2003; 275(2):1081-1101.
 31. Hapasalo H, Kontulainen S, Sievanen H, Kannus P, Jarvinen M, Vuori I. Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: A peripheral quantitative computed tomography study of the upper arms of male tennis players. Bone 2000; 27:351-357.
 32. Bembem DA, Sharma-Ghimire P, Chen Z, Kim E, Kim E, Bembem MG. Effects of whole-body vibration on acute bone turnover marker responses to resistance in young men. J Musculoskel Neuron Interact 2015; 15: 23-31.
 33. Zhou Y, Guan X, Liu T, Wang X, Yu M, Yang G, Wang H. Whole body vibration improves osseointegration by up-regulating osteoblastic activity but down-regulating osteoblast-mediated osteoclastogenesis via Erk1/2 pathway. Bone 2015; 71:17-24.
 34. Naruse K, Uchida K, Suto M, Miyagawa K, Kawata A, Urabe K, Takaso M, Itoman M, Mikuni-Takagaki Y. Alendronate does not prevent long bone fragility in an inactive rat model. J Bone Miner Metab 2015; 1-12.