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ORIGINAL ARTICLE

Is there a potential dual effect of denosumab for treatment of osteoporosis and sarcopenia?

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Abstract

Background The prevalence of sarcopenia with osteoporosis results in a higher risk of falling and fractures. It was noted that patients who had completed their planned 5-year denosumab therapy course as treatment for these conditions started to sustain falls.

Purpose To assess (a) whether denosumab has a unique dual effect on both bone and muscle in comparison to other anti-resorptive agents and (b) its effectiveness in the follow-up period post-treatment completion compared to other anti-resorptive agents.

Method One hundred thirty-five patients diagnosed to have postmenopausal/senile osteoporosis and who were prescribed denosumab were compared to a control group of 272 patients stratified into 2 subgroups – 136 prescribed alendronate and 136 prescribed zoledronate. All patients were assessed for: BMD (DXA), falls risk (FRAS), fracture risk (FRAX), and sarcopenia measures. All were re-assessed after 5 years of denosumab/alendronate therapy and 3 years of zoledronate and 1 year after stopping the osteoporosis therapy.

Results No significant baseline demographic differences between the 3 groups. On completion of the 5-year denosumab therapy, there was significant decrease in falls risk ($P=0.001$) and significant improvements in all sarcopenia measures ($P=0.01$). One-year post-discontinuation of denosumab, a significant worsening of both falls risk and sarcopenia measures ($P=0.01$) noticed.

Conclusion Denosumab displayed positive impact and significant improvements in BMD and sarcopenia measures. It also enhanced multidirectional agility as depicted by Timed Up and Go (TUG). Collectively, this would explain the reduction of falls risk which got worse on stopping the medication.

Key points
- *The coexistence of osteoporosis and sarcopenia has been recently considered in some groups as a syndrome termed 'osteosarcopenia'.*
- *Bone and muscle closely interact with each other not only anatomically, but also at the chemical and metabolic levels.*
- *Denosumab displayed positive impact and significant improvements in all sarcopenia measures, and enhanced multidirectional agility with consequent reduction in falls risk.*
- *Denosumab can be considered as a first osteoporosis therapeutic option in this group of patients presenting with osteosarcopenia manifestations.*

Keywords Osteoporosis · Sarcopenia · Treatment · Alendronate · Denosumab · Zoledronate

Introduction

The coexistence of osteoporosis and sarcopenia has been recently considered in some groups as a syndrome termed "osteosarcopenia". Osteoporosis describes low bone mass and deterioration of the micro-architecture of the bone [1], whereas sarcopenia is defined as a type of muscle loss

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(muscle atrophy) that occurs with aging and/or immobility. It is characterized by the degenerative loss of skeletal muscle mass, quality, and strength [2].

Bone and muscle closely interact with each other not only anatomically but also chemically and metabolically [3]. Based on this relationship, osteoporosis and sarcopenia share similar risk factors, highlighting muscle-bone interactions, which may result in debilitating consequences, such as falls, fractures, and hospitalizations [4].

The rate of muscle loss in sarcopenia is dependent on exercise level, comorbidities, nutrition, and other factors [2]. The international agreement by the European Working Group on Sarcopenia considers low muscle strength as a key characteristic of sarcopenia, uses detection of low muscle quantity and quality to confirm the diagnosis of sarcopenia, and identifies poor physical performance as indicative of severe sarcopenia [5].

The decline of muscle and bone strength manifests clinically in the form of the reduction of mobility and functionality, greater predisposition to falls, fractures, functional dependence, as well as increased morbidity and mortality risk. Older adults who sustain osteosarcopenia generally require more health care and specialized long-term care which represents high costs and considerable social impact [6].

Osteosarcopenia can be evaluated using imaging methods (i.e., dual-energy X-ray absorptiometry). DXA has the advantage of quantifying both muscle and bone mass. Osteosarcopenia can be also evaluated by assessing muscle strength (i.e., grip strength) and functional capacity (i.e., gait speed). A comprehensive geriatric assessment including medical history should expand to encompass osteoporosis and sarcopenia risk factors. Treatment of this syndrome should include osteoporotic drugs (bone anabolics/antiresorptives (such as teriparatide, denosumab, bisphosphates) where indicated, as well as progressive resistance and balance exercises for at least 2–3 times/week. To maximize musculoskeletal health, nutritional recommendations (protein: 1.2–1.5 g/kg/day; vitamin D: 800–1000 IU/day; and calcium: 1300 mg/day) must also be met [7].

It was proved that bone remodeling and homeostasis are mainly controlled by the receptor-activator of nuclear factor kB (RANK), its ligand RANKL, and the soluble decoy receptor osteoprotegerin (OPG) pathway. The binding of RANKL to its cognate receptor RANK leads to a cascade of signaling events triggering differentiation, activity, and survival of osteoclasts. Osteoprotegerin (OPG) is a soluble decoy receptor that binds to RANKL, preventing its interaction with RANK and thus restraining osteoclastogenesis and preventing bone loss [8]. This bone pathway extends beyond bone remodeling to involve muscle atrophy and dysfunction [9]. It was found that fully differentiated skeletal muscles express RANK on the membranes of fast- and slow-twitch myofibers. Despite a strong association between osteoporosis and skeletal muscle dysfunction, the biological pathway that regulates bone and skeletal muscle pathophysiology remains unclear [10]. Consequently, a monoclonal antibody targeting RANKL, denosumab (Dmab), has been shown to reduce fracture risk and is broadly used to treat osteoporosis [11]. Interestingly, it was noted that the incidence of falls reduced after starting Dmab therapy, whereas the incidence of falls increased once again after stopping Dmab therapy. These observations led us to hypothesize that RANKL inhibitors could exert a positive influence on muscle mass and strength, particularly in conditions of osteoporosis and/or sarcopenia.

This study was undertaken to compare the therapeutic effect of Dmab to the established osteoporotic treatment (zoledronate Zol, alendronate Aln) on sarcopenia and to assess the relationship between osteoporosis and sarcopenia.

Materials and methods

Study design

The work was a longitudinal multicenter, controlled, prospective study.

Ethical standards

Local ethical approval for the study was gained and methodological protocols followed. In accordance with the principles of the Declaration of Helsinki (2008), patients who were invited to participate in the study were given comprehensive information about the purpose of the study, assurance of data protection, confidentiality, and signed an informed consent form.

Target population and case definition

Patients eligible for the study were approached as soon as a diagnosis of osteoporosis was established.

Inclusion criteria:

- Patients diagnosed to have postmenopausal/senile osteoporosis.
- Diagnosis of osteoporosis was based on DXA scan (T-score at the spine/hip − 2.5) and/or absolute fracture risk score (FRAX) of > 20% for major osteoporosis fracture or > 3% for hip fracture.

Exclusion criteria:

- Patients diagnosed with pathological fractures.

Process of patients' stratification

Patients included in this study (Fig. 1) are classified into two groups: Study group (135 patients) and control group (272 patients). The control group patients were stratified into 2 subgroups of 136 patients in each.

Patients' eligibility and enrolment onto the study were undertaken by one of the authors who was not involved in the process of stratifying the patients into the three study groups. Participants were not aware of their classification either in the study or the control group.

Study (active) group: This included 135 osteoporotic patients who received Dmab therapy. This included 70 patients who received Dmab as first line of osteoporosis therapy)patients have contra-indication to bisphosphonate therapy) and 65 patients who received former bisphosphonate therapy, and Dmab was their second treatment option. Those 65 patients switched to Dmab received formerly bisphosphonate therapy in the form of Aln (24 patients), risedronate (21 patients), or Zol (20 patients). The patients stopped the bisphosphonate therapy for intolerability, side effects, or lack of efficacy. Medical history was taken with thorough clinical examination for every patient. Baseline assessment included: osteoporosis, (1) bone mineral density (BMD) using dual x-ray absorptiometry (DXA) (Hologic), (2) blood tests for osteoporosis bone profile (calcium, phosphorus, alkaline phosphatase, vitamin D, kidney functions), and (3) fracture risk using (FRAX), and falls – falls risk was evaluated by using the self-reported falls risk assessment score (FRAS) [12].

Diagnosis and assessment of sarcopenia: Patients were evaluated based on the revised European consensus on definition and diagnosis of sarcopenia [5]. Assessment for sarcopenia was mainly based on physical muscle strength and performance. This included (1) physical muscle strength, assessed by testing for handgrip strength using a calibrated dynamometer (the best of three trials of the dynamometer testing was recorded), and (2) physical performance: (a) short physical performance battery (SPPB), (b) Timed Up and Go (TUG), and (c) the 4-m walk gait speed [13].

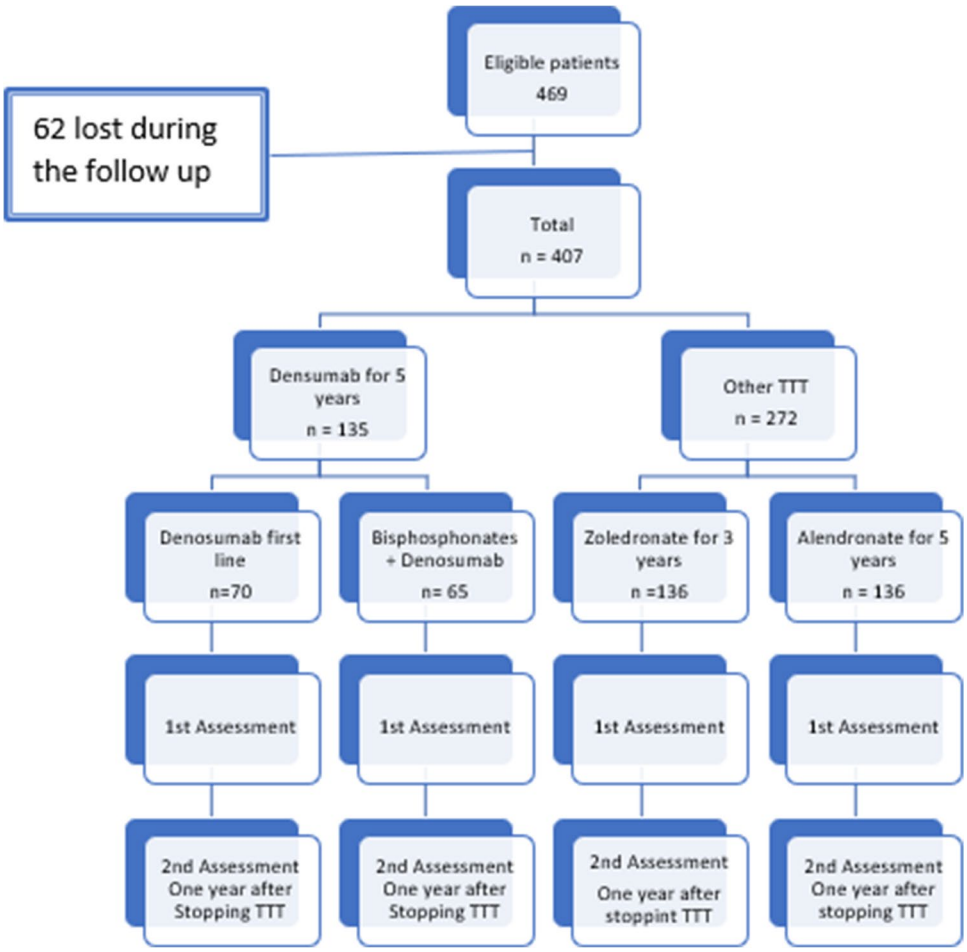

Fig. 1 Flowchart for the patients included in this study

Control group: Patients were stratified into 2 subgroups: a subgroup which included 136 patients who were treated with Zol, once yearly 5 mg IV injection, and another subgroup of 136 patients treated with once weekly with oral Aln 70 mg.

Both groups were assessed for the baseline parameters as in the Dmab therapy.

Duration of osteoporosis therapy: National guidelines for osteoporosis management were followed [14]. Both Dmab and Aln therapy cohorts received treatment for 5 years, whereas the group of patients who received Zol therapy took it for 3 years.

Follow-up: All patients were assessed at 6 months and then at 2 years of osteoporosis therapy for BMD and FRAS. After completion of osteoporosis therapy duration which was 5 years for the Dmab and Aln groups of patients and 3 years for the Zol group of patients, all the baseline measures were reassessed. One year after discontinuing the osteoporosis therapy, all the patients, in both the active and control group, had a repeat assessment for falls and sarcopenia. All patients took supplement therapy of calcium and vitamin D on a daily basis. Patients with vitamin D deficiency/insufficiency were treated with vitamin D supplementation before starting the osteoporosis therapy.

Outcome measures: Primary: Whether Dmab has a unique dual effect on both bone and muscle in comparison to other anti-resorptive agents.

Secondary: Its effectiveness in the follow-up period post-treatment completion compared to other anti-resorptive agents.

Statistical analysis: Data are collected and entered into a database for data management and statistical analysis. Categorical variables are expressed as number and percentage, i.e., frequency tables, while quantitative scaled variables are presented as mean and standard deviation.

Alpha error was always set at 0.05. All statistical manipulation and analyses were performed using the 16th version of SPSS.

Results

Assessment of the demographics (Table 1) did not reveal any significant difference between the 3 groups in terms of age, BMI, and bone profile (serum calcium, phosphorous, alkaline phosphatase). Similarly, laboratory tests did not reveal any significant difference regarding the kidney functions between the 3 patient groups. In comparison to the baseline, there is significant increase in the BMD at both spine and hip; vitamin D levels and significant decrease in FRAX in the 3 groups, Dmab /Zol/Aln ($P=0.001$) at 5, 3, and 5 years of treatment respectively (Table 2). In the Dmab group, at 5 years of therapy, there was highly significant decrease in falls risk score (-1.9, 95% CI $= -2.8$ to -0.7; $P=0.001$), significant improvements in the grip strength ($+4.3$ kg, $P=0.01$), TUG (1.5 s; 95% CI $= -2.2$ to 0.1; $P=0.001$), and gait speed (0.1 m/s; 95% CI $=0.03$–0.2; $P=0.001$).

Table 3 shows a comparison between Post-treatment measures of Dmab, Zol, and Aln therapy, stratified according to the patients' sex. There was no significant difference on comparing the sarcopenia measures as well as BMD between the subgroup who received Dmab as a first osteoporosis treatment option and the subgroup who received Dmab as a second osteoporosis treatment option. Both subgroups showed significant improvement of the BMD and

Table 1 Demographic data and baseline measures of osteoporotic patients included in the study stratified according to the patients' sex

	Females (303 patients)					Males (104 patients)				
	Aln Mean ± SD	Zol Mean ± SD	Dmab Mean ± SD	*F* value	*P* value	Aln Mean ± SD	Zol Mean ± SD	Dmab Mean ± SD	*F* value	*P* value
BMI	28.7 ± 2.0	28.9 ± 2.0	28.8 ± 2.3	.107	.898	28.5 ± 1.67	28.7 ± 1.7	28.3 ± 2.02	.341	0.712
DXA spine	−2.9 ± 0.2	−2.9 ± 0.2	−2.8 ± 0.2	.076	.926	−2.8 ± 0.2	−2.9 ± 0.3	−2.8 ± 0.3	.165	0.848
DXA hip	−2.69 ± 0.17	−2.69 ± 0.18	−2.69 ± 0.17	.010	.990	−2.7 ± 0.17	−2.6 ± 0.19	−2.6 ± 0.18	.112	0.894
Calcium	2.19 ± 0.007	2.19 ± 0.007	2.19 ± 0.007	.006	.994	2.1 ± 0.007	2.2 ± 0.005	2.1 ± 0.006	3.04	0.62
Vitamin D	52.88 ± 7.19	52.88 ± 7.19	52.88 ± 7.19	.000	1.000	54.9 ± 7.88	54.6 ± 7.76	54.7 ± 7.23	.203	.817
FRAX major	20.58 ± 2.06	20.58 ± 2.06	20.51 ± 2.16	.037	.964	20.71 ± 2.26	20.57 ± 2.19	20.74 ± 2.27	.055	.946
FRAX hip	3.75 ± 0.56	3.74 ± 0.57	3.74 ± 0.58	.013	.987	3.86 ± 0.63	3.83 ± 0.6	3.85 ± 0.61	.024	.976
FRAS	2.96 ± 0.95	2.95 ± 0.94	2.92 ± 0.95	.052	.949	3.01 ± 0.66	2.92 ± 0.81	3.04 ± 0.83	.212	.81
Grip St	21.37 ± 3.21	21.37 ± 3.21	21.36 ± 3.20	.000	1.000	32.7 ± 5.1	32.5 ± 4.8	32.6 ± 4.9	.014	.986
TUG	10.0 ± 1.4	10.0 ± 1.4	10.2 + 1.9	.001	.999	10.34 ± 1.9	10.3 ± 1.8	9.9 ± 1.4	.005	.995
4-m walk	1. 06 ± 0.06	1. 06 ± 0.06	1. 06 ± 0.06	.002	.998	1.187 ± 0.8	1.188 ± 0.9	1.191 ± 0.9	.024	.976

**SD* standard deviation. *Aln* alendronate, *Zol* zoledronate, *Dmab* denosumab

Table 2 Comparison between both bone mineral density as well as sarcopenia measures of the Dmab, Zol, and Aln groups at baseline and after therapy

	Zoledronate			Alendronate			Denosumab		
	Base line	After 3 years (SD)	*P* value	Base line (SD)	After 5 years (SD)	*P* value	Base line (SD)	After 5 years (SD)	*P* value
DEXA Spine	−2.89 (0.24)	−2.26 (0.17)	<0.001	−2.89 (0.24)	−2.25 (0.17)	<0.001	−2.89 (0.25)	−2.26 (0.17)	<0.001
DEXA hip	−2.69 (0.18)	−2.26 (0.14)	<0.001	−2.69 (0.18)	−2.26 (0.15)	<0.001	−2.69 (0.18)	−2.27 (0.14)	<0.001
Calcium	2.19 (0.007)	2.20 (0.06)	0.110	2.19 (0.005)	2.20 (0.05)	0.140	2.19 (0.008)	2.20 (0.07)	0.104
Vitamin D	53.34 (7.3)	58.48 (6.1)	<0.001	53.40 (7.4)	58.54 (6.2)	<0.001	53.10 (7.2)	58.36 (6.1)	<0.001
FRAX major joints	20.6 (2.1)	12.1 (1.4)	<0.001	20.6 (2.1)	12.1 (1.5)	<0.001	20.6 (2.2)	12.1 (1.4)	<0.001
FRAS	2.93 (0.9)	2.91 (0.9)	0.181	2.97 (0.88)	2.96 (0.87)	0.252	2.92 (0.9)	1.9 (0.7)	<0.001
Grip strength (Kg)	24.2 (6.1)	25.7 (6.5)	<0.05	24.3 (6.2)	25.4 (6.5)	<0.05	24.2 (6.1)	28.5 (6.1)	<0.001
TUG (sec.)	10.1 (1.5)	9.4 (1.3)	<0.05	10.1 (1.6)	9.3 (1.3)	<0.05	10.1 (1.6)	8.6 (1.2)	<0.001
4-m walk (m/sec)	1.09 (0.09)	1.16 (0.11)	<0.05	1.1 (0.09)	1.17 (0.1)	<0.05	1.1 (0.09)	1.43 (0.1)	<0.001

SD standard deviation

Table 3 Comparison between Post-treatment measures of Dmab, Zol, and Aln therapy, stratified according to the patients' sex

	Females						Males				
		N	Mean	SD	*F*	Sig	*N*	Mean	SD	*F*	Sig
DXA spine	Aln	101	−1.5406	4.12512	.000	1.000	35	−2.2543	.18684	.051	.950
	Zol	101	−1.5436	4.12556			35	−2.2686	.19519		
	Dmab	101	−1.5436	4.12556			34	−2.2647	.19677		
DXA hip	Aln	101	−2.2683	.14692	.002	.998	35	−2.2343	.14337	.409	.665
	Zol	101	−2.2693	.14611			35	−2.2514	.13799		
	Dmab	101	−2.2693	.14611			34	−2.2647	.13901		
Calcium	Aln	101	2.2036	.07021	.000	1.000	35	2.1974	.00505	.164	.849
	Zol	101	2.2036	.07021			35	2.1969	.00530		
	Dmab	101	2.2036	.07021			34	2.1968	.00535		
Vitamin D	Aln	101	57.5644	5.75919	.000	1.000	35	61.3714	6.76099	.081	.922
	Zol	101	57.5644	5.75919			35	61.1143	6.54744		
	Dmab	101	57.5644	5.75919			34	60.7353	6.43527		
FRAS	Aln	101	2.941	.92002	47.706	.000	35	2.9714	.74698	23.720	.000
	Zol	101	2.90	.92002			35	2.917	.80570		
	Dmab	101	1.9158	.72825			34	1.9265	.55230		
FRAX Major	Aln	101	12.1485	1.53223	.001	.999	35	12.1429	1.28665	.016	.984
	Zol	101	12.1584	1.50155			35	12.1714	1.22440		
	Dmab	101	12.1584	1.50155			34	12.1176	1.20012		
FRAX Hip	Aln	101	2.6010	.24678	.001	.999	35	2.5400	.21989	.137	.872
	Zol	101	2.6050	.24915			35	2.5571	.22134		
	Dmab	101	2.6079	.24400			34	2.5676	.22391		
Grip strength	Aln	101	23.5198	3.25297	14.964	.000	35	27.3343	4.65466	13.805	.000
	Zol	101	23.5297	3.25228			35	27.8200	4.64776		
	Dmab	101	25.666	3.13018			34	31.315	4.74534		
TUG	Aln	101	9.462	1.20847	11.021	.000	35	9.198	1.60662	10.005	.000
	Zol	100	9.588	1.21812			35	9.204	1.61715		
	Dmab	101	8.772	1.04241			34	8.500	1.68990		
4-m walk	Aln	101	1.066	.09484	9.046	.00	35	1.267	.10140	11.013	.00
	Zol	100	1.0710	.09684			35	1.257	.10090		
	Dmab	101	1.2695	.09752			34	1.5935	.09319		

SD standard deviation

sarcopenia measures in comparison to the baseline measures ($P < 0.001$). Zol and Aln showed significant improvement, TUG (0.7 and 0.8 s; $P = 0.05$) and gait speed (0.07 and 0.07 m/s; $P = 0.05$) respectively, however, there was no significant change in the falls risk ($P = 0.18$ and 0.25, respectively). One year after stopping Dmab, there is significant worsening of the falls risk score, grip strength, TUG, and gait speed ($P = 0.001$) (Table 4). There is no difference in all the measures 1 year after stopping Zol and Aln (Table 4).

Discussion

This study was carried out to assess whether Dmab exhibits a unique positive impact on measures of sarcopenia, namely skeletal muscle strength and physical performance which may underlie the reductions in fall rates. Results of the study revealed that Dmab not only improved the BMD, but also it reduced falls risk. In comparison to bisphosphonates, Dmab showed the highest significant positive effect on both the physical performance and skeletal muscle strength. This is evidenced by improvement of the gait speed, TUG and 4-m walk test ($P < 0.001$) in the Dmab group, versus 0.05 in the Aln and Zol group). These results agree with the outcomes of the FREEDOM (Fracture Reduction Evaluation of Dmab in Osteoporosis every 6 months) trial which revealed that not only Dmab treatment reduced the risk of vertebral, nonvertebral, and hip fracture over 36 months, but also the Dmab-treated group had fewer falls (4.5%) compared to the other groups (5.7%) ($P = 0.02$) [15].

This data highlights that osteoporosis and sarcopenia may share similar underlying risk factors and that the muscle-bone interactions are important to minimize the risk of falls, fractures, and hospitalizations [16]. The biological mechanisms linking the bone and muscle enzyme are indistinct and necessitate further investigation. A study published in the American Journal of Physiology (Cell Physiology) revealed that RANK is expressed in fully differentiated C2C12 myotubes and skeletal muscles [17]. Further research found that deletion of muscle RANK favorably guards fast-twitch fibers. Fast-twitch fibers are important for brief and powerful muscle contractions. They are mainly affected whether indirectly or directly in aging and in variable forms of muscle disease as well as chronic illness such as congestive heart failure, chronic heart disease, diabetes, renal failure, and chronic obstructive pulmonary disease. Furthermore, recent studies [11, 18] tested the effect of Dmab on animals and humans (postmenopausal women). The authors reported that RANKL deteriorates, while its inhibitor improves the muscle strength and insulin sensitivity in osteoporotic mice and humans. These data demonstrate that the role played by RANK/RANKL/OPG pathway extends beyond bone health and that skeletal muscles as well as other tissues may share the RANK/RANKL/OPG pathway as a common denominator [18]. The persistence of the positive impact of Dmab on both the bones and muscles regardless of whether Dmab was given as first or second osteoporosis treatment option confirms the dual effect of the medication at both sites.

Table 4 Osteosarcopenia and falls risk assessment in patients on Dmab after 1 year from stopping treatment

	After 5 years	One year after stopping TTT	*P* value
Grip strength	28.5 (6.1)	26.6 (6.2)	< 0.001
TUG (s)	8.6 (1.6)	9.3 (1.4)	< 0.001
4-m walk speed (m/s)	1.2 (0.1)	1.01 (0.08)	< 0.001
FRAS	1.9 (0.7)	2.9 (0.7)	< 0.001

Dmab has a half-life of 25–32 days with its effects dissipating within 6 months of the cessation of treatment, as opposed to bisphosphonates which accumulate and persist in bone for years after stopping therapy [19–21]. This was the reason for choosing 12-month period after stopping the medications to assess for the changes in the bone and muscles. The rebound effect noted 1 year after stopping treatment with Dmab, evidenced by rapid loss of the gains in the sarcopenia measures achieved with treatment can explain the ricochet increase of falls risk to pre-treatment levels. This comes in concordance to its rebound effect on bones where rapid loss of the gains in bone mineral density has been reported. An earlier study revealed that stopping Dmab after long-term exposure resulted in losses of the bone mineral density of large magnitude at all measured sites. One-year after discontinuation, bone mineral density had decreased by − 9.1% (lumbar spine) and − 12.7% (total hip) vs. year 10 of Dmab therapy [22].

This study revealed significant improvement in the muscle strength and performance in the cohort of patients taking bisphosphonates (both Aln and Zol), yet there was no significant reduction in the falls risk. The bisphosphonate positive impact on muscles has been reported. A case cohort study by Park et al. reported increased grip strength with combination Aln and calcitriol, but no change in muscle mass [23]. In another retrospective cohort, case–control study [24], Aln therapy was associated with increased 2.5-fold of the appendicular muscle mass and 4.4-fold of the lower limb muscle mass compared to the controls, even after adjusting for initial muscle mass. The Aln possible association of increased muscle mass has been attributed to a direct action on muscle cells induced by proliferation of muscle cells or activates muscle metabolism via a direct pharmacological action on as yet unknown muscle stem cells or myocytes. An indirect action has also been postulated, through the positive impact of Aln on bone metabolism, based on the well-understood suppression of osteoclasts, inducing a secondary muscle improvement state [25, 26]. Another hypothesis was assumed based on the Aln-induced increase of bone strength and lower fracture risk while also reducing pain, improving activities of daily living [27], and raising quality

of life [28]. Improvement in activities of daily living may be linked to improved muscle mass through increased movement. On the other hand, Vitamin D preparations have also been associated with increase in the both bone and muscle mass [29, 30]. All patients included in this study were taking supplement calcium and vitamin D therapy.

The assessment of body composition using DXA scanning pre- and post-Dmab therapy was not carried out in this work and can be considered as a limitation in this study.

In conclusion, Dmab displayed positive impact and significant improvements in all sarcopenia measures and enhanced multidirectional agility as depicted by TUG. Collectively, this would reflect and explain the reduction of falls risk associated with Dmab therapy. Osteoporosis and sarcopenia share similar risk factors, highlighting muscle-bone interactions, which may result in falls and fractures. RANK/RANKL/OPG pathway, which is a key regulator of bone homeostasis, may contribute also to the regulation of skeletal muscle integrity and function. In addition to its role as a treatment for osteoporosis, Dmab could be considered a novel therapeutic approach for sarcopenia. Consequently, Dmab can be considered as a first osteoporosis therapeutic option in this group of patients presenting with osteosarcopenia manifestations. Measures should be considered to maintain the positive Dmab effects on muscle strength and physical performance after stopping the treatment.

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Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dr. Yasser El Miedany, Dr. Maha El Gaafary, Dr. Mathias Toth, Dr. Mohamed Osama Hegazi, Dr. Nadia El Aroussy, Dr. Waleed Hassan, Dr. Samah Almedany, Dr. Annie Nasr, Dr. Sami Bahlas, and Dr. Salwa Galal. The first draft of the manuscript was written by Dr. Salwa Galal and Prof. Yasser El Miedany. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability All data and material are available and will be sent when required.

Code availability Not applicable.

Declarations

Consent for publication All listed authors have seen and approved the final version of the manuscript.

Conflict of interest Yasser El-Miedany, Maha El Gaafary, Mathias Toth, Mohamed Osama Hegazi, Nadia El Aroussy, Waleed Hassan, Samah Almedany, Annie Nasr, Sami Bahlas, and Salwa Galal declare that they have no conflict of interest and have full control of all primary data and that they agree to allow the journal to review their data if requested.

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