Original paper

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Effects of antiresorptive agents on body composition: a case-control retrospective study

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Abstract

Introduction: Osteoporosis is the most represented metabolic bone disease and is characterized by the reduction of bone mineral density (BMD), exposing patients to high fracture risk and disability. Bisphosphonates (BPs) are the main compounds exploited in treatment of osteoporosis and significantly reduce fracture risk. Sarcopenia is the pathological reduction of muscle masses and strength, and many studies highlighted its co-existence in patients with impaired bone mass. Indeed, the pathological reduction of lean tissue has been linked to a higher risk of falls and, consequently, fractures and disability. Moreover, the pathological reduction of lean tissue seems to share many pathological mechanisms with impaired bone strength and structure; thus, in this context, we decided to conduct a retrospective case-control study aimed at evaluating the effects of BPs on lean mass and body composition.

Material and methods: We enrolled postmenopausal women from our metabolic bone diseases outpatient clinic who underwent at least two consecutive dual-energy X-ray absorptiometry (DXA) examinations concomitantly to the beginning of an antiresorptive agent. The body composition of patients and controls was compared by fat masses, lean masses and android-to-gynoid ratio (A/G ratio).

Results: A total of 64 female subjects were considered for the study: 41 starting a BPs and 23 without treatment were used as control. The fat masses and lean masses appeared to be unaffected by BPs. Conversely, A/G ratio was lower in BPs group after 18 months of therapy compared to baseline ($p < 0.05$). From the stratification based on the single BP we failed to highlight any significant difference between the tested variables.

Conclusions: Bisphosphonates treatment did not modify lean tissues, however a significant reduction of A/G ratio in BP group was documented. Thus the BPs seems to act on patients body composition and extra-skeletal tissues but larger prospective studies are needed to evaluate whether these modifications have clinical relevance.

Key words: antiresorptive agents, bisphosphonates, dual-energy X-ray absorptiometry, sarcopenia, body composition.

Introduction

Osteoporosis is the most represented metabolic bone disease and is characterized by the reduction of bone mineral density (BMD), exposing patients to a high fracture risk and disability [1].

Bisphosphonates (BPs) are the corner stone of osteoporosis treatment and are successfully exploited in reducing fracture risk. Sarcopenia is the pathological reduction of muscle masses and strength according to the latest European Working Group of Sarcopenia definition [2], and many studies highlighted its strict

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association with impaired bone metabolism as well as osteoporosis [3].

Although there are several effective therapies for low BMD, this is not true for sarcopenia; indeed, the only real therapeutic alternatives for the pathological reduction of lean tissue are represented by physical exercise and the implementation of a correct dietary approach [4].

Moreover, sarcopenia seems to share many pathological mechanisms with osteoporosis; thus, in this context, we decided to conduct a retrospective case-control study aimed at evaluating the effects of BPs on body composition with particular attention to lean masses.

Material and methods

Study design

We enrolled postmenopausal women from our metabolic bone diseases outpatient clinic who underwent at least two consecutive dual-energy X-ray absorptiometry (DXA) examinations concomitantly to the beginning of an antiresorptive agent.

The dual-energy X-ray absorptiometry machinery used was a Lunar Prodigy® version 1.72 which underwent daily calibration as suggested by the manufacturer. We retrospectively collected the variables over a standard 18-month observation period.

The body composition of patients and controls was compared by fat and lean masses of total body, appendicular lean mass (ALM, kg/m^2) was calculated as the sum of fat-free mass minus bone mineral content of lower and upper limbs, skeletal muscle mass index (SMI, kg/m^2) was calculated as ALM divided by height squared according to Baumgartner's criteria [5].

A low muscle mass was identified for women when it was found to be 2 SD below the mean of young adults (women: < 5.5 kg/m^2). The dual-energy X-ray absorptiometry scansions were performed by a trained physician with more than 10 years of experience in the field. Anthropometric variables such as weight, height, body mass index (BMI), concomitant medications, and main diseases were investigated.

Exclusion criteria

Exclusion criteria which forbid the patients from being considered in the present study were diabetes, autoimmune diseases, cancer, neurological disorders, malabsorption syndromes, inflammatory arthropathies, renal and cardiovascular impairment (NYHA III–IV).

Study populations

We divided our patients in two groups: those starting a BPs and those without impaired bone metabolism (that underwent a DXA scan for being postmenopausal) were used as control. Anthropometric variables are reported in Table I.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 8.4.2 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. Age, postmenopausal age, body mass index (BMI, kg/m^2), total body lean mass (TBLM, kg), total body fat mass (TBFM, kg), SMI (kg/m^2) and android-to-gynoid ratio (A/G ratio) were analyzed with descriptive statistics, normality was checked with Shapiro-Wilk test and Wilcoxon test was used to compare each studied variable at baseline and after 18 months in each group. Subsequently, statistical analysis was repeated after BPs stratification.

Ethical standards

This study was conducted in accordance with the Declaration of Helsinki and its late amendments, moreover it was approved by the Local Ethical Committee (protocol number 22271).

Results

We enrolled 64 female patients: 41 starting a BP and 23 patients without treatment were used as control. Age appeared to be higher in BPs group compared to control group, BMI and postmenopausal age were similar between groups (Table I).

The skeletal muscle mass index, TBLM and TBFM appeared to be unaffected by BPs. Conversely, A/G ratio was lower in BPs group after 18 months of therapy compared to baseline observation ($p < 0.05$) (Table II).

The subsequent stratification for BPs failed to highlight any significant difference regarding body composition at end of study compared to baseline (Table III).

Table I. Anthropometric variables between groups

Parameters	Bisphosphonates (n = 41)	Controls (n = 23)	Bisphosphonates vs. controls
Age [years]	79.88 ±11.08	72.34 ±6.64	$p < 0.05$
Body mass index [kg/m^2]	23.86 ±4.04	24.51 ±2.97	$p < 0.05$
Postmenopausal age [years]	47 ±5.56	48.23 ±8.15	$p < 0.05$

Table II. Effects of antiresorptive treatments on body composition measured with dual-energy X-ray absorptiometry

Bisphosphonates vs. controls groups	Parameters – baseline observation	Parameters – after 18 months of therapy	*p*-value
Skeletal muscle index [kg/m^2]			
Bisphosphonates (n = 41)	6.24 ±0.74	6.36 ±0.86	$p > 0.05$
Controls (n = 23)	6.23 ±0.78	6.16 ±0.82	$p > 0.05$
Android-to-gynoid ratio			
Bisphosphonates	1.02 ±0.21	0.99 ±0.2	$p > 0.05$
Controls	0.99 ±0.16	1 ±0.17	$p > 0.05$
Total body fat mass [kg]			
Bisphosphonates	22.21 ±7.64	22.43 ±8.49	$p > 0.05$
Controls	24.52 ±8.03	24.63 ±8.07	$p > 0.05$
Total body lean mass [kg]			
Bisphosphonates	37.22 ±4.89	37.31 ±5.33	$p > 0.05$
Controls	37.07 ±4.64	36.98 ±4.68	$p > 0.05$

Discussion

Sarcopenia and cachexia are transversal problems in medicine and their prevalence is high among elderly patients as much as osteoporosis and fractures. The cornerstone of osteoporosis treatment passes through the fracture risk estimation, achieved with scores such as fracture risk assessment tool (FRAX) that is highly exploited in the clinical decision to identify treatment threshold. Nevertheless, most scores do not take into consideration the sarcopenia as a major risk for frailty fractures [6].

Indeed, it is well known that the reduction of muscle tissue representation is related to a higher incidence of falls and, consequently, fractures and disability. Although for osteoporosis the physician disposes of a plenty of drugs such as anti-resorptive therapies and anabolic treatments (abaloparatide, teriparatide and romosozumab) there is a lack of real therapeutic options for the pathological reduction of muscle masses [7].

Indeed, although some molecules are under study, the state of the art of the clinical management of sarcopenia is based on the implementation of physical activity and on the correct nutritional intake. Moreover, muscle and skeletal tissue cannot be considered as two separate entities, but as an endocrinologically, immunologically, and mechanically united syncytium [8].

Previous papers documented the positive effect of BPs on lean tissues after burn-injuries [9]. The BPs are molecules classified in 3 generations which differ for mechanism of action: the first generation of BPs (clodronate, etidronate, tiludronate) are incorporated as adenosine tri-phosphate analogues by osteoclasts on bone surface and induce their apoptosis, whether second and third BPs generations (nitrogen containing: risedronate, ibandronate, alendronate, pamidronate, and zoledronic acid) are capable to interfere with the mevalonate pathway by inhibiting farnesyl pyrophosphate synthase [10].

A previous paper, aimed at investigating the role of BPs alone or enriched with highly dense protein supplements in patients that underwent hip replacement after fracture, failed to highlight any significant difference in BPs treated group against control [11].

In line with these observations, the present study could not demonstrate any positive effect of antiresorptive agents on lean masses: our group of patients treated with BPs displayed any significant change in SMI compared to baseline. Furthermore, by displaying a different mechanism of action the second and third generation of BPs are held responsible for their extra-skeletal effects such as anti-tumoral activity and cardiovascular risk reduction [12].

Indeed, A/G ratio has been widely linked to an increased cardiovascular risk in literature [13] and, in accordance with this evidence [13], we highlighted the reduction of A/G ratio at end of study when compared to baseline in patients undergoing treatment with BPs.

This observation could be possibly linked to the extra-skeletal and cardioprotective effects of BPs. Nevertheless, after BPs stratification, we failed to highlight any significant difference between baseline and end of study regarding body composition variables.

Study limitations

This study has several limitations mainly bound to its retrospective nature: the age of patients appeared to be higher in BPs group compared to controls, therefore this difference may have influenced the results section;

Table III. Body composition analysis according to bisphosphonates stratification

Bisphosphonates	Parameters – baseline observation	Parameters – after 18 months of therapy	*p*-value
Skeletal muscle index [kg/m^2]			
Alendronate (16)	6.49 ±0.68	6.54 ±0.83	$p > 0.05$
Zoledronate (9)	6.22 ±0.90	6.22 ±1.15	$p > 0.05$
Risedronate (7)	6.19 ±0.60	6.34 ±0.74	$p > 0.05$
Ibandronate (4)	6.22 ±0.07	6.53 ±0.32	$p > 0.05$
Clodronate (3)	5.45 ±0.62	6.00 ±0.66	$p > 0.05$
Neridronate (2)	6.61 ±1.75	6.59 ±1.67	n.a.
Android-to-gynoid ratio			
Alendronate	1.07 ±0.14	1.07 ±0.14	$p > 0.05$
Zoledronate	1.03 ±0.27	1.03 ±0.28	$p > 0.05$
Risedronate	1.05 ±0.15	0.99 ±0.13	$p > 0.05$
Ibandronate	0.93 ±0.03	0.79 ±0.17	$p > 0.05$
Clodronate	0.92 ±0.05	0.91 ±0.07	$p > 0.05$
Neridronate	1.23 ±0.29	1.15 ±0.17	n.a.
Total body fat mass [kg]			
Alendronate	24.61 ±8.80	25.76 ±8.80	$p > 0.05$
Zoledronate	21.97 ±6.41	21.69 ±7.28	$p > 0.05$
Risedronate	22.58 ±7.66	22.11 ±7.70	$p > 0.05$
Ibandronate	20.97 ±8.20	18.03 ±8.65	$p > 0.05$
Clodronate	19.42 ±6.73	21.21 ±7.94	$p > 0.05$
Neridronate			n.a.
Total body lean mass [kg]			
Alendronate	37.68 ±4.56	37.83 ±5.05	$p > 0.05$
Zoledronate	39.62 ±7.32	39.74 ±7.82	$p > 0.05$
Risedronate	35.42 ±2.23	35.61 ±2.82	$p > 0.05$
Ibandronate	36.2 ±3.51	35.36 ±3.14	$p > 0.05$
Clodronate	34.04 ±2.12	34.34 ±2.48	$p > 0.05$
Neridronate	38,06 ±10.68	38.62 ±12.21	n.a.

n.a. – not applicable

the small sample size of BPs group did not allow to highlight any significant difference among BPs group after stratification, thus not allowing to ascertain the hypothesis that second and third generation BPs may positively influence patients body composition.

Moreover, even if most of our patients were undertaking vitamin D orally, any information was available regarding its punctual dose and 25(OH)D sera levels variations during the observation period.

Indeed, adding other information such as waist-to-hip and albumin/globulin ratio may have helped strengthen the evidence that BPs may act by reducing A/G ratio and define patients nutritional status at baseline.

Conclusions

The observations made in this study did not evidence any muscle-sparing effect of BPs on lean tissues, however the improvement of A/G ratio testify that BPs may act on patients' body composition.

Further larger studies are needed to ascertain the real effect of BPs on body composition and whether A/G ratio improvement in these subjects may reduce cardiovascular events.

The authors declare no conflict of interest.

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