Minireview Article

Lean body mass in osteoporotic postmenopausal women treated with NandroloneDecanoate: a systematic search review

Abstract:

Aims: Along with the bone loss due to aging and postmenopausal osteoporosis (PMO) is the muscle mass loss, with an increasing occurrence of poorer body composition and osteosarcopenia. The current pharmacological recommendation guidelines for PMO treatment does not include any drugs that promote muscle hypertrophy.NandroloneDecanoate(ND) is an anabolic steroid that has proven to increase bone and muscle mass in several pathologic conditions. Thus, we aimedto search for studing with body composition measurements, especially lean body mass, in postmenopausal women undergoing pharmacological treatment with ND for PMO.

Study design:review with systematic search strategy

Methodology:
We used free and structured MeSh terms combined in a PICO strategy, searching for studies in PubMed, CENTRAL, LILACS, Scielo, Open Grey, and TRIP database

Results:
Three studies were found and included for analysis, two of which were randomized controlled and one observational. All studies observed positive increments in muscle mass concomitant with an increase in bone mass, and a reduction in body fat mass, due to the treatment of PMO with ND. Side effects were predominantly androgenic (voice deepening, increased hirsutism), considered mild, well tolerated, and without serious adverse events.

Conclusion:
ND was an effective drug for increasing lean body mass, reduce body fat, concomitantly improving several bone health parameters (bone mineral content and density) and outcomes (fractures), showing adequate clinical safety, therefore becoming a potential adjuvant to be considered in the medical therapeutic armamentarium for optimized PMO treatment.

Keywords:

Nandrolone Decanoate, Anabolic Steroid, Post-Menopausal Osteoporosis, Menopause, Osteoporosis

Introduction:

The annual rate of bone loss is about 2%, beginning one to three years before menopauseand lasting 5 to 10 years, resulting in an average loss of bone mineral density of 10-12% in the spine and hip during menopause transition [1 , 24].

After this relatively rapid bone loss interval, bone density decreases by 0.5% per year, and this imbalance in bone remodeling continues into advanced age, where an additional deficit in osteoblast function limits bone formation [1,2].Thereby, by the age of 80, women can lose approximately 30% of their peak bone mass at younger ages [2].

Bone and muscle are the main components of musculoskeletal system, and its healthymaintenance is a successful aging important component [3]. Therefore, a poor bone and muscle integrity, often due to inadequate dietary intakes, low or absent physical activity, sleep deprivation, alcohol consumption, chronic diseases, and prescribed medicines, can predispose to functional decline, increased disability, dependence, falls, pain, higher health care costs, and early mortality [3].

In addition to bone loss, from the age of 50, there is a muscle mass loss in the lower limbs of approximately 1 to 2% per year, concomitantly with a strength loss of 1.5 to 5% per year[4].

Longitudinal studies showedthat in people over 75 years, muscle mass can be lost at a rate of 0.64–0.7%/year in women and 0.8–0.98%/year in men [5].This loss occurs due to a combination in satellite cell numbers reduction in muscle fibers and a preferentialfast twitch fibers (type II) reduction[6].

Given that muscle contractions produce the greatest physiological stresses experienced by bones, it is not surprising that muscle function and morphology, such as strength and mass, positively influence the shape, volume, and increase in structural strength of bone mass throughout life [7].

Evidence about this multilevel relationship led to the formulation of the bone-muscle unit concept, in the sense that strength and muscle mass are strongly related to bone mass [8].

In postmenopausal osteoporosis (PMO) treatment, the pharmacological efficacy to increase bone mass well documented, with high quality evidence (A grade) recommendation for HRT, Alendronate, Ibandronate, Risendronate, Zoledronic acid, Denosumab, Raloxifene and Teriparatide, however, none of these drugs act directly to increase muscle mass, which could be of great value for an optimized treatment[9,10, 25,26].

Nandrolone Decanoate (ND) is an anabolic androgenic steroid hormone derived from the 19-nortestosterone family, whose first indication in its package insert (on-label) is osteoporosis treatment[11-13, 14]. In fact, we have previously documented, through a bibliographical systematic search, the efficacy and adequate clinical safety of its therapeutic use to increase bone mass[13].

But, in most of reviewed studies, there is no routinely measurement of any muscle mass parameters, neither of the potential influence of its increase on the outcome of PMO treatment[13]. Furthermore, none of the most recent recommendations postulate ND as a potential usable drug, whether for isolated use (since there is adequate efficacy and clinical safety) or for adjuvant treatment in PMO[9,10].

Thus, the main objective of this review is tosearchfor studing with muscle mass measurements in postmenopausal women undergoing pharmacological treatment with ND for osteoporosis.

Material and methods:

- Search strategy

Search strategies in electronic scientific databases, LILACS (www.bvsalud.org), PUBMED (www.pubmed.gov), CENTRAL (www.cochranelibrary.org), TRIPDATABASE (www.tripdatabase.com), SCIELO (www .scielo.br), OPEN GRAY (www.opengrey.eu), were

carried out to search for randomized controlled studies, using Nandrolone Decanoate in postmenopausal women, published in English, without publication time limit, using several MeSH terms (Medical Sub Headings) and keywords, described below.

The PICO strategy (patient, intervention, comparator, outcome) was used as a search guide whenever possible in the database browser, and thus:

P: post-menopausal women;
I: Nandrolone Decanoate
C: placebo, standard treatment;
O: Lean body mass, muscular mass, body composition

Finally, an additional search was carried out in studies selected and included for analysis, aiming to find other studies not included in the described search.

- LILACS database search strategy:

(filters: randomized controlled trial): MH:"Osteoporose Pós-Menopausa" MH:"Osteoporosis Posmenopáusica" OR MH:"Osteoporosis, Postmenopausal" OR (postmenopausal osteoporosis) OR (Postmenopausal bone loss) OR (perimenopausal bone loss) OR (bone loss postmenopausal) OR (bone loss perimenopausal) OR (postmenopausal osteoporoses) OR (postmenopausal bone losses) OR (post-menopausal osteoporosis) OR (post-menopausal osteoporosis) OR (post-menopausal osteoporoses) OR (perimenopausal bone losses) OR (osteoporosis post menopausal) OR (osteoporoses postmenopausal) OR (osteoporoses post-menopausal) OR (bone losses postmenopausal) OR (bone loss perimenopausal) OR (osteoporosis post-menopausal) OR (osteoporosis postmenopáusica) OR (pérdida ósea postmenopáusica) OR (pérdida ósea posmenopáusica) OR (pérdida ósea perimenopáusica) OR (perda óssea pos-menopausa) OR (perda óssea perimenopausa) OR MH:C05.116.198.579.610$ OR MH:C18.452.104.579.610$ AND MH:Nandrolona OR MH:Nandrolone OR (19-Nortestosterona) OR Estrenolona OR Norandrostenolona OR Nortestosterona OR Nandrolone OR (17-Hydroxy-Estr-4-Ene-3-One) OR (17beta-Hydroxy-19-Nor-4-Androsten-3-One) OR (17beta Hydroxy 19 Nor 4 Androsten 3 One) OR (19-Nortestosterone) OR Estrenolone OR Norandrostenolone OR Nortestosterone OR mh:D04.210.500.365.415.638$ OR mh:D06.472.334.851.968.976$

- PUBMED database search strategy:

((("Osteoporosis"[Mesh] OR Osteoporoses OR (Osteoporosis, Post-Traumatic) OR (Osteoporosis, Post Traumatic) OR (Post-Traumatic Osteoporoses) OR (Post-Traumatic Osteoporosis) OR (Osteoporosis, Senile) OR (Osteoporoses, Senile) OR (Senile Osteoporoses) OR (Osteoporosis, Involutional) OR (Senile Osteoporosis) OR (Osteoporosis, Age-Related) OR (Osteoporosis, Age Related) OR (Bone Loss, Age-Related) OR (Age-Related Bone Loss) OR (Age-Related Bone Losses) OR (Bone Loss, Age Related) OR (Bone Losses, Age-Related) OR (Age-Related Osteoporosis) OR (Age Related Osteoporosis) OR (Age-Related Osteoporoses) OR (Osteoporoses, Age-Related)) OR ("Osteoporosis, Postmenopausal"[Mesh] OR (Perimenopausal Bone Loss) OR (Bone Loss, Postmenopausal) OR (Bone Losses, Postmenopausal) OR (Postmenopausal Bone Losses) OR (Osteoporosis, Post-Menopausal) OR (Osteoporoses, Post-Menopausal) OR (Osteoporosis, Post Menopausal) OR (Post-Menopausal Osteoporoses) OR (Post-Menopausal Osteoporosis) OR (Postmenopausal Osteoporosis) OR (Osteoporoses, Postmenopausal) OR (Postmenopausal Osteoporoses) OR (Bone Loss, Perimenopausal) OR (Bone Losses, Perimenopausal) OR (Perimenopausal Bone Losses) OR (Postmenopausal Bone Loss))) AND ("Nandrolone"[Mesh] OR (19-Nortestosterone) OR (17beta-Hydroxy-19-Nor-4-Androsten-3-One) OR (17beta Hydroxy 19 Nor 4 Androsten 3 One) OR Estrenolone OR Nortestosterone OR (17-Hydroxy-Estr-4-Ene-3-One) OR Norandrostenolone OR (17 beta Hydroxyestr 4 en 3 one decanoate) OR (19 NortestosteroneDecanoate) OR (19 nor 4 Androstene 17 beta ol 3 one 17 decanoate) OR

Retabolil OR Retabolyl OR Decadurabolin OR Decadurobolin)) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh])))

- CENTRAL database search strategy:

#1 MeSH descriptor: [Osteoporosis, Postmenopausal] explode all trees

#2 Osteoporosis OR (Post-Menopausal) OR (Bone Losses, Postmenopausal) OR (Bone Loss, Perimenopausal) OR (Bone Losses, Perimenopausal) OR (Postmenopausal Osteoporoses) OR (Osteoporoses, Post-Menopausal) OR (Osteoporoses, Postmenopausal) OR (Perimenopausal Bone Loss) OR (Postmenopausal Bone Loss) OR (Post-Menopausal Osteoporosis) OR (Postmenopausal Bone Losses) OR (Bone Loss, Postmenopausal) OR (Osteoporosis, Post Menopausal) OR (Post-Menopausal Osteoporoses) OR (Perimenopausal Bone Losses) OR (Postmenopausal Osteoporosis)

#3 #1 OR #2

#4 MeSH descriptor: [NandroloneDecanoate] explode all trees

#5 (19 nor 4 Androstene 17 beta ol 3 one 17 decanoate) OR (19 nor 4 Androstene 17 beta ol 3 one 17 decanoate) OR Retabolil OR Retabolyl OR Decadurobolin OR Decadurabolin OR (17 beta Hydroxyestr 4 en 3 one 17 decanoate) OR (17 beta Hydroxyestr 4 en 3 one 17 decanoate) OR (19 NortestosteroneDecanoate) OR (19 NortestosteroneDecanoate)

#6 #4 OR #5

#7 MeSH descriptor: [Nandrolone] explode all trees

#8 (19 Nortestosterone) OR (17beta Hydroxy 19 Nor 4 Androsten 3 One) OR (17beta Hydroxy 19 Nor 4 Androsten 3 One) OR (Estrenolone) OR (Nortestosterone) OR (17 HydroxyEstr 4 Ene 3 One) OR (Norandrostenolone)

#9 #7 OR #8

#10 #3 AND #6 AND #9

- TRIP database search strategy

(title: (post menopausal osteoporosis) OR (osteoporosis) (title:(nandrolone Decanoate) OR (nandrolone)

- SCIELO database search strategy:

(nandrolone) OR (nandrolone decanoate) OR (Norandrostenolone) OR (retabolyl) OR (esterolone) OR (decadurabolin) OR (Nortestosterone Decanoate) OR (Retabolil) OR decadurobolin) OR (19-nortestosterone)

- OPENGREY database search strategy:

(Individual terms) Nandrolone, Nandrolone Decanoate, Nortestosterone , Retabolil, Retabolyl, Decadurobolin, Decadurabolin, Esterolone, Norandrostenolone.

Results:

Three studies [15-17]evaluated bone mass and body composition before and after ND in osteoporotic postmenopausal women, and as observed, there was a significant increase in bone mass and lean body mass (**Table 1**).

Hassager C, et al. (1989)[16] presented the results of one-year DN use on body composition in women (n=44; 55 to 75 years) with PMO.

Enrolled patients who participated in a previous randomized controlled trial [14] received 50 mg of ND every 3 weeks or placebo (associated with 500 mg of oral calcium) for 12 months. As results after one year, the experimental group (ND) significantly increased lean mass (+4 kg), and significantly reduced body fat (-5 kg), maintaining body weight without significant change [16].

Hassager C, et al. (1989) [15]explored the long-term effects after stopping ND use (follow-up for at least 6 months, without intervention) on bone mass parameters and body composition, in twenty-two women with PMO.

Thus, they published the results of an observational study [16]involving patients who participated in two previous randomized controlled studies (Johansen JS, 1989; and Hassager C, 1989) [14,15] using of 50 mg of ND every 3 or 4 weeks (associated with 500 mg of oral calcium), for 12 to 24 months. Yet, they continued to be followed up and evaluated every 3 months, after at least 6 months of stopping NDuse as treatment for PMO [16].

The presented results showed that in the first one or two years of therapy, in the DN groups, there was a significant improvement in body composition, with an increase in lean body mass (3.3 to 4.4 kg/year), and a reduction in fat mass (- 3.2 to 4.9 kg/year) [16].

After DN use cessationthere was a significant reduction in gains from treatment, with an average loss of lean body mass of -2.1 kg/year, and gain in fat mass of + 2.7 to 4.0 kg/year, bringing the results closer to the pre-treatment values [16].

Frisoli A, et al. (2005) [17] aimed to measure ND efficacy on bone parameters, body composition and fractures in PMO women (n=65) over 70 years, comparing ND 50 mg use every 3 weeks versus placebo, for 2 years. All patients also received oral calcium supplementation (500 mg/day) and underwent periodic evaluations every 3 months. As results, they observed a significant muscle mass increase (2 kg/year), equivalent to +6.2 ± 5.8% of lean mass in the first year, and +11.9 ± 29.2% in the second year, with ND therapy [17].

Table1–Study description of ND use effects on body composition and bone mass, in PMO women

Author / Year	Sample	Intervention	Clinical Effects
Hassager C, 1989 [15]	44 WPMO	- RCT - ND 50mg / 3-4 weeks versus placebo - All 500 mg/day de calcium - 3/3 month evaluation - 1 year	After one year, the experimental group (ND) significantly increased lean mass (+4 kg), and significantly reduced body fat (-5 kg), maintaining body weight without significant change.
Hassager C, 1989 [16]	22 WPMO	- Observational (RCT) - ND 50mg / 3-4 weeks versus placebo - All 500 mg/day de calcium - 3/3 month evaluation - 2 years (Post RCT) - At least 6 month without DN - 3/3 month evaluation	First 1-2 years of therapy (RCT) in the DN groups, there was a significant improvement in body composition, with an increase in lean body mass (3.3 to 4.4 kg/year), with a reduction in fat mass (- 3.2 to 4.9 kg/year). After DN use cessation there was a significant reduction in gains from treatment, with an average loss of lean body mass of -2.1 kg/year, and gain in fat mass of + 2.7 to 4.0 kg/year, bringing the results closer to the pre-treatment values.
Frisoli A, 2005 [17]	65 WPMO	- RCT - ND 50mg / 3weeks versus placebo - All 500 mg/day de calcium - 3/3 monthevaluation	Significant increase in muscle mass (2 kg/year), equivalent to +6.2 ± 5.8% of lean mass in the first year, and +11.9 ± 29.2% in the second year

		- 2 years	

PMO: postmenopausal osteoporosis; RCT: randomized controlled trial

Discussion:

According to our initial objective, and as the main result, this present review verified a significant increase in lean body mass and muscle mass in PMO women treated with ND.

Muscle hypertrophy in pathological conditions, also observed in this review with PMO women, is in alignment with earlier propositions of this effect described in the 70's, documenting the efficacy of ND clinical use to increase muscle mass in different scenarios of increased catabolism and body consumption [18,19].

As stated in the introduction, to maintain or increase muscle mass, especially in aging, is highly desirable, since these factors may be associated with an increase in falls and fractures [4-6]. In this sense, Frisoli A, et al. (2005) [17] verified asmaller absolute number of fractures in ND treated PMO women (-50%), observing an average of 3.73 versus 3.13 fractures per patient in 2 years, and 3.91 versus 3.25 in 4 years, respectively for the placebo or DN group.

Another relevant data contained in present reviewed studies [15-17] is the concomitant significant improvement of different bone health parameters. Thus, Hassager C, et al. (1989) [15] described an approximate mean increase of 3% in bone mineral content and thickness in the proximal forearm region, and Hassager C, et al. (1989) [16], a significant increase in forearm bone mineral content (+2.7 to 3.5 % / year).

Additionally, Frisoli A, et al. (2005) [17] described significant increases in lumbar spine bone mineral density (BMD) at 12 and 24 months (+3.4 ± 6.0% and 3.7 ± 7.0%), in trochanteric BMD at 12 months (+ 4.8 ± 9.3%), and in Femoral BMD at 12 and 24 months (+4.1 ± 7.3% and 4.7 ± 8.0%), in the ND treated group.

Whether the bone health positive effects observed with ND isolated use (as previously reviewed) can be added to the effects of currently recommended treatments for osteoporosis remains to be better explored.

In this sense, Kirilov N &Kirilova E.[20] carried out a comparative clinical study with 51 patients (69 to 72 years) with osteoporosis who did not respond to treatment (for one year) with denosumab or ibandronic acid, which were divided for a new treatment associating denosumab + ND (47%) or ibandronic acid + ND (53%), for one year.

As results, they observed a significant improvement in bone mass at lumbar spine, of 10.3% with denosumab + ND (+0,31 T-score), 5.5% with ibandronic acid + ND (+0,16 T-score), and concluded that the addition of ND to conventional treatment provides additional positive effects and that the combination denosumab + ND promotes greater benefits [20].

Another study (randomized, parallel groups, open label) [21] by Indian researchers (Dave B, et al.), which will provide additional clarification, is still ongoing (CTRI/2019/08/020843, at www.trialsearch.who. int)and have the objective of evaluating the chronic effects on body composition, bone pain, quality of life, and clinical safety of ND (50 mg / 3 weeks) combined with Alendronate (70 mg / day) versus Alendronate alone in women (45 85 years old) with bone fragility.

Previous reviews that addressed the androgenic role in metabolism and bone mass increase pointed out that the addition of androgens even in the presence of estrogen hormone therapy can enhance the positive treatment results [21,22].

Two of the presented studies [15,16] also found a significant reduction in body fat mass, ranging from -3.2 to -4.9 kg of fat at 1 and 2 years (respectively), to -5.0 kg at one year (REF). The improvement in body composition, with a reduction in the body fat percentage, is often related to a lower level of subclinical inflammation, reducing signaling of inflammatory cascades, which can also positively contribute to the reduction of bone loss [23].

The use of ND was not free of potential side effects, as shown in **Table 2**. Androgenic effects such as increased facial and body hair, voice deepening, were the main observed effects, and were related to the higher ND applications frequency [15,17].

However, as previously reviewed by our group [13], the side effects due to ND use were considered mild, tolerable for most patients, without serious adverse events occurrence, and with a good improvement rate after drug stop.

In fact, these safety data were also verified acutely even in the presence of higher doses, for example in the randomized controlled study by Sloan P, et al. (1992) [24], who used 2 mg/kg in 29 frail elderly women with hip fractures, using an average dose approximately four times higher (100 to 120 mg/week) than those observed here and in our previous review[13].

Table2 – Side effects of ND use in osteoporotic postmenopausal women

Author / Year	Side effects
Hassager C, 1989 [15]	Significant reduction in HDL in ND group. Metabolicamente, observaram uma redução significante do HDL no grupo DN. Additionally, 17 women had some side effect reported during the study (increase in facial hair = 2; acne = 2; change in voice timbre = 16).
Hassager C, 1989 [16]	During the initial treatment period (2 studies), there were complaints of voice deepening in 11 of 14 participants in the ND group every 3 weeks, and in 4 of 11 in the ND group every 4 weeks. Of the total, 5 patients reported increased facial hair. However, only one patient dropped out of the study.
Frisoli A, 2005 [17]	Increased hemoglobin at 12 and 24 months (7 and 14%), 2/32 patients had hoarseness, 2/32 with facial hirsutism, 2 patients withdrew from the study (1 for hoarseness, 1 for hirsutism).

Finally, despite observed significant data on improvement in body composition and bone health, this review is not free of potential limitations, especially about the certainty of being exclusively due to ND use.

For example, although lifestyle modification isa mandatory recommendation in the osteoporosis and sarcopenia treatment, such as performing regular exercises emphasizing strength training, adequate dietary intake and supplementation (Calcium, Magnesium, Vitamin D, creatine, proteins), these factors were not objectively measured in the presented studies [15-17], remaining to be better investigated in future studies.

Conclusion:

Differently from all drugs currently proposed as standard for PMO treatment, aiming improve bone health, DN apparently is an unique drug that can positively influence body composition (increasing lean body mass and decreasing body fat mass) in addition to bone effects.

This broad review, with a scientific literature systematic search, verified that ND was an effective drug for increase lean body mass, reduce body fat, concomitantly improving several bone health parameters (bone mineral content and density) and outcomes (fractures), showing adequate clinical safety, therefore becoming a potential adjuvant to be considered in the medical therapeutic armamentarium for optimized PMO treatment.

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