Title page

Effective Brief, Low-impact, High-intensity Osteogenic Loading in Postmenopausal Osteoporosis

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Short running head:

Osteostrong® use in Osteoporosis

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Abstract

Background: Osteoporosis is characterized by reduced bone mineral density (BMD) and disrupted microarchitecture estimated by trabecular bone score (TBS), resulting in increased bone fracture risk. "Osteostrong®" is a bone-strengthening system implementing 4 devices and incorporating brief (10-minute), weekly, low-

impact, and high-intensity osteogenic loading exercises. We evaluated the efficacy of the Osteostrong® intervention in postmenopausal osteoporotic women.

Methods and Subjects:

147 postmenopausal osteoporotic women were separated into two groups: Group A comprised 74 women receiving Osteostrong® intervention (mean age 58.8 years, 56.6-61 years 95% CI), and was subdivided into G1 receiving no antiresorptive medication, and G2 on such medication. Group B comprised 73 women that received no Osteostrong® intervention (mean age 61.8 years, 59.4-64.1 95% CI) and was subdivided into G3 on no antiresorptive therapy, and G4 on such treatment. All participants underwent a physical examination and had an assessment for secondary osteoporosis. Dual-energy X-ray absorptiometry (DXA) examinations (Horizon W [S/N 300472M]) were performed at the time of trial inclusion and 12 months later.

Results: Statistically significant increases were observed in the following parameters: i) BMD of the lumbar spine (L1-L4) in G1($p=0.0039$), G2($p<0.001$), and G4($p=0.0059$): ii) TBS in G2($p=0.0078$): iii) BMD of the right femoral neck in G1($p=0.0382$) and G4($p=0.032$): iv) BMD of the left femoral neck G2($p=0.0089$) and in G4($p=0.0498$) and total femur in G2($p=0.0162$).

Conclusions: Osteostrong® improved BMD of the lumbar spine in women with osteoporosis both off and on antiresorptive treatment. Furthermore, Osteostrong® enhanced the effect of antiresorptive therapy on BMD and TBS of the spine, hip and femoral neck.

Introduction

At the dawn of the 21st century, health and wellness-directed measures in Western civilization seem to have successfully addressed many problems of everyday life. Nevertheless, an increased fracture risk state, known as osteoporosis, which is characterized by decreased bone mineral density (BMD) and disrupted microarchitecture due to various factors, remains a global health burden. The endpoint of osteoporosis is the low-energy fracture, and pain, immobilization, and disability, in general, remain some of the main reasons for drug development and research on alternative methods to delay or postpone their incidence. Expected fragility fractures per year rise to 4.5 million in the European Union and 1.5 million in the USA, at a 12- to 18-billion-dollar expense for the healthcare systems with a previous report projecting even higher costs in the years to come (1, 2). Almost ¾ of these fractures affect postmenopausal women. This makes the prevention of osteoporotic fractures a global priority for healthcare systems.

Apart from dual-energy x-ray absorptiometry (DXA), which is currently considered the gold standard for evaluating BMD, measurement of the trabecular bone score (TBS) that consists of a grey-level textural measurement, which is typically obtained from conventional lumbar spine DXA- BMD images, serves as a validated index of bone microarchitecture that is correlated with the mechanical properties of bone (3). TBS has been added to the already established methods of fracture risk assessment tool (FRAX) and BMD for predicting fracture risk (3).

Despite the plethora of drugs used to delay and/or treat osteoporosis, very few non-pharmaceutical methods have been tested and even fewer have succeeded. Until recently, the treatment of osteoporosis in the setting of bone fractures, especially those of the lumbar spine level, consisted of pharmacotherapy, surgery, and the avoidance of everyday exercise, with controversial results. The literature describes non-pharmaceutical methods to reduce fracture risk due to osteoporosis as traditional, complementary, and integrative medicine (4). Patients often use these methods without informing their physicians, making it even more difficult to evaluate the possible protective effects of these practices against osteoporosis (4). Among these proposed methods, supplementation of calcium and vitamin D along with exercise remains the most often recommended modality for osteoporosis prevention according to worldwide clinical practice guidelines, although specific parameters of exercise are not defined (4-6).

There is substantial patient interest in non-pharmacologic approaches to treating or preventing osteoporosis and Osteostrong® is one such intervention, whose efficiency, however, has not been evaluated in clinical trial yet. Interestingly, suggestions for exercise to strengthen the musculoskeletal system and to increase balance have been provided in recent treatment guidelines for osteoporosis and fracture prevention, without specific instructions for the duration, extension, type of exercise, and other important parameters (7, 8).

Osteogenic loading is based on Wolff's law suggesting that a healthy animal's bone will adjust to the forces applied to it (9). The internal structure of trabeculae experiences adaptive alterations, which are subsequently followed by secondary adjustments to the external cortical part of the bone. This process could result in

the thickening of the bone. Conversely, when the load on a bone is reduced, the bone experiences a decrease in density and strength due to the absence of the necessary stimulus required for continuous remodeling (10-12). Osteostrong®, a brief, low-impact, and high-intensity osteogenic loading training modality with once-weekly, 10-minute sessions, using patented devices, known as “Spectrum”, is described below. Although several people have used the Osteostrong® intervention with reportedly beneficial effects on bone density, the method has been less studied for its efficacy in improving bone density and quality in subjects with osteopenia or osteoporosis.

Methods and Study Population

Osteostrong® Method

Osteostrong® consists of a series of brief, 10-min total, weekly exercises of osteogenic loading tailored specifically for every person to ameliorate osteoporosis. This exercise is facilitated using four different apparatuses and is characterized by low impact but high intensity, making it more attractive for patients to adhere to and to avoid possible risks of lumbar or other injury, especially for the elderly and individuals with more severe osteoporosis. This equipment applies a certain dosage of force specific to the participants’ multiples of bodyweight (MOB), allowing for an increased likelihood of osteogenesis. Spectrum devices emulate these forces in a safe and controlled environment. Designed to enable users to assume optimal leverage positions, each device allows high-force application in static postures, aiming to achieve bone-strengthening impact without actual high-impact activity, taking advantage of the individual’s physiological strength limit preventing injury. The four Spectrum devices are based on Growth Trigger (GT),

indicating each device's objective to facilitate bone adaptation (Upper GT, Lower GT, Postural GT, and Core GT), each focusing on distinct regions of the musculoskeletal system. The Upper GT targets the kinetic chain from hands to clavicle; the Lower GT from feet to hip; the Postural GT from feet to neck; finally, the Core GT focuses on the rib cage. Moreover, the Osteostrong® intervention program includes falls prevention and balance training, with a focus on posture, stability, mobility, and coordination.

Study Population

A total of 147 postmenopausal women with osteoporosis of the lumbar spine and/or femoral neck or total hip, who were followed at and recruited from the Unit on Clinical and Translational Research in Endocrinology, National and Kapodistrian University of Athens, Greece, were enrolled. All participants were Caucasian adults of Greek origin. A consent form was obtained from all the participants. Inclusion criteria were female gender, menopause that presented either early or at the expected age, osteoporosis measured by DXA in either lumbar spine and/or hip. Exclusion criteria were secondary osteoporosis and recent bone fracture. Patients were assigned to the various treatment groups according to their status and preference, after they had been informed about the Osteostrong® intervention. Patients were divided into two groups. Group A included 74 women treated with Osteostrong® (mean age: 58.8y, 95%CI 56.6-61); Group A was subdivided into G1, which included women who had no parallel antiresorptive treatment, and G2, which included women who were treated in parallel with either oral bisphosphonates or denosumab. Group B included 73 women who had no Osteostrong® intervention (mean age 61.8y, 95%CI 59.4-64.1). Group B was subdivided into G3, which

included women who did not receive antiresorptive treatment, and G4, which included women who were treated with such medication. Data regarding BMI and age are shown in Table 1. None of the patients from either groups G1 or G3 had previous antiresorptive treatment. Regarding groups G2 & G4, for detailed information, see the supplementary Table S1 (13). In groups G2 and G4, Denosumab, alendronate and risendronate were the antiresorptive drugs used. All patients received 1200 mg calcium and Vitamin D supplementation as required.

All participants underwent a complete physical examination and an assessment for exclusion of secondary osteoporosis. Details from medical history, such as uptake of glucocorticoids or previous fragility bone fracture were retrieved, and laboratory tests to exclude primary hyperparathyroidism, connective tissue disorders, hypercortisolism, Vitamin D insufficiency or other conditions, such as sarcoidosis or blood malignancy, were conducted. DXA examination [Horizon W (S/N 130472M)] twice, at the time of inclusion in the trial and 12 months later, was performed. Bone markers [C-terminal telopeptide of type I collagen (CTX-I) and N-terminal propeptide of type I procollagen (PINP)] were examined after the intervention in groups G1 and G2. Statistical analysis was performed using the freeware R (4.2.2) and examined during the study period for significant mean differences in the recorded response variables.

Results

The main adverse event that was feared by the participants and closely monitored by the Osteostrong® facility personnel was a new bone fracture at any site and/or a muscle or tendon trauma during the procedure. None of these events occurred to any participant. In total, 13 patients experienced joint pain, and 3 patients

dropped out from the study because of it. BMD measurements at baseline and 12 months later are shown in Table 2. Paired Student t-test of all the parameters before and after the Osteostrong® intervention showed the following: a statistically significant increase in T-score (L1-L4) and BMD of the lumbar spine (L1-L4) in groups G1 (n=50, % of positive differences (End-Start) = 72 %, Mean difference 0.245, p<0.001) and (n=48, % of positive differences (End-Start): 56.2%, p<0.0039) respectively, G2 (n=21, % of positive differences (End-Start) = 85.7%, p<0.001) and (n=21, % of positive differences (End-Start) = 76.2%, p<0.001) respectively, and G4 (n=25, % of positive differences (End-Start) = 72%, p=0.0024) and (n=26, % of positive differences (End-Start) = 65.4%, p=0.0059), respectively. A statistically significant increase in T-score (TBS), as well as TBS, was found in the G2 group (n=18, % of positive differences (End-Start) = 66.7%, p=0.0025) and (n=20, % of positive differences (End-Start) = 60%, p=0.0078), respectively. A statistically significant increase in T-score and BMD of the right femoral neck BMD was shown in G1 group (n=44, % of positive differences (End-Start) = 47.7%, p=0.0496) and (n=44, % of positive differences (End-Start) = 47.7%, p=0.0382), respectively. A statistically significant increase in T-score and BMD of the Left femoral neck was shown in G2 group (n=22, % of positive differences (End-Start) = 54.5%, p=0.0152) and (n=22, % of positive differences (End-Start) = 63.6%, p=0.0089) respectively. A statistically significant increase in T-score and BMD of the Left femur total was shown in G2 group (n=22, % of positive differences (End-Start) = 54.5, p=0.0162) and (n=21, % of positive differences (End-Start) = 66.7%, p=0.0304), respectively, and G4 but only regarding BMD (n=27, % of positive differences (End-Start) = 70.4%, p=0.0498). All data are shown in Figure 1 and Table 2. Regression analysis regarding age and BMI was assessed, but no

statistically significant results were observed, Table S2 (13). For G2 and G4 patients receiving Denosumab, a regression analysis regarding TBS changes was performed, but although a trend for increased TBS was observed, it was not statistically significant (Table S3, Figure S1)(13) . For G3 patients who received neither Osteostrong® intervention nor antiresorptive treatment a slight deterioration was seen in all parameters but none of them was statistically significant. No statistically significant correlations were found in either P1NP or CTX-1 levels and BMD changes, in any of the groups.

Discussion

This is the first study that clearly demonstrates benefit from Osteostrong® intervention in postmenopausal women. A significant improvement in BMD and T-score in the lumbar spine in subjects who had an Osteostrong® intervention regardless of antiresorptive medication was found. Additionally, the TBS of the spine was significantly improved in the group that received the combination of Osteostrong® intervention and anti-osteoporotic medication. Moreover, BMD and T-score of the femoral neck and hip in both left and right side improved significantly in subjects who had an Osteostrong® intervention and furthermore in those who also had anti-osteoporotic treatment. As expected, patients without any pharmaceutical or training intervention showed a slight, non-significant decline in all mentioned bone parameters.

Osteoporosis reflects the risk of bone fracture, often resulting in pain, surgery, and complications owing to prolonged hospitalization and workforce loss. Osteoporosis is a global socioeconomic burden that affects millions of people and is associated with a low quality of life. Despite the administration of numerous treatment

modalities over the years, no nonpharmacological approach has demonstrated satisfactory results.

Literature has extensively discussed various exercise modalities and their effects on bone mass and, eventually, osteoporosis. The notion of a “mechanostat” on bone was introduced by Wolff and then described in detail by Frost (9-12). The idea of a bone sensor that responds positively to external forces through muscle training, resulting in improved thickness and microarchitecture has been compelling but never shown in a clinical trial. This is the first time that the administration of training in a calculated and individually tailored manner has shown a positive effect on the density of the bone marrow of the spine. The lack of contraindications to this treatment modality, as it does not interfere with any other medication, makes it more attractive irrespectively of age, socioeconomic status, and comorbidities, resulting in strong adherence to an exercise plan.

Earlier studies have shown a positive effect of low-load, high-repetition resistance exercise on the lumbar spine BMD of otherwise healthy postmenopausal women compared to controls who did not exercise (14). Although the beneficial effect of progressive resistance training on the lumbar spine was not indicated in any of the literature reviews (15), perhaps because of the large variation in the studies included, the approach of low-intensity, high-repetitive exercise tends to be abandoned as more recent evidence emerges. Alternative methods of training, such as Tai Chi Chuan, have also shown beneficial effects on lumbar spine BMD (16), but availability is certainly an issue. In men with osteopenia, High-intensity resistance, and impact training (HiRIT) has shown a beneficial effect on bone geometry and strength in the femoral neck compared to isometric training based

on machines (17). Similarly, stable values for lumbar spine BMD after 12 months of high-intensity exercise were shown in men with osteosarcopenia according to the Franconian Osteopenia and Sarcopenia Trial (FrOST) (18).

Previous studies have shown that osteogenic loading positively affects spinal osteoporosis. HiRIT has been assessed previously in postmenopausal women with encouraging results (17-23). Additionally, the high-intensity exercise implemented not only did not cause extra-vertebral fractures but also improved thoracic kyphosis in this group of patients (17, 20, 22). Moreover, HiRIT was associated with greater improvement in BMD of the lumbar spine of osteoporotic postmenopausal women compared with medium-intensity resistance and impact training (MiRIT), thus diminishing the fear of new fractures in this sensitive population, despite the small number of clinical trials evaluating HiRIT (23-26).

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (27), literature reviews based on (a) controlled trials, (b) isolated DRT with at least one exercise and one control group, (c) intervention durations ≥ 6 months, (d) BMD assessments at the lumbar spine or proximal femur, and (e) cohorts of postmenopausal women, revealed that once-weekly exercise benefitted postmenopausal women with osteoporosis in comparison to more frequent exercise concerning lumbar spine BMD, and was the sole parameter that could be suggested regarding the modus of exercise (25, 26, 28-30). Similar positive results for lumbar spine BMD after high-intensity exercise were reported in another review further supporting this argument (31). Moreover, positive effects of high-intensity exercise on lumbar spine BMD in postmenopausal women with osteopenia or osteoporosis were also shown in the ACTLIFE-RCT trial

(32). Nevertheless, it is difficult to address all parameters needed for optimal outcomes through exercise. Even when classified according to the type of exercise (weight-bearing, dynamic resistance, and mixed interventions), no clear differences were observed, as all were beneficial for the lumbar spine BMD of postmenopausal women (29). A recent review and meta-analysis isolated 14 of 780 studies concerning the mode (resistance only *vs.* combined resistance and weight-bearing exercises), frequency, volume, load, and program length (33). It was shown that increases in BMD were favored by combined resistance and weight-bearing exercises, lower volumes, and higher loads, although lumbar spine BMD did not benefit from current resistance exercise programs, leaving room for improvement in this domain (33). To address the difficult aspects of the optimal resistance training modality, a new trial is currently underway (34).

The beneficial effect of progressive resistance training with specifically tailored, multicomponent exercise programs, along with other health adjustments for balance and nutrition, have been recommended for the management of patients with osteoporosis. Implementation of these encouraging results fueled the recent UK guidelines. Resistance and impact training is recommended for patients with osteoporosis; however, it is clearly stated that the benefit of physical activity often outweighs the risk of harm (28). Nevertheless, a more careful approach regarding the intensity of exercise was adopted because of the lack of evidence of the beneficial effect of high- *vs.* moderate-intensity training.

Exercise recommendation for osteoporosis is often a sensitive matter, especially in the lumbar spine, as the incorrect application of force by the individual may result in new fractures, causing more pain and disability. Osteostrong®, which consists of

a series of brief, 10-min, weekly exercises of osteogenic loading tailored specifically for every person to ameliorate osteoporosis, showed opposite results. It was well-tolerated by patients of different ages and socioeconomic levels who followed this program for an entire year. Additionally, despite the intensity of the exercise, no adverse events such as new fractures, muscle trauma, or other injuries were reported, thus enhancing patient commitment to the exercise program. This exercise is facilitated using four different apparatuses and is characterized by low impact but high intensity, making it more attractive for patients to adhere to and avoid possible risks of lumbar injury, especially for the elderly and individuals with more severe osteoporosis. A previous pilot study on just one subject, who was an astronaut, of weekly 15-min exercise for 6 months showed an increase in body strength but no other osteoporosis parameters, perhaps due to the short period of assessment (35, 36).

Similar results were reported from another group, as HiRIT showed a beneficial effect in total hip, femoral neck volumetric and geometric section modules in comparison to a low intensity Pilates based exercise (LiPBE). This effect was further augmented in patients that received antiresorptive treatment in addition to HiRIT (24).

The beneficial results of exercise in diminishing fracture risk, the main endpoint of all anti-osteoporotic interventions, was observed in a retrospective, observational study of men (37). This study demonstrated that vigorous but not moderate exercise resulted in a decreased hazard ratio for fracture risk in life-long athletes, and this effect was progressively more evident with passing years. These results

encourage the future application of Osteostrong® principles in other groups of individuals vulnerable for osteopenia or osteoporosis.

Our study had some limitations. Not all patients who were asked to take part in the study accepted to participate with various explanations (difficult to adhere to the weekly appointments due to long distance, work schedule, lack of time, other responsibilities, fear of trauma). Also, inadvertently, some serum parameters, such as CTX and NTX concentrations, were not obtained. Furthermore, some patients failed to follow-through and remain in the study during the entire year of treatment.

On the other hand, the study had certain advantages. The patients were recruited from both the public and private medical sector, thus reflecting a socioeconomically balanced group. Measurements of BMD and TBS were performed in the same DXA machine in all patients, decreasing the variability and increasing the validity of the results. Furthermore, the patients were referred from the entire Athens metropolitan area to the same principal investigators, who screened and evaluated all the participants in the study, using a similar approach.

In conclusion, the study demonstrated that the Osteostrong® intervention is a safe, brief method with a significant positive impact on the BMD and TBS of the lumbar spine, hip and femoral neck, in women with postmenopausal osteoporosis. The study suggests that Osteogenic loading has an additive/synergistic effect with anti-osteoporotic medication, augmenting the latter's efficacy and resulting in improved bone strength and quality, and, hopefully, a reduced risk of bone fractures.

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Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and supplementary materials (13) and can be available upon request.

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Table 1: *BMI and age in the different subgroups.*

	G1		**G2**		**G3**		**G4**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
age	57.71	7.86	61.05	12.07	58.78	9.83	64.38	9.36
BMI	24.08	4.71	22.84	2.22	25.42	4.28	25.07	4.02

Table 2: *Statistics in parameters measured at baseline and 12 months later.*

Parameters	Mean G1	SD	Mean G2	SD	Mean G3	SD	Mean G4	SD
BMD L1-L4 (start)	0,812	0,08771	0,768	0,1032	0,87	0,1074	0,832	0,1556
BMD L1-L4 (end)	0,821	0,08737	0,8	0,104	0,856	0,1144	0,84	0,1209
BMD NECK LEFT (start)	0,64	0,07427	0,6	0,06343	0,655	0,08191	0,608	0,08176

BMD NECK LEFT (end)	0,636	0,07025	0,621	0,06817	0,682	0,1016	0,612	0,08575
BMD NECK RIGHT (start)	0,64	0,07152	0,6	0,06495	0,664	0,08356	17,779	101,4818
BMD NECK RIGHT (end)	0,645	0,06874	0,611	0,06537	0,683	0,09976	0,633	0,08424
BMD TOTAL LEFT (start)	0,752	0,0842	0,708	0,07276	0,685	0,515	0,744	0,08974
BMD TOTAL LEFT (end)	0,752	0,07694	0,739	0,05876	0,79	0,1096	0,745	0,1048
BMD TOTAL RIGHT (start)	0,757	0,0769	0,724	0,06329	0,77	0,09892	0,749	0,08316
BMD TOTAL RIGHT (start)	0,757	0,07789	0,736	0,07131	0,778	0,09414	0,74	0,09188
TBS (start)	1,235	0,09561	1,18	0,1228	1,277	0,08472	1,221	0,09591
TBS end	1,254	0,1298	1,218	0,09899	1,242	0,1246	1,212	0,07276
vitamin d(ng/ml) (end)	32,834	8,2531	33,218	6,3648	28,623	8,8252	33,242	7,7111
vitamin d (ng/ml) (start)	27,846	8,127	29,541	7,5346	27,53	9,5668	40,453	46,5642
BMI	24,08	4,7143	22,836	2,2203	25,418	4,2792	25,068	4,0199
PINP (ng/ml) (end)	48,32	19,41	23,71	13,06	69,1	36,2	21.40	19,94
CTX-1(ng/ml) (end)	0,57	0,26	0,55	0,49	0,77	0,24	0,32	0,02

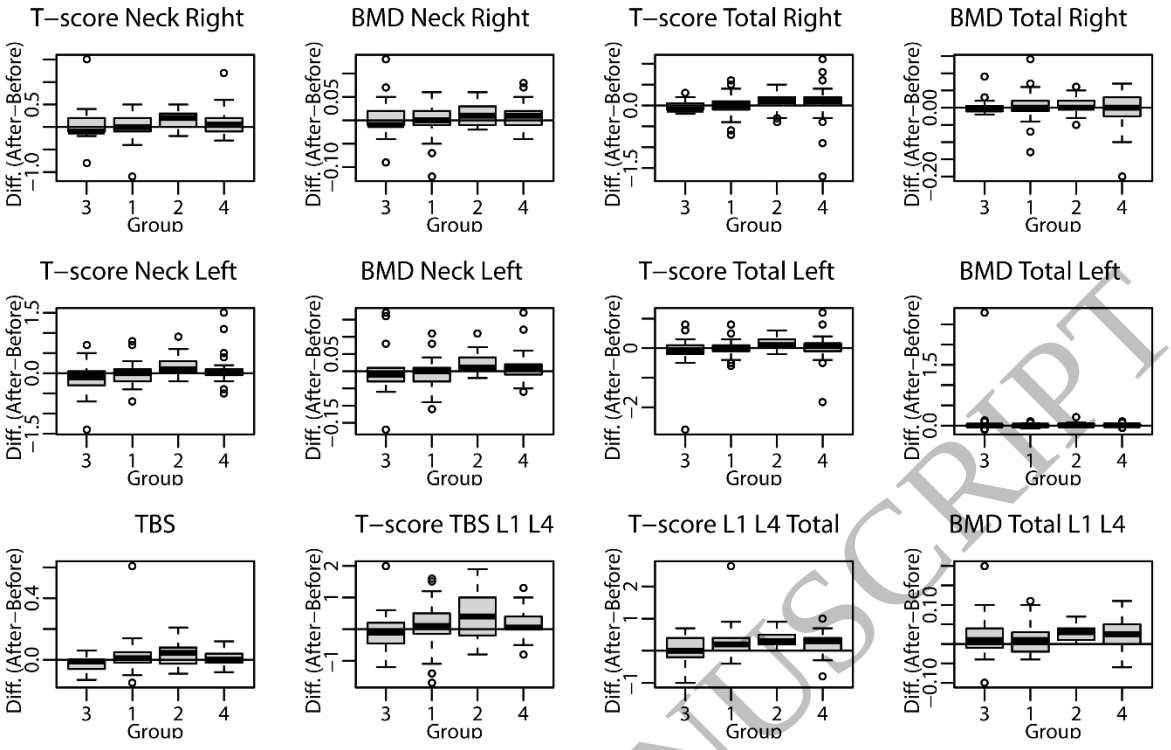

Figure 1
162x104 mm (DPI)