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Original Research

The Effect of Group Training or Spinal Orthosis on Quality of Life and Potential Plasma Markers of Pain in Older Women With Osteoporosis. A Randomized Controlled Trial

Elin Uzunel, MD [a,b], Ann-Charlotte Grahn Kronhed, RPT, PhD [c], Christina Kaijser Alin, RPT, PhD [a], Aisha Siddiqah Ahmed, PhD [d], Per Wändell, MD, PhD [a], Helena Salminen, MD, PhD [a,b]

[a] *Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden*
[b] *Academic Primary Health Care Centre, Stockholm, Sweden*
[c] *Division of Prevention, Rehabilitation and Community Medicine, Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden*
[d] *Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden*

KEYWORDS
Biomarkers;
Osteoporosis;
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Quality of life;
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Women

Abstract *Objective:* Primary purpose was to examine the effects of exercise and use of a spinal orthosis on quality of life (QoL). Secondary, to explore the effects of above-mentioned interventions on plasma levels of potential markers of pain: substance P (SP), calcitonin gene-related peptide (CGRP), and interleukin-6 (IL-6).
Design: Randomized controlled trial.
Setting: Community-dwelling women in Stockholm.

List of abbreviations: CGRP, calcitonin gene-related peptide; ELISA, enzyme-linked immunosorbent assay; IL-6, interleukin-6; LS means, least squares means; MCS, mental component summary score; QoL, quality of life; QUALEFFO-41, quality of life questionnaire of the European Foundation for Osteoporosis; RCT, randomized controlled trial; SF-36, The Short Form health survey; SP, substance P.

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Disclosures: Elin Uzunel, Ann-Charlotte Grahn Kronhed, Christina Kaijser Alin, Aisha Siddiqah Ahmed, Per Wändell, and Helena Salminen declare that they have no conflict of interest.
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Participants: A total of 113 women aged 60-93 years suffering from back pain and self-reported osteoporosis (n=113).
Interventions: The randomized controlled trial was 3-armed: participation in an equipment exercise group, treatment with an activating spinal orthosis or controls. The intervention time was 6 months.
Main Outcome Measure(s): QoL (QUALEFFO-41 and SF-36), plasma levels of SP, CGRP, and IL-6 measured at baseline and after 6 months in all 3 arms.
Results: No improvement of QoL was found. Comparing change in mobility (QUALEFFO-41), the effect in least squares means was lower in the spinal orthosis group compared with controls. In the exercise group, the role emotional score (SF-36) deteriorated during the intervention. Effect size varied between 0.02 and 0.6. There was no change in the levels of CGRP or SP, while IL-6 levels were lower at 6 months in the spinal orthosis group compared with the other groups. At least 1 previous vertebral fracture was verified by X-ray in 46 women.
Conclusion: The interventions showed none or negative effect on QoL, which was unexpected. The modest effect size may prompt a cautious interpretation. We found a lowering of IL-6 levels in the spinal orthosis group, but more studies are needed.

Osteoporosis and fragility fractures are especially common in postmenopausal women.[1] A survey in the European Union in 2010 estimated 22 million women to suffer from osteoporosis and that 3.5 million new fragility fractures occurred.[2] Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue. This leads to enhanced bone fragility and increased fracture risk even from mild to moderate trauma such as fall from standing height or less. Common sites of fragility fractures are the hip, distal forearm, and vertebra.[3-5] Vertebral fractures are the most common fragility fracture.[6] Fragility fractures of the hip and vertebra are associated with increased mortality.[6-8] Furthermore, they frequently lead to pain, disability, and deterioration in quality of life (QoL).[4,9-11]

Women with osteoporosis and vertebral fracture often have weak back extensor muscles and may develop thoracic kyphosis that may influence balance performance.[12-15] Supervised multicomponent exercise programs that are individually tailored should be included at least 2 times per week for people with osteoporosis.[16-20] Exercise seems to have positive effects on QoL and daily functioning in older women with osteoporosis.[5,21-24]

Different types of spinal orthoses have been used after vertebral fractures. In the acute phase, the role is to stabilize the vertebra and promote healing, relieve pain, and improve postural stability. Data from subacute vertebral fractures also show evidence for reduced kyphosis, increased muscle strength, improved postural stability, and better function in the elderly population as well.[25,26] Because of the diversity of the studies, meta-analyses have difficulties to draw clear conclusions. The activating spinal orthosis Spinomed showed positive effects on back extensor muscular strength, pain, and functioning after 6 months but not at 12 months.[25-28]

The mechanisms of pain in osteoporosis are insufficiently understood. Acute pain associated with fractures is mainly nociceptive and influenced by inflammatory cytokines like interleukin-6 (IL-6) and prostaglandins. Sensitization to chronic pain, involving neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP), may occur.[29,30] Levels of SP were lower in saliva and plasma in patients with chronic lumbar backpain compared with controls in a small study (n=9).[31] CGRP in serum and synovial fluid is associated with pain and progression in osteoarthritis.[32] The role of these markers and the association to pain in patients with osteoporosis has not, to our knowledge, been explored. Both SP and CGRP are also involved in bone metabolism as well.[33,34] Pain and QoL may be measured by different self-assessment tools.[30,35,36]

The main aim of this study was to investigate if the effect on QoL differed between exercise and wearing Spinomed compared with controls. We hypothesized that there is a positive effect on QoL by exercise and by an activating spinal orthosis, Spinomed. A second aim was to explore whether such an effect could be correlated to plasma levels of sensory neuropeptides SP and CGRP, or the inflammatory cytokine IL-6. This study present secondary outcomes of a previously published randomized controlled trial (RCT).[27] Pain is common in patients with osteoporosis and fractures and ways to better understand and to relieve pain is important.

Methods

Study design

This was a RCT with 3 arms: group equipment exercise combined with home exercises, wearing an activating spinal orthosis, and controls. Primary outcome studied was QoL (evaluated by SF-36 and QUALEFFO-41) and the secondary outcome studied was effect on plasma levels of SP, CGRP and IL-6. The intervention time was 6 months. Inclusions were made in 4 rounds between 2012 and 2014.

Participants

Participants were women ≥60 years, living in Stockholm County, with self-reported osteoporosis and back pain with or without vertebral fracture. They were recruited from 3 different sources. Women born between 1920 and 1930 who

participated in the Primary Health Care and Osteoporosis project in 2011-2013 were invited.[14] Thirteen were eligible. Women who participated in an Osteoporosis school were invited, and 15 women were eligible. Advertisements in local newspapers led to the recruitment of 85 women. Exclusion criteria were inability to follow the research protocol, insufficient Swedish language skills, or being diagnosed with spinal stenosis. Totally 113 women were included (see appendix for flowchart and dropouts, available online only at http://www.archives-pmr.org/). They were randomized to 1 of the 3 arms by computer block randomization. Numbered envelopes were given to the participants in turn at the end of the first visit. The trial was registered at Clinicaltrials.com, registration number NCT03263585.

Interventions and controls

The intervention has been described in detail previously.[27,37,38] Briefly, the intervention included a baseline visit and follow-ups at 3 and 6 months after baseline for all participants. At inclusion and the 6-month-visit, blood samples regarding SP, CGRP, and IL-6 were taken. Also, a sagittal X-ray (thoracic and lumbar spine) was taken at baseline to investigate the presence of vertebral fractures.

Spinal orthosis (n=38)

Participants were told to wear the activating orthosis Spinomed for 10 minutes the first days, and then successively increase the treatment time during the following 2 weeks to 2 hours or more per day. Individual adjustments were performed by an orthopedic technician. A logbook was used with estimated wearing time (weekly) and possible adverse events. Spinomed has a steel rail from the seventh cervical vertebrae to the sacrum (C7 to S1). The rail that is adapted to the spinal curvature gives feedback when bending resulting in continuous activation of the back-extensor muscles. The spinal orthosis Spinomed was provided by Medi AB.

Exercise (n=38)

The equipment exercise group was led by a physiotherapist 1 hour once a week at rehabilitation units in Stockholm. The program was a stationary circuit program (3 sets, 20 repetitions) that started with a warm-up phase. The program involved gym machines, resistance band, balance plate, and Bobath ball. The exercises were individually tailored, and the focus was back-extensor and shoulder muscle strength, leg muscle strength, balance, and posture (see appendix for a detailed description, available online only at http://www.archives-pmr.org/). A home exercise program was also performed at least 4 times a week and the participants were reminded of that when they attended the group exercise, but no record was kept.[27]

Controls (n=37)

The controls were told to continue living as usual.

Measurements

Participants met a physiotherapist or a physician on 3 occasions. Demographic data, self-reported medical history, present diagnoses (including osteoporosis), medications, need for community care/home health care, need for walking aid, lifestyle factors such as physical activity, and smoking were recorded. The **Downton Fall Risk Index** (DFRI) was used to estimate the risk of falls (high risk $\geq$3 of 11).[39]

Pain and QoL were measured by self-assessment instruments.

SF-36 (version 1) is a generic instrument validated in different populations and conditions. It gives 8 domain scores: vitality, social function, physical function, bodily pain, general health, mental health, role physical, and role emotional and 2 summary scores: the physical component summary and mental component summary (MCS). Zero indicates the worst and 100 the best QoL.[35]

QUALEFFO-41 is a disease-specific instrument validated in osteoporosis with vertebral fractures. It gives 7 domain scores: pain, activities of daily living, jobs around the house, mobility, social function, general health perception, mental functioning, and a total score. Zero indicates the best and 100 the worst QoL.[11,36,40]

Visual Analog Scale means a rating of pain on a 100 mm scale. Zero mm corresponds to no pain and 100 mm corresponds to the worst possible pain.[41] The perceived pain for the last week and their present pain were rated.

Borg CR10 means rating of back pain on a scale from 0 (no pain) to 10 (extremely strong pain).[42] Present pain and pain for the last week were rated.

Isometric back extensor strength was measured using the device Digi-Max.[27,28,a] The results were presented as the mean force in Newtons meter for 6 seconds.

Hand grip strength was measured using the JAMAR dynamometer and presented in kilograms.[43-45]

Biochemical analyses were performed retrospectively on plasma. Venous blood was drawn, centrifugated and then the plasma was stored at - 70°C until analysis. Enzyme-linked immunosorbent assay as used to measure the plasma levels of SP, CGRP, and IL-6. Commercially available enzyme-linked immunosorbent assay kits for SP,[b] CGRP,[c] and IL-6[d] were used for the analysis. Assays were performed according to protocols set by the manufacturer and absorbance was measured at 450 nm.

Statistical analysis

Power calculations were performed in relation to the primary endpoints of the RCT, but not in relation to the secondary endpoints of this study. Normally distributed continuous variables were presented as mean and SD. If distributions were skewed, medians with interquartile range were presented. Dichotomous variables were presented as numbers and frequencies. Baseline characteristics comparisons between intervention and control groups were analyzed with the Kruskal–Wallis test for skewed variables, one-way ANOVA for normally distributed variables, and Chi-square test or Fisher's exact test for dichotomous variables. Bartlett's test for variance was used to assure that the variance was homogenous. *P* values $\leq$.05 were considered significant for baseline characteristics. These analyses were performed with STATA version 14.2. Changes in QoL were analyzed by comparing the difference in group mean between baseline, 3, and 6 months. A mixed model for repeated-measures according to intention to treat adjusted for age was used to

compare the groups and results were presented as least squares means (LS means). If ≥30% of the items in QUALEFFO-41 or ≥50% of the items in SF36 were absent, the score was considered missing. Analyses were performed with SAS version 9.4.[46] Wilcoxon signed-rank test was used to compare QoL values at baseline, 3 months, and 6 months within groups. *P* values ≤.01 were considered significant regarding QoL.[40] This significance level was chosen because the large number of QoL variables and thus a risk of random significances. Mann-Whitney test was used to compare controls to intervention groups regarding change of CGRP, IL-6, and SP from baseline to 6 months. *P* values ≤.05 were considered significant. Effect size was calculated as the difference between the change (6 months − baseline values) in the interventions minus the change in controls divided by the mean value of the standard deviations at baseline. The magnitude was interpreted as no effect (<0.20), small effect (0.20-0.49), medium effect (0.50-0.79), and large effect (≥0.80).[47]

Ethics

All participating women gave a signed consent after written and oral information about the study and that the participation was voluntary and could be ended at any time. Ethical approval was obtained from the Regional Ethical Review Board of Stockholm Dnr 2011/142-31/3. The study was conducted following all guidelines of the Declaration of Helsinki.

Results

There were 113 women, median 76 years (interquartile range: 68-83), in the study. There was no significant difference in age between the groups. The baseline X-ray revealed at least 1 previous vertebral fracture in 46 women; 13 in the controls; 16 in the spinal orthosis group; and 17 in the exercise group (not significant). There were significant differences between the 3 groups at baseline concerning pain medication (controls had the highest and exercise group the lowest proportion). No one in the exercise group had previous stroke. Risk of falling assessed by **Downton Fall Risk Index** differed at baseline (highest risk in spinal orthosis group and the lowest risk in exercise group). There were no significant differences between groups on the remaining variables (table 1).

QoL

For results of QUALEFFO-41 and SF-36, see figure 1.

There were significant differences between groups in QUALEFFO-41 domains of pain and jobs around the house at baseline. There were no differences between the groups in SF-36 domains or scores (table 1).

QUALEFFO-41 and SF-36 domain scores/total scores in the 3 groups were analyzed and compared as LS means between baseline and 6 months. A significant difference was found only regarding mobility in QUALEFFO-41 comparing the spinal orthosis group (6.2, *P*=.01) with controls, indicating a smaller effect on mobility in the spinal orthosis group. We also found a tendency of worsened mobility (QUALEFFO-41) in LS means in the exercise group compared with controls (*P*=.05) and a tendency to worsened activities of daily living (QUALEFFO-41) in LS means comparing exercise to controls. There were no significant differences in mean change comparing baseline and 6 months between the groups evaluated by SF-36. A tendency of worsened vitality (SF-36) in LS means comparing spinal orthosis group to controls (*P*=.02) and MCS index in spinal orthosis and exercise groups compared with controls (*P*=.04, respectively, .02; table 2).

Comparing intragroup changes, a significantly worse score was found in the role emotional domain of SF-36 in the exercise group at 6 months compared with baseline (but not at 3 months). There was a significant change in the pain domain of the QUALEFFO-41 in the spinal orthosis group comparing values at baseline and 3 months that was not detected at 6 months. No other domains showed significant change in the groups at 3 or 6 months (table 3).

Effect size

The effect size of the differences of the domains between the groups varied, but none exceeded 0.8 and most did not exceed 0.5, indicating that the difference was of medium size at best and most often negligible (table 4).

CGRP, SP, and IL-6

Regarding CGRP and SP, there were neither differences between groups, nor change within groups. IL-6 was significantly lower at 6 months compared with baseline in the spinal orthosis group. The change was significant comparing with both controls and the exercise group (table 5).

Discussion

The first aim of this study was to investigate if the effect on QoL (QUALEFFO-41 and SF-36) differed between supervised exercise and wearing a spinal orthosis and controls. The second aim was to explore whether such an effect could be correlated to plasma levels of sensory neuropeptides SP and CGRP, or the inflammatory cytokine IL-6. We found no significant improvement in QoL comparing change from baseline to 6 months between the intervention groups and controls as LS means, which represent the average treatment effect over time between groups. On the contrary we found that there was a decrease in effect in the spinal orthosis group compared with controls regarding mobility (QUALEFFO-41). In the exercise group, we similarly found a significantly worsened score in the role emotional domain (SF-36) comparing median value at baseline to 6 months (but not at 3 months). Nor, did we find any significant correlation to plasma levels of CGRP or SP. However, IL-6 levels were lower at 6 months in the spinal orthosis group compared with the other groups.

We expected a positive effect on QoL after 6 months of intervention, but there was no clear positive change. One explanation may be that we had a relatively small number of participants. Another explanation might be that recruitment partly came from an Osteoporosis school and that controls might have continued with osteoporosis targeted home exercises during study period. In addition, the low effect size

Table 1 Baseline characteristics and QoL in the different groups

	n=113	Controls n=37 Median (IQR)	Spinal Orthosis n=38 Median (IQR)	Exercise n=38 Median (IQR)	*P* Value
Age (years)	*113*	72.9 (67.6-78.3)	78.0 (68.1-84.2)	77.7 (67.5-84.2)	0.19*
BMI (kg/m^2)	*113*	25.0 (21.6-28.3)	24.3 (22.7-27.8)	23.4 (21.3-25.4)	0.29*
Borg-CR last week	*111*	3.0 (3.0-5.0)	4.0 (3.0-5.0)	3.0 (2.0-4.0)	0.07*
VAS last week	*109*	42.5 (20.0-60.5)	49.5 (27.5-68.5)	39.0 (20.0-52.0)	0.21*
Back extensor strength in Newtons	*109*	54.0 (43.1-81.9)	53.9 (38.9-79.9)	52.2 (32.9-79.4)	0.71*
		n (%)	**n (%)**	**n (%)**	
No need of walking aid	*113*	26 (70.3%)	26 (68.4%)	29 (76.3%)	0.84†
Downton Fall Risk Index ≥3	*113*	**13 (35%)**	**22 (58%)**	**12 (32%)**	**0.04**‡
Vertebral fractures (x-ray verified)	*105*	13 (38%)	16 (47%)	17 (46%)	0.73‡
Previous history of hip fracture (self-reported), Yes	*113*	3 (8.1%)	2 (5.3%)	4 (10.5%)	0.77†
Smoking yes	*113*	2 (5.0%)	0 (0.0%)	2 (5.0%)	0.47†
Time spent outdoors >30 min/day, Yes	*113*	31 (83.8%)	27 (71.1%)	31 (81.6%)	0.35‡
Community care, Yes	*113*	4 (10.8%)	7 (18.4%)	7 (18.4%)	0.62†
Home care, Yes	*113*	1 (2.7%)	1 (2.6%)	0 (=%)	0.77†
Type 2 diabetes, Yes	*112*	3 (8.3%)	0 (0%)	3 (5.3%)	0.20†
Previous stroke Yes	*112*	**2 (5.6%)**	**6 (15.8%)**	**0 (0%)**	**0.02**†
COPD/asthma, Yes	*112*	4 (11.1%)	7 (18.4%)	4 (10.5%)	0.65†
Breast cancer, Yes	*112*	3 (8.3%)	1 (2.6%)	3 (7.9%)	0.63†
Pain medication‖, Yes	*112*	**13 (35.1%)**	**8 (21.1%)**	**4 (10.5%)**	**0.04**†
		Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Handgrip Jamar (kg) non-dominant	*112*	18.6 (5.7)	17.5 (5.8)	19.2 (5.8)	0.45§
Handgrip Jamar (kg) dominant	*113*	20.6 (5.4)	19.6 (5.8)	19.2 (6.2)	0.54§
QUALEFFO-41¶		**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	
Pain	*112*	**60 (40-70)**	**60 (40-75)**	**43 (35-50)**	**0.01***
ADL	*111*	13 (6-19)	19 (6-25)	13 (6-19)	0.11*
Jobs around the house	*111*	**25 (10-40)**	**40 (25-50)**	**20 (10-40)**	**0.005***
Mobility	*111*	28 (13-41)	28 (16-45)	19 (13-34)	0.20*
Social function	*109*	33 (19-58)	46 (26-57)	32 (18-63)	0.54*
General health	*112*	58 (42-67)	58 (42-67)	50 (33-67)	0.69*
Mental function	*112*	36 (31-44)	39 (31-44)	33 (25-44)	0.51*
Total score	*111*	36 (28-42)	40 (28-48)	33 (20-42)	0.10*
SF-36#					
Physical function	*111*	60 (40-75)	50 (30-70)	65 (50-75)	0.09*
Role physical	*111*	25 (0-75)	13 (0-50)	50 (25-100)	0.02*
Bodily pain	*113*	41 (32-61)	41 (31-52)	47 (41-62)	0.12*
General health	*111*	52 (40-62)	50 (37-67)	55 (40-67)	0.65*
Vitality	*109*	50 (30-60)	50 (35-60)	55 (40-75)	0.38*
Social function	*113*	75 (63-100)	63 (50-88)	88 (75-100)	0.03*
Mental health	*109*	72 (60-88)	68 (56-84)	80 (64-88)	0.30*
Role emotional	*113*	67 (0-100)	100 (0-100)	100 (33-100)	0.39*
PCS	*108*	34 (29-42)	31 (24-39)	38 (30-44)	0.07*
MCS	*108*	47 (39-53)	48 (36-57)	52 (46-58)	0.26*

Abbreviations: ADL, activities of daily living; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PCS, physical component summary; MCS, mental component summary index; VAS, visual analog scale.

* Kruskal–Wallis.

† Fisher's exact test.

‡ Chi-square test.

§ One-way ANOVA.

‖ Opioid analgesics, paracetamol, doloxene, NSAID, or tramadol.

¶ In the QUALEFFO-41, zero indicates the best and 100 the worst possible QoL.

\# In the SF-36, zero indicates the worst possible and 100 the best QoL.

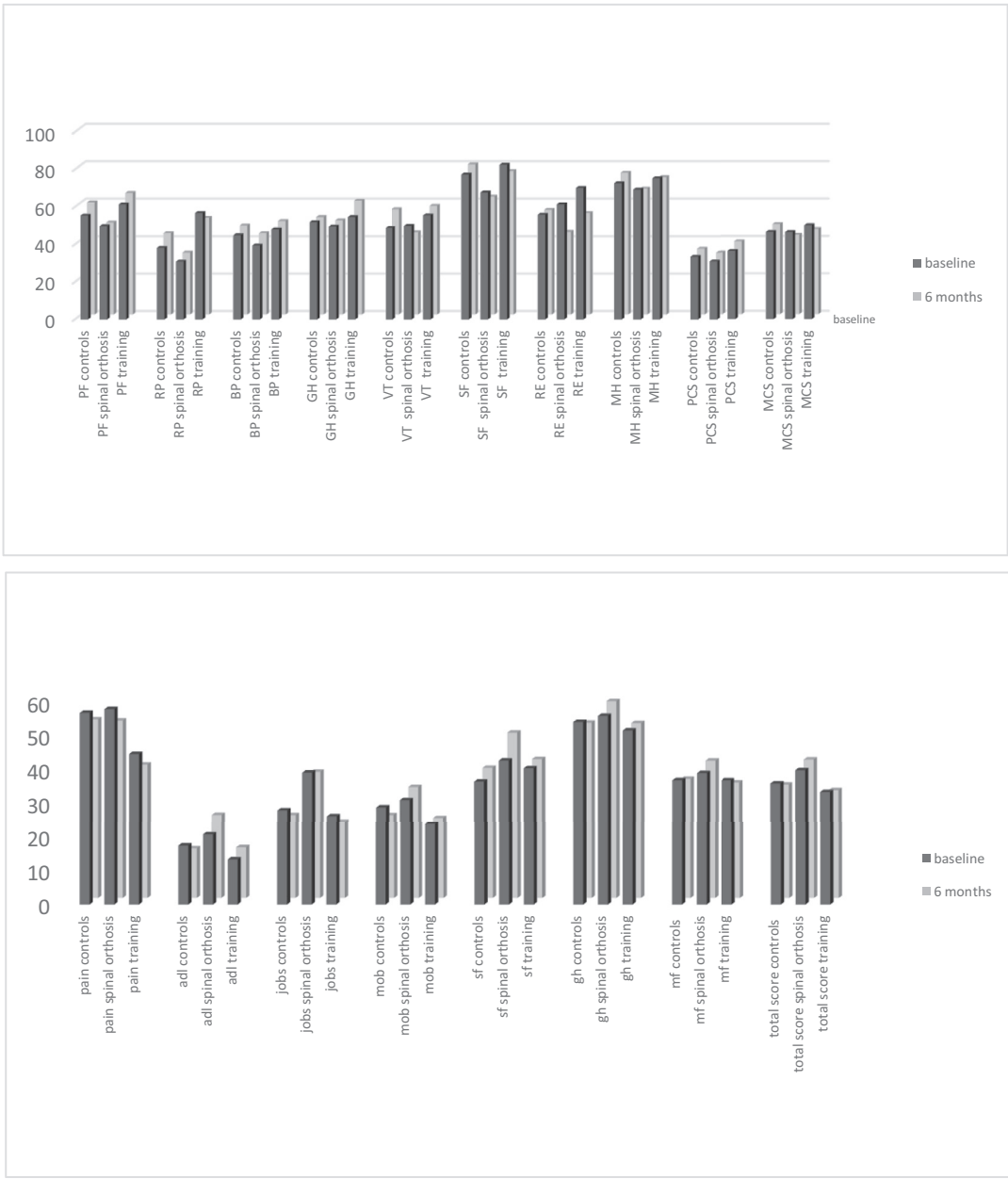

Fig 1 SF-36 (upper panel) and QUALEFFO-41 (lower panel) measurements as mean values at baseline and at 6 months. BP, bodily pain; GH, general health; jobs, jobs around the house; mf, mental function; MH, mental health; mob, mobility; Pain, bodily pain; PF, physical function; RE, role emotional; RP, role physical; SF, social function; total score, sum of all domains; VT, vitality.

indicates that the results should be interpreted with caution. Bergland et al also calculated effect sizes regarding change in QUALEFFO-41 and showed similar effect sizes.[48] However, in their study they showed that a combined 3-month course of circle exercise twice weekly and a 3-hour theory session had positive effect on mental function evaluated by QUALEFFO-41 in older women with osteoporotic vertebral fractures. After 1 year, the exercise group still had better mental function, and in addition better physical function, pain, and total QUALEFFO-41 score compared with the control group.[48] In our study, the diagnosis of osteoporosis was self-reported, and fewer than half of the women had vertebral fractures. This may have influenced the results of the disease-specific QUALEFFO-41. Regarding the worsened score in the role emotional domain it might be of importance that we used SF-36 version 1, improved reliability regarding role emotional scale have been observed using version 2.[49] Also, that both exercise and spinal orthosis group had the best possible role emotional score already at baseline. In a study of 4-month supervised exercise twice weekly in older women with osteoporosis significant improvements were found in 6 domains in the SF-36 and MCS, but no significant improvement was detected by QUALEFFO-41.[23]

Stanghelle et al did not find clear positive effects on QoL assessed by QUALEFFO-41 and SF-36 after a 12-week exercise program twice weekly in older women with osteoporotic vertebral fractures. They reasoned that the high QoL already at baseline may have influenced their results.[20] In our study,

Table 2 Mean values and least squares mean (LS mean) changes within and between the groups, measured by QUALEFFO-41 and SF-36 at baseline and 6 months

	Mean Values (SD)						Comparison of Change in LS Means (*P* Value) Between Groups*		
	Controls n=37		Spinal Orthosis n=38		Exercise n=38				
QUALEFFO-41	Baseline	6 months	Baseline	6 months	Baseline	6 months	Spinal Orthosis vs Controls	Exercise vs Controls	Spinal Orthosis vs Exercise
Pain	56.8 (19.0)	52.9 (19.2)	57.9 (20.7)	52.6 (27.2)	44.6 (19.9)	39.5 (22.6)	−1.9 (*P*=.065)	−0.3 (*P*=.95)	−1.6 (*P*=.70)
ADL	17.2 (15.0)	14.5 (12.9)	20.5 (15.5)	24.6 (18.3)	13.2 (10.3)	14.8 (13.6)	6.3 (*P*=.02)	4.1 (*P*=.14)	2.2 (*P*=.44)
Jobs	27.8 (20.5)	24.6 (18.1)	39.0 (18.1)	37.4 (26.8)	26.1 (19.4)	22.5 (16.1)	2.7 (*P*=.40)	−0.8 (*P*=.81)	3.5 (*P*=.29)
Mobility	28.7 (18.2)	24.5 (17.2)	30.9 (19.4)	32.9 (20.9)	23.6 (16.8)	23.6 (15.7)	6.2 **(*P*=.01)**	4.7 (*P*=.05)	1.5 (*P*=.54)
Social function	36.4 (20.8)	38.6 (22.0)	42.6 (22.5)	49.0 (29.0)	40.3 (24.8)	41.2 (24.7)	4.8 (*P*=.28)	−1.0 (*P*=.83)	5.8 (*P*=.21)
General health	54.1 (19.5)	52.0 (16.9)	55.9 (21.4)	58.3 (23.3)	51.5 (19.4)	51.8 (18.9	3.7 (*P*=.31)	3.5 (*P*=.32)	0.1 (*P*=.97)
Mental function	36.8 (13.4)	35.3 (13.1)	38.9 (13.9)	40.7 (18.8)	36.8 (16.1)	34.2 (15.2)	3.0 (*P*=.25)	0.7 (*P*=.79)	2.3 (*P*=.38)
Total score	35.8 (13.5)	33.6 (12.6)	39.8 (14.6)	41.1 (19.7)	33.3 (13.1)	32.0 (13.3)	3.5 (*P*=.08)	1.5 (*P*=.45)	2.0 (*P*=.33)
SF-36									
Physical function	55.4 (21.9)	59.9 (22.8)	49.7 (24.4)	49.0 (28.2)	61.4 (21.7)	64.8 (19.8)	−4.59 (*P*=.20)	−1.92 (*P*=.59)	−2.67 (*P*=.46)
Role physical	38.2 (39.9)	43.4 (44.1)	30.9 (38.3)	33.1 (41.0)	56.8 (38.9)	51.6 (40.1)	−2.69 (*P*=.79)	−11.03 (*P*=.27)	8.35 (*P*=.41)
Bodily pain	44.9 (18.5)	47.5 (16.1)	39.5 (18.1)	43.4 (26.3)	48.1 (17.2)	49.8 (16.4)	0.42 (*P*=.94)	−2.85 (*P*=.59)	3.28 (*P*=.54)
General health	51.9 (18.0)	52.0 (20.3)	49.5 (19.9)	50.2 (20.9)	54.6 (17.3)	60.8 (18.8)	2.22 (*P*=.55)	5.32 (*P*=.15)	−3.10 (*P*=.40)
Vitality	48.9 (21.0)	56.2 (20.7)	49.9 (20.7)	43.9 (29.2)	55.5 (20.7)	58.0 (21.7)	−11.75 (*P*=.02)	−6.00 (*P*=.24)	−5.75 (*P*=.26)
Social function	77.4 (22.2)	80.1 (21.3)	67.8 (26.1)	62.9 (32.2)	82.6 (21.1)	76.6 (20.5)	−7.98 (*P*=.15)	−9.58 (*P*=.09)	1.6 (*P*=.78)
Mental health	72.7 (15.9)	75.6 (17.9)	69.3 (16.6)	67.2 (23.4)	75.4 (15.4)	73.4 (19.8)	−18.47 (*P*=.08)	−22.73 (*P*=.03)	4.26 (*P*=.68)
Role emotional	55.9 (42.3)	55.9 (46.9)	61.4 (44.9)	44.1 (45.9)	70.2 (40.1)	54.2 (42.1)	−7.57 (*P*=.11)	−5.96 (*P*=.20)	−1.61 (*P*=.74)
PCS	33.4 (10.2)	35.1 (10.1)	31.0 (9.8)	33.0 (11.6)	36.5 (8.6)	38.9 (9.3)	1.04 (*P*=.61)	1.07 (*P*=.60)	−0.03 (*P*=.99)
MCS	46.6 (10.6)	48.1 (12.4)	46.5 (12.2)	42.4 (13.7)	50.1 (9.9)	45.5 (11.8)	−5.93 (*P*=.04)	−6.53 (*P*=.02)	0.60 (*P*=.83)

NOTE. In the QUALEFFO-41, zero indicates the best and 100 the worst possible QoL. In the SF-36, zero indicates the worst possible and 100 the best QoL.

Abbreviations: ADL, activities of daily living; PCS, physical component summary; MCS, mental component summary index.

* Mixed model for repeated-measures according to treat adjusted for age.

Table 3 Median values for the SF-36 domains and QUALEFFO-41 domains in the study groups at baseline and at the 6-month follow-up

	Median Baseline/Median 6 months/*P* Value*		
	Controls n=37	Spinal Orthosis n=38	Exercise n=38
SF-36			
Physical function	60/63/*P*=.22†	50/45/*P*=.52†	65/68/*P*=.25†
Role physical	25/38/*P*=.79†	12.5/0/*P*=.47†	50/50/*P*=.63†
Bodily pain	41/46/*P*=.95†	41/41*P*=.29†	47/51/*P*=.76†
General health	52/54/*P*=.71†	50/52/*P*=.66†	55/62/*P*=.17†
Vitality	50/60/*P*=.14†	50/40/*P*=.14†	55/58/*P*=.94†
Social function	75/88/*P*=.41†	63/63/*P*=.19†	88/75/*P*=.06†
Role emotional	67/83/*P*=.86†	100/33/*P*=.03†	100/67/***P*=.001**†
Mental health	72/80/*P*=.62†	68/76/*P*=.29†	80/80/*P*=.85†
PCS	34/32/*P*=.54†	31/31/*P*=.23†	38/41/*P*=.05†
MCS	47/51/*P*=.91†	48/44/*P*=.04†	52/48/*P*=.05†
QUALEFFO-41			
Pain	60/53/*P*=.47†	60/55/*P*=.09‡(*P*=.002)	43/35/*P*=.25†
ADL	13/9/*P*=.22†	19/19/*P*=.11†	13/6/ *P*=.98†
Jobs	25/25/*P*=.22†	40/35/*P*=.81†	20/18/*P*=.17†
Mobility	28/20/*P*=.03†	28/31/*P*=.97†	19/19/*P*=.89†
Social function	33/38/*P*=.27†(*P*=.02)	46/45/*P*=.11†	32/46/*P*=.90†
General health	58/50/*P*=.67†	58/58/*P*=.92†	50/46/*P*=.26†
Mental function	36/36/*P*=.28†	39/39/*P*=.58†	33/32/*P*=.75†
Total score	36/33/*P*=.23†	40/37/*P*=.86†	33/31/*P*=.97†

NOTE. In the QUALEFFO-41, zero indicates the best and 100 the worst possible QoL. In the SF-36, zero indicates the worst possible and 100 the best QoL.

Abbreviations: ADL, activities of daily living; PCS, physical component summary; MCS, mental component summary index.

* Wilcoxon signed rank test.

† Not significant (*P*>.01) at 3 months either.

‡ Significant (*P*<.01) at 3 months.

Table 4 Effect size of QUALEFFO-41 domains and total score and SF-36 domains and indexes*

	Spinal Orthosis vs Controls	Exercise vs Controls
QUALEFFO-41		
Pain	−0.07	−0.06
ADL	0.45	0.34
Jobs around the house	0.08	−0.02
Mobility	0.33	0.24
Social function	0.19	−0.06
General health	0.22	0.12
Mental function	0.24	−0.07
Total score	0.25	0.07
SF-36		
Physical function	−0.22	−0.05
Role physical	−0.08	−0.26
Bodily pain	0.07	−0.05
General health	0.03	0.35
Vitality	**−0.64**	−0.23
Social function	−0.31	−0.40
Role emotional	−0.31	−0.31
Mental health	−0.40	−0.39
PCS	0.03	0.07
MCS	−0.49	**−0.60**

Abbreviations: ADL, activities of daily living; PCS, physical component summary index; MCS, mental component summary index.

* Calculated as the difference at baseline and 6 months between the intervention and the control group divided by the mean value of the standard deviations of the groups at baseline.

there were significant differences between groups in the QUALEFFO-41 domains of pain and jobs around the house at baseline. This may have influenced the result of the pain domain in QUALEFFO-41 that was significantly improved in the spinal orthosis group at 3 months but not at 6 months. Our results are difficult to interpret as they do not consistently show either improvement or deterioration in QoL. The absence of clear positive effects on QoL from exercise may also be due to the dosage, as the recommended frequency of weight-bearing physical activity is 2-3 times a week.[16]

According to a recent systematic review, progressive resistance exercise improves physical function and QoL and reduces pain in women and men ≥50 years with low bone mineral density, fracture history, or who are at risk of fracture.[17] However, they also state heterogeneity among studies regarding QoL and that some studies, like our study, do not report effect on QoL.

In an earlier qualitative study of this cohort, women wearing the spinal orthosis stated that the orthosis was perceived as a "close friend" and a support in everyday life.[37] In our previous study, increased back extensor strength within the groups as well as a non-significant tendency for decreased back pain in the spinal orthosis group was found after 6 months but there was no difference in back pain between groups.[27]

Spinal orthoses are not supported as a treatment in the national guidelines for treatment of osteoporosis in Sweden and it is difficult to draw clear conclusions from recent meta-analyses.[25,26,50] Spinal orthoses are also used as a

Table 5 Median values for CGRP, IL-6, and SP levels at baseline and 6 months and *P* values

	A Controls	B Spinal Orthosis	C Exercise	Differences Between Groups. *P* Values†		
		Median (IQR)/Missing		A vs B	B vs C	A vs C
CGRP (ng/mL)				0.33§	0.88§	0.43§
Baseline	50.5 (60.9-44.1)/7	55.6 (62.9-46.2)/8	53.3 (61.1-44.0)/8	0.52	0.41	0.96
6 months	54.9 (61.9-46.2)/ 5	50.8 (60.2-38.9)/16	55.6 (58.7-47.4)/10	0.41	0.54	0.88
Change in group‡	*P*=.38	*P*=.65	*P*=.97			
IL-6* (pg/mL)				**0.04**§	**0.01**§	0.54§
Baseline	3.5 (5.7-0.0)/5	4.0 (9.4-1.9)/8	0.0 (4.1-0.0)/8	0.20	**0.002**	0.07
6 months	3.5 (6.0-0.0)/7	1.2 (4.4-0.0)/16	3.0 (4.9-0.0)/10	0.26	0.44	0.69
Change in group‡	*P*=.81	***P*=.02**	*P*=.25			
SP (pg/mL)				0.69§	0.22§	0.08§
Baseline	107.1 (361.2-0.0)/3	134.8 (403.8-71.7)/8	143.0 (284.4-0.0)/8	0.70	0.81	0.99
6 months	135.4 (318.2-0.0)/5	107.1 (202.3-0.0)/16	323.0 (405.2-94.3)/10	0.45	0.02	0.14
Change in group‡	*P*=.70	*P*=.99	*P*=.07			

Abbreviations: IQR, interquartile range

* Two outliers with very high values in the control group are not shown.

† Mann–Whitney test.

‡ Signed rank test.

§ Changes between baseline and 6 months compared between groups.

treatment for vertebral fractures solely and in our study just above 40% had vertebral fractures which may have influenced our results. According to a recent systematic review the use of spinal orthosis still is a controversial treatment and cannot be recommended in general.[51]

Regarding SP and CGRP, we found no differences between the groups. IL-6 levels were lower at 6 months compared with baseline in the spinal orthosis group compared with both controls and exercise. There are no other similar studies to our knowledge. Palada et al found elevated levels of inflammatory proteins in cerebrospinal fluid in osteoarthritis patients, but no evidence for serum levels as markers of pain.[52] In patients with chronic pancreatitis, lower serum levels of IL-6 and SP was observed in patients with severe pain.[53] In an osteoporotic mouse model, IL-6 inhibitors decreased mechanical hyperalgesia.[54] In humans, monoclonal antibodies targeting IL-6 alleviate pain and fatigue in rheumatoid arthritis and antibodies targeting CRGRP are effective against migraine.[55] In a study investigating effect of exercise on SP levels in the trapezius muscle in patients with chronic neck and shoulder pain they found a lowering of SP as well as pain.[56] Participants in our study had chronic back pain, but we did not consider for how long and other possible causes for the pain in those without vertebral fractures. This may have led to a heterogeneity that may have influenced the results.

Study strengths and limitations

The length of the intervention of 6 months is a strength though many other studies have shorter intervention periods. Another strength is the randomized design with 2 intervention groups and controls.

A limitation is that power calculations were not performed in relation to endpoints of QoL and pain markers and the power might have been too low for these analyses. Another limitation may be the presence of recruitment bias in our study. Also, we did not have the opportunity to blind the research investigators because we in the research group were too few. Also, the fact that osteoporosis was self-reported and that some of the participants had vertebral fractures meanwhile others had not may have led to heterogenicity that may have been limiting for the study. One limitation regarding the pain markers was many missing values and a large standard deviation.

Conclusions

We found no significant improvement in QoL in the intervention groups, and our results together with those of others may indicate that the well-established benefits of exercise in older women with osteoporosis regarding bone mineral density, pain, muscle strength, and in preventing falls is not as noticeable in terms of QoL. However, varying results and the relatively modest effect size may suggest that these results should be interpreted with caution. Regarding the decreased IL-6 levels, but no effect on SP or CGRP levels, further research is needed. The mechanisms of pain in established osteoporosis are insufficiently understood. If treatments targeting the effect of inflammatory cytokines and neuropeptides might reduce pain, it is of great interest to explore further, as pain is common in patients suffering from osteoporosis and fractures.

Suppliers

a. Digi-Max; MechaTronic
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Corresponding author

Elin Uzunel, Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Alfred Nobels allé 23, 14183 Huddinge, Stockholm, Sweden. *E-mail address:* elin.uzunel@ki.se.

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