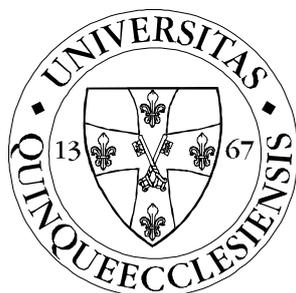


**UNIVERSITY OF PÉCS**  
**FACULTY OF HEALTH SCIENCES**  
**DOCTORAL SCHOOL OF HEALTH SCIENCES**

**Head of the Doctoral school: Prof. Dr. Bódis József**

**Program leader: Prof. Dr. Kráncz János Ph.D.**

**Supervisor: Prof. Dr. Kráncz János Ph.D.**



**DIRECT EFFECTS OF WALKING AND TRAINING ON MARKERS OF  
BONE METABOLISM IN WOMEN WITH DIFFERENT BONE MASS;  
IMPACT ANALYSIS OF A SENSORIMOTOR TRAINING PROGRAM**

**Doctoral (Ph.D.) thesis**

**Császárné Gombos Gabriella**

Pécs, 2015.

## INTRODUCTION

Aiming at and maintaining balance and harmony is essential in all areas of life, including the operation of the organism. The bone tissue is an active tissue that undergoes constant remodelling while aiming to maintain a balance between bone formation and bone resorption. Normally, these two processes are closely connected. Their balance is maintained via various systemic and local regulatory mechanisms. Age, growth, disorders of bone metabolism, physical activity and therapeutic interventions and several other factors all play a role in maintaining this balance. While bone strength and structure are difficult to examine in live tissues, bone mass can be analysed readily. As opposed to static indices, investigating the molecular markers of bone metabolism can assist with monitoring the dynamism of metabolic balance.

Osteoporosis and consequent bone fractures pose a significant problem in aging societies. Our inactive lifestyle affects the peak bone mass and the maintenance of bone matrix, and it results in weak skeletal muscles, falls and fractures. Therefore, balance is important not only at the molecular level: it prevents us from falls and decreases the risk of falls if our bone tissues and muscles are strong. The balance of our muscles and muscle groups helps to prevent the development of various chronic locomotor diseases, the strength of abdominal, back, hip and ankle muscles increases coordination thereby reducing the risk of fractures associated with falls.

## AIMS OF THE STUDY

My doctoral thesis summarises three separate investigations in the field of osteoporosis. Two of the investigations analyse the direct effects of an exercise program on the biochemical markers of bone tissue in women with peak bone mass (study 1) and women with decreased bone density (study 2). The third investigation examined the efficiency of sensorimotor training based on functional and stability indices in a group of women with decreased bone density.

Our investigations had the following objectives:

- 1) To demonstrate the effects of a single exercise program / physiotherapy on the biochemical markers of bone in women with peak bone mass and women with decreased bone density.
- 2) To find out whether there is a difference between the effects of walking and training on the biochemical markers, and to analyse the influential role of lifestyle.
- 3) To demonstrate the effects of a 24-session sensorimotor training on the risk of falls in a group of women with decreased bone density compared to a conventional, 10-session physiotherapy exercise program by using functional and stability indices.

## MATERIALS AND METHODS

The **first study group** included 50 young female volunteers (mean age  $25\pm 2$  years) with normal menstrual cycle and presumably maximal peak bone mass. 25 participants performed a special, 60-minute exercise program under the supervision of a physiotherapist (TG=training group). At the same time and for the same length of time, members of the control group (CG) had to walk briskly on an even surface outdoors.

Before and directly after the intervention, we determined Bone-Specific Alkaline Phosphatase (BALP), Alkaline Phosphatase (ALP) and Carboxyterminal cross-linked telopeptide of type I collagen (CTX/  $\beta$ -CrossLaps) levels. During inclusion, all participants had to undergo laboratory tests as well as a bone ultrasound scan to evaluate the condition of their bones and verify peak bone mass. Body height and body composition were also measured and the participants were asked to fill in a self-compiled questionnaire.

The **second study group** included 60 female volunteers (mean age  $59.1\pm 7.1$  years) with decreased bone density, who had no disorders affecting the biology of their musculoskeletal system and who have received no medical treatment for osteoporosis. The resistant training group (RT) included 30 women, who performed a resistance training program for 45 minutes. At the same time and for the same length of time, members of the control group (WG) had to walk outdoors with moderate intensity.

The assessed markers were the following: BALP for bone formation; CTX for bone resorption; sclerostin, which inhibits osteoblastic bone formation and facilitates its apoptosis and prevents overfilling of the basic multicellular unit (simple negative feedback mechanism in the osteon, Wnt signalling inhibition) (Moester 2010). As part of the investigation, we measured the participants' body height and body weight, as well as their bone mineral density to check that they meet the inclusion criteria. The participants were asked to fill in a self-compiled questionnaire.

The **third study group** included 60 postmenopausal women (mean age  $65.3\pm 4.1$  years). Subgroup I. (n=20) took part in a progressive, 3-month, 24-session sensorimotor training, subgroup II. (n=20) participated in a 10-session training based on the protocol of the Physiotherapy Department, while the members of subgroup III. (n=20) were not subjected to any intervention. As part of the physical examination, we applied the Berg Balance scale (BBS), the Functional Reach test (FRT), the Timed Up & Go test and the One leg standing test (OLST). Participants had their blood pressure, body height and body weight measured,

they were interviewed under the supervision of a physiotherapist and we also performed a digital biometric assessment (MultiSensor Electronic Baropodometry) to examine static foot pressure and stabilometric platform parameters.

All statistical analyses were performed using SPSS (IBM SPSS, Inc., Version 20.0, 2011), and carried out descriptive statistical analysis of the data. Regarding mathematical statistics, we used T-test / Wilcoxon's test or independent sample T-test / Mann-Whitney test depending on the normality of the distribution. A two (time) by three (intervention) analysis of variance (ANOVA) with repeated measures was conducted to explore between- and within-group differences and Scheffe post hoc analysis was used to determine the significance of all possible comparisons or Kruskal-Wallis test was applied. Depending on the distribution, we used the Spearman / Pearson correlation coefficient was used to evaluate the correlation. The  $\alpha$ -level was set at 0.05 for all analyses.

## RESULTS

In the **first study** there were no significant baseline differences between the groups regarding the anthropometric and main lifestyle data. Baseline and post-intervention serum BALP, CTX and ALP concentrations for the TG and CG are shown in Table I. Post-intervention BALP concentrations did not significantly differ from baseline values in the TG ( $-4.63\% \pm 13.14\%$ ); however, there were significant between group differences in the change of the CG ( $-7.65\% \pm 13.88\%$ ). Compared to baseline and post-intervention values, there was a significant decrease in CTX values as a result of training and walking ( $-28.89\% \pm 34.82\%$  vs.  $-52.54\% \pm 31.75\%$ ). ALP values also showed a significant decrease ( $-6.84\% \pm 7.34$  vs.  $-4.57\% \pm 4.79\%$ ) in both groups.

**Table I. BALP, CTX and ALP concentrations in the TG and CG at baseline and post-intervention**

<i>Variables</i>	<i>TG (n = 25)</i>	<i>CG (n = 25)</i>
<b>BALP</b>		
Baseline [E/L]	79.32 ± 21.83	73.27 ± 17.33
Post-intervention[E/L]	75.64 ± 24.45	67.66 ± 18.02
Change [E/L]	3.67 ± 10.42	5.61 ± 10.18
<i>p</i>	<i>0.091</i>	<i>0.011</i>
<b>CTX</b>		
Baseline [pg/mL]	380.36 ± 164.31	319.04 ± 148.43
Post-intervention[pg/mL]	270.44 ± 140.89	151.4 ± 63.19
Change [pg/mL]	109.92 ± 132.50	167.64 ± 101.33
<i>p</i>	<i>0.001</i>	<i>0.001</i>
<b>ALP</b>		
Baseline [E/L]	144.82 ± 39.01	150.38 ± 36.34
Post-intervention[E/L]	134.91 ± 41.04	143.49 ± 32.98
Change [E/L]	9.91 ± 10.64	6.88 ± 7.22
<i>p</i>	<i>0.001</i>	<i>0.001</i>

TG: training group, CG: walking / control group

There was no significant difference between the groups regarding the ALP ( $p=0.414$ ), the BALP ( $p=0.678$ ) and the BALP% ( $p=0.308$ ). There were significant differences in CXT values in contrast to BALP ( $p=0.049$ ): we found greater changes in the walking group.

Considering lifestyle factors, smoking, alcohol consumption, and physical activity of the whole study group correlated with other analysed factors. There was a negative correlation between alcohol intake and BMI ( $r=-0.29$ ,  $p=0.040$ ) so higher alcohol intake was associated with lower weight. Smoking negatively correlated with post-intervention BALP levels ( $r=-0.32$ ,  $p=0.021$ ), while it showed a positive correlation with serum phosphate ( $r=0.323$ ,  $p=0.022$ ), the change of ALP baseline and post-intervention ( $r=0.43$ ,  $p=0.002$ ), and the change of BALP baseline and post-intervention ( $r=0.30$ ,  $p=0.035$ ). Thus smokers had slightly lower post-intervention BALP levels, higher phosphate level, and ALP and BALP levels decreased to a greater extent than in non-smokers. Physical activity positively correlated with T-scores ( $r=0.44$ ,  $p=0.001$ ), BMD ( $r=0.44$ ,  $p=0.001$ ), post-intervention BALP levels ( $r=0.28$ ,  $p=0.048$ ), and the change of CTX baseline and post-intervention ( $r=0.37$ ,  $p=0.007$ ). Thus, physically active people had higher BALP levels in this age group.

The average age of the participants in the **second study** ranged from 36 to 69 (mean age:  $59.11 \pm 7.01$ ), the BMI values were 14.85-39.45 (mean:  $27.59 \pm 5.39$ ). There were no significant baseline differences between the groups regarding the anthropometric data except for the height. The participants' T-scores varied between -4.7 and -1.0 (mean:  $-2.11 \pm 0.77$ ). Baseline and post-intervention serum BALP, CTX, and sclerostin concentrations for the RG, WG, and CG are shown in Table II. Baseline BALP concentrations ranged from 15.9-70.9% (mean:  $41.97 \pm 10.99$ ). CTX levels ranged from 30.0-685.0 pg/ml (mean:  $282.16 \pm 152.07$  pg/ml), and sclerostin levels ranged from 7.3-69.3 pmol/l (mean:  $24.96 \pm 12.65$  pmol/l).

**Table II. BALP, CTX and sclerostin concentrations in the RG, WG at baseline and post-intervention**

<i>Variables</i>	<i>RG (n = 30)</i>	<i>WG (n = 30)</i>
<b>BALP</b>		
Baseline [%]	$42.0 \pm 13.5$	$41.8 \pm 7.8$
Post-intervention [%]	$41.7 \pm 11.9$	$42.7 \pm 8.6$
Change [%]	$0.3 \pm 1.6$	$-0.8 \pm 0.7$
<i>p</i>	<i>0.763</i>	<i>0.069</i>
<b>CTX</b>		
Baseline [pg/ml]	$316.5 \pm 178.5$	$247.8 \pm 112.8$
Post-intervention [pg/ml]	$288.6 \pm 159.8$	$252.5 \pm 110.3$
Change [pg/ml]	$27.9 \pm 18.6$	$-4.7 \pm 2.4$
<i>p</i>	<i>0.001</i>	<i>0.489</i>

<b>SCLEROSTIN</b>		
Baseline [pmol/l]	26.7 ± 13.8	23.1 ± 11.2
Post-intervention [pmol/l]	30.0 ± 16.1	29.5 ± 11.7
Change [pmol/l]	-3.2 ± 2.3	-6.3 ± 0.5
<i>p</i>	0.191	<b>0.017</b>

Abbreviations: BALP, bone specific alkaline phosphatase; CTX, C-terminal telopeptide of type-I collagen; RG, resistance exercise group; WG, walking group

<sup>a</sup> BALP expressed as a proportion of the total value of serum ALP.

<sup>b</sup> Difference between baseline and post-intervention data.

The between group differences were analysed with paired sample t-test or Wilcoxon-test depending on data distribution. Post-intervention BALP concentrations did not significantly differ from baseline values (0.8%±11.78% vs. -2.02%±10.0%), and there were no significant between group differences in the change of the means from baseline to post-intervention using the independent sample t-test ( $p=0.345$ ). Post-intervention CTX concentrations did significantly differ from baseline values in the TG but there were not any changes in the CG (8.82%±10.45% vs. -1.9%±2.19%) and there were significant between group differences in the change of the means from baseline to post-intervention using the Mann-Whitney U-test ( $p=0.001$ ). The RG and CG both experienced only a non-significant rise in serum sclerostin concentrations from baseline (-12,23%±16,72 vs. -27,25%±4,61%), while the WG experienced a significant increase in serum sclerostin and there were no significant between group differences in the change of the means from baseline to post-intervention using the Mann-Whitney U-test ( $p=0.121$ ). The effect of smoking, coffee consumption and sport activity were analysed in this study together with their relationship with bone biochemical markers.

There was no correlation between smoking and baseline T-score, between smoking and BALP baseline, and between smoking and CTX baseline in this study.

Contrarily, there is a moderate positive correlation between smoking and baseline sclerostin ( $r=0.30$ ;  $p=0.016$ ). There is no correlation between coffee consumption and biochemical markers, or between biochemical markers and T-scores. Sport activity positively correlated with T-scores ( $r=0.44$ ,  $p=0.001$ ), BMD ( $r=0.44$ ,  $p=0.001$ ), post-exercise BALP levels ( $r=0.28$ ,  $p=0.048$ ), and the change of baseline and post-intervention CTX ( $r=0.37$ ,  $p=0.007$ ). We compared the osteoporotic and osteopenic participants to determine if there were any differences in the baseline and post-intervention data of biochemical markers. There was no

significant difference between osteoporotic and osteopenic participants either in BALP, CTX or sclerostin levels ( $p>0,05$ ).

A comparison was made **between the group of peak bone mass and the group of low bone mass** regarding the BALP and CTX values. There is significant difference between the baseline and post-intervention BALP values ( $p<0.001$ ), between the baseline values of CTX ( $p=0.020$ ) and between the differences of the two CTX measures ( $p<0.001$ ). Considering all variables – where significant differences are found – the values were higher in the group with peak bone mass. Minimal change is detected in BALP% due to the interventions in each group. The BALP% value is 50% in the group of young people; in the older group it is around 42%. The greatest change occurred in the group of young participants performing the walking activity. The baseline main CTX value is 350 U/l in the group of participants with peak bone mass, while in the group of participants with low bone mass it is 280 U/L. Regarding the CTX, interesting results were found when physical activities were compared. In the group with peak bone mass walking provoked a significantly higher impact, in the group with low bone mass the resistance training was the more effective activity.

In the **third study** there were no significant differences between the three groups regarding the anthropometric data (age, BMI). The mean age was  $64.4\pm 6.1$  years. The values of the functional stability are shown in Table III. The baseline FRT scores were 15.3 to 51.3 points in the whole sample (mean:  $27.7\pm 6.7$ ). The within-group change was analysed with paired sample t-tests or Wilcoxon-test - depending on the data distribution. In Group I, we found a significant change; 4.1-point improvement was achieved, while in Group II the value significantly decreased by 2.6 points, in Group III there was no significant change; the mean value changed only by 0.5 point. There was significant difference between the groups.

The baseline TUG value in the whole sample was between 6.28 to 15.6 points (mean:  $9.6\pm 2.4$  points). In Group I there was a significant improvement, in Group II there was a decline, while Group III showed no change. Analysing the rate of the change the difference was significant. The baseline values of BBS in the whole study sample were between 37-54 points (mean:  $46.65\pm 4.09$ ). Group I values improved by 4.1 points, while the other two groups had no significant change. No significant differences were measured between the groups. In Group I there was a 5.3-sec (25%) improvement in the OLST-test, while in Group II there was a 1.2-sec increase, and in Group III the rise was 0.7 sec. In Group I the improvement was 3.2 sec with closed eyes, in Group II it was 0.9 sec, in contrast to Group III, where the value

decreased by 0.6 sec. Significant improvement was detected in Group I when examined with open and closed eyes, and there is significant difference between the groups.

Table III. Values of functional stability tests

Variables	Group I.	Group II.	Group III.
FRT [cm] b	25.3 ± 5.6	31.2 ± 5.2	28.6 ± 9.2
FRT [cm] a	29.4 ± 5.4	28.6 ± 4.8	28.1 ± 8.2
$p_1$	<b>&lt;0.001</b>	<b>0.031</b>	<b>0.641</b>
ANOVA	<b><math>p &lt; 0.001</math></b>		
Post hoc test	<b><math>p_{1-2} &lt; 0.001</math>; <math>p_{1-3} = 0.002</math>; <math>p_{2-3} = 0.310</math></b>		
TUG [sec] b	9.5 ± 2.5	8.3 ± 1.0	11.2 ± 2.6
TUG [sec] a	8.8 ± 1.6	8.4 ± 0.9	11.3 ± 2.7
$p_1$	<b>0.023</b>	<b>0.571</b>	<b>0.713</b>
ANOVA	<b><math>p = 0.022</math></b>		
Post hoc test	<b><math>p_{1-2} = 0.024</math>; <math>p_{1-3} = 0.395</math>; <math>p_{2-3} = 0.428</math></b>		
BBS [pont] b	46.3 ± 3.4	49.1 ± 3.1	44.7 ± 4.9
BBS [pont] a	50.4 ± 3.2	49.7 ± 3.0	43.75 ± 5.5
$p_1$	<b>&lt;0.001</b>	<b>0.414</b>	<b>0.090</b>
ANOVA	<b><math>p &lt; 0.001</math></b>		
Post hoc test	<b><math>p_{1-2} = 0.002</math>; <math>p_{1-3} &lt; 0.001</math>; <math>p_{2-3} = 0.373</math></b>		
OLST[sec] OE b	21.1 ± 5.9	23.2 ± 6.3	22.6 ± 7.6
OLST [sec] OE a	26.4 ± 5.2	24.4 ± 8.2	23.3 ± 8.2
$p_1$	<b>0.023</b>	<b>0.124</b>	<b>0.186</b>
ANOVA	<b>0.041</b>		
Post hoc test	<b><math>p_{1-2} = 0.014</math>; <math>p_{1-3} &lt; 0.001</math>; <math>p_{2-3} = 0.412</math></b>		
OLST[sec] CE b	9.5 ± 4.2	9.3 ± 5.4	10.8 ± 3.4
OLST [sec] CE a	12.7 ± 3.1	10.2 ± 3.2	10.2 ± 4.1
$p_1$	<b>&lt;0.001</b>	<b>0.213</b>	<b>0.634</b>
ANOVA	<b>0.003</b>		
Post hoc test	<b><math>p_{1-2} = 0.003</math>; <math>p_{1-3} &lt; 0.001</math>; <math>p_{2-3} = 0.456</math></b>		

b: before the intervention; a: after the intervention; OE: open eyes; CE: closed eyes;

$p_1$ : paired-sample t-test

We compared the differences with Mann-Whitney U-test; the results are presented in Table IV. Group I showed significantly better results than Group II in the TUG-test.

In the case of the FRT-test the results of Group I were significantly better compared with Group II and III, and the same results are true for BBS and OLST tests.

**Table IV. Comparison of the changes between the groups**

<i>Variables</i>	<b>Group I-II.</b>	<b>Group I-III.</b>	<b>Group II-III.</b>
TUG			
<i>p</i>	<b>0.036</b>	<i>0.281</i>	<i>0.292</i>
FRT			
<i>p</i>	<b>&lt;0.000</b>	<b>0.003</b>	<i>0.268</i>
BBS			
<i>p</i>	<b>0.002</b>	<b>&lt;0.001</b>	<i>0.131</i>
OLST OE			
<i>p</i>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<i>0.211</i>
OLST CE			
<i>p</i>	<b>0.003</b>	<b>0.029</b>	<i>0.261</i>

There was 5% static foot-load difference (45-55%) compared to the normal 50-50% distribution of all participants. As shown by the second measurement in Group I, the static bipedal foot-load difference decreased by 1.3% (compared to the original value of 7.2, the decrease was 18%). Contrarily, in Group II and III the data were increased although neither of the groups accomplished the level of significance, and there were no significant differences between the groups.

Considering the stabilometric parameters, one of the most important indicators is the Romberg-index, which adjusts the elliptical surfaces to each other by analysing the visual control. Minimal changes occurred in the variables, a slight decrease was detected in all groups, but none of them reached the level of significance, and there were no significant between group differences. Observing the elliptical surface, the baseline values were higher in the case of closed eyes in all three groups. In Group I the post-interventional value was 3.5 mm<sup>2</sup> better with open eyes and 6.2 mm<sup>2</sup> with closed eyes. In the other two groups the variables showed deterioration but not on a significant level, and there were no significant differences between the groups.

There was no meaningful change regarding the anteroposterior (AP) mean-velocity and velocity-rate within groups and no changes could be found between the groups. In Group I the open-eye mediolateral (ML) mean-velocity decreased appreciably, however, there was a slight change under the closed-eye circumstances. There were significant differences between the open and closed eyes comparison regarding the ML mean-velocity rate ( $p=0,003$ ), although there were no significant between group differences.

We investigated the correlations between the analysed biometric variables. Moderate positive correlation can be demonstrated between the AP and ML directions of displacements with open and closed eyes and also between the AP-ML mean-velocity ratio ( $r = 0.3$  to  $0.7$ ,  $p < 0.05$ ). Significant correlations were found between two additional variables in the whole sample, so between the static foot-load differences and the AP mean-velocity rate ( $r = 0.28$ ,  $p = 0.031$ ) furthermore between the static foot-load differences and ML mean-velocity rate ( $r = 0.41$ ,  $p = 0.001$ ).

We compared the rate of changes between the groups regarding the results of the biometric analysis. We found no differences between the groups in the static foot-load, in the elliptical surface analysis, in the Romberg-index data and in the AP mean-velocity rate values. However, differences were found between Group I and II in ML mean-velocity rate values.

Correlations were analysed between the results of the functional tests. The age influenced the value of the TUG test by 26% in all participants and that of the BBS by approximately 40%. We investigated whether there is a correlation between the results of the elliptical surface and the values of the functional tests. There are moderate positive correlations between the baseline TUG values and baseline and post interventional elliptical surface values in the case of open eyes. Similarly, there are connections between post interventional TUG test values and post interventional elliptical surface values with opened eyes, furthermore between post interventional TUG test and the change of the elliptical surface. Correlation between FRT, BBS and elliptical surface could also be found.

## DISCUSSION

### **The direct effect of physical activity on BALP and CTX levels**

Exercise-induced change in bone turnover is triggered by the mechanical deformation in osteoblasts and osteocytes (Turner, 2009). In live tissues, osteocytes react fast to mechanical impacts. Gene expression and / or protein expression of bone turnover markers also occurs rapidly (Qi, 2009; Mantila Roosa, 2011). Our investigation confirmed that both a 60-minute, moderate intensity, targeted physiotherapy session and brisk walking have an immediate effect on BALF levels. While physiotherapy did not decrease BALP significantly, walking did; however, the difference between the changes in the two groups was not significant. In contrast, CTX values showed a considerable drop in the group of women with a peak bone mass; the extent of the decrease being significant in the walking group. Continuous axial loading present during brisk walking may provide more stimuli for bone metabolism in younger people.

The findings of participants with decreased bone density were partly concordant, partly conflicting. Both investigation groups showed a relatively minor change in BALP values. However, we detected a significant decrease in CTX values in the physiotherapy group, while the walking group did not produce significant changes. There is a significant difference between the two groups, i.e. between the two types of exercise, as physiotherapy produced a more pronounced decrease in CTX values, therefore it has more influence.

Several meta-analyses have investigated the long-term efficiency of training programs in postmenopausal women and they found that specific exercise programs have beneficial effects: while walking can slow down the reduction of bone mass, strengthening exercises provide a powerful stimulus to increase bone density (Sapir-Koren, 2013). It can account for the significant change in CTX values in the physiotherapy group and the less pronounced changes in the walking group, as physiotherapy induces powerful muscle activity in the large skeletal muscles and it utilizes the full range of movement in the large joints, while the walking group used a smaller range of movement with less muscle activity. At older ages, more powerful stimuli are necessary to trigger bone turnover and walking plays a maintenance role only. In order to increase and maintain bone mass, a much more intense strengthening training program is needed.

Although the physical load used in the two investigation groups was not completely synchronized, it is still clear that brisk walking resulted in a more pronounced change in CTX levels in younger women; subjects with decreased bone density produced more significant CTX changes as a result of a physiotherapy session that involved various postures and exercised bigger muscle groups. The basis of the mechanical stimulus that stimulates bone formation is muscle activity, which controls the adaptation of the bone to the tension (Rittweger, 2008). Presumably, as we get older the skeletal systems needs a more powerful biophysical stimulus associated with more intense muscle contraction, rather than the musculoskeletal weight alone. The relationship between bone strength and age-related skeletal loading in women is not completely understood. It seems that exercises of the same type that increase bone density in younger women might be ineffective in older ones and vice versa (Zittermann, 2002), which is also supported by our present study.

### **The effect of physical activity on sclerostin levels**

It was only the group of women with decreased bone density where we could examine sclerostin levels. Sclerostin levels increased as a result of both types of physical activity; they increased by 12% in the physiotherapy group and 27% in the walking group. The effect proved to be significant in the walking group but the difference between the two groups is not significant. The main sensor of the mechanical impact is the network of osteocytes; their sensitivity to the change in tension and the fine-tuning of osteoblast-osteoclast function result in bone transformation (Turner, 2002). We postulate that bone destruction occurs first as a result of a faster response to mechanical impact. Bone formation starts at the same time but at a smaller extent, so the mechanical impact triggers a rise in sclerostin levels produced by osteocytes (Lombardi, 2012). In our study, sclerostin bound to osteocytes reacted to the mechanical impact fast.

The normal level of sclerostin depends on age and gender. In women, the premenopausal level is  $24.6 \text{ pmol/l} \pm 5.7 \text{ pmol/l}$ , while the postmenopausal one is  $30.3 \text{ pmol/l} \pm 8.8 \text{ pmol/l}$ . In our study, we measured  $26.7 \pm 13.8 \text{ pmol/l}$  in the physiotherapy, and  $23.1 \pm 11.2 \text{ pmol/l}$  in the walking group. Amrein *et al.* (2012) found that the sclerostin level of healthy adults shows a positive correlation with age and BMI. In our study, we found a significant, positive, moderate correlation between baseline sclerostin levels and BMI, which is concordant with the findings of Amrein. Research into treatment modalities that use sclerostin inhibition can provide promising results in the management of bone loss of various origin **Hiba! A könyvjelző nem létezik.**

### **Comparison of the two study groups**

The mean age of the first study group is 25 years, while that of the second one is around 60 years. Both variables are about 19% higher in the peak bone mass group (BALP: 19,05; CTX: 19,3%), which confirms the faster bone metabolism of the younger age group. The degree of change due to physical activity is also considerable; though the exercise regimes were not completely the same, CTX levels decreased significantly in the peak bone mass group and they showed a pronounced change in the other study group as well. Our findings confirm the positive effects of physical exercise on bone metabolism in all age groups, therefore it has to be included in the management of osteoporosis as a supplement to medical treatment.

The lower efficiency of postmenopausal training programs compared to young and healthy women can be attributed to age-related changes, especially the lower levels of oestrogen. At a younger age, oestrogen has a beneficial effect on the relationship of skeletal muscles and bone density (Thorsen, 1997). We can conclude that in the peak bone mass group brisk walking, which is associated with axial loading, is more effective concerning bone turnover, while in the decreased bone density group physiotherapy that included more joint movement and muscle contraction was more effective.

### **The efficiency of sensorimotor training**

The third investigation (third study group) supports the usefulness of physiotherapy concerning postural balance, thereby confirming the results of several previous studies (Oliveira, 2014; Alfieri, 2012; Resende, 2008). The aim of the investigation was to prove the efficiency of sensorimotor training compared to conventional training and the control group. Although posture and balance are not conscious motor functions, it has been established that postural reactions provide adaptation to environmental requirements and/or motor learning (Melzer, 2004). Older people will not use the reflex response if it results in falling, rather they will learn to control their posture in an unusual sensorimotor environment (Nashner, 1976).

As regards the examined biometric indices, we found no significant change in the static and stabilometric indices, except for ML mean velocity rate, which is the result of reduction in open-eye ML mean velocity. It has been established earlier that postural sway parameters are more sensitive to different sensory conditions and they tend to change in ML direction, total sway path and sway area (Rugelj, 2007). Our study detected only a slight change in ML direction. However, if we check training-induced changes in the stabilometric literature, we get conflicting results. Some authors report changes in stabilometric results and attribute these

changes to improvement in balance, possibly related to the intervention (Binda, 2003; Hue, 2004). By contrast, other researchers found no changes in stabilometric indices as a result of physical exercise (Nagy, 2007; Steadman, 2003).

When checking the *static loading* of the lower limbs, we found asymmetry in body weight distribution, similarly to the research of Blaszczyk *et al.* (2000). On the first measurement we found a 10% difference between the two legs concerning all investigations. This finding can result from several factors, such as the different development of the two sides, concomitant scoliosis or contraction of the muscles around the hip. Blaszczyk *et al.* found that the asymmetry in leg load and AP sway correlated with each other. Our findings showed a weak correlation between static loading of the lower limbs and the mean velocity rate of AP sway, and moderate correlation when examining the ML direction. When analysing open – and closed eye leg loading, we can find a significantly greater difference between the two in the elderly, but no difference in the younger age group, so we can conclude that the decreased postural stability in the elderly can be attributed to the difference in leg loading (Maranhão-Filho 2011). Wang *et al.* (2012) found that asymmetric loading of the lower limbs has an influence on coordination dynamics and also on the shift of the centre of mass. Presumably, weight distribution deficit in the lower limbs affects lateral balance in the examined sample group.

### **Change in values indicating functional stability**

The risk of falling can be estimated and reduced via a supervised and challenging strengthening training program in balancing (Gillespie, 2000; Perry, 2012). The best and most simple indicator of the risk of falling is BBS. A decrease in BBS score correlates with an increased risk of falling and this relationship is not linear. A reduction of one single point in the score range of 54-56 increases the risk of falling by 3-4%; however in the range of 46-54 it does so by 6-8%. Below 36 points, the risk of falling is almost 100% (Shumway-Cook, 1997). The participants of our study had a score of 46.65, which falls 9.35 points below the ideal value, so their risk of falling is 50.1-66.8%. Sensorimotor training resulted in an increase of 4.1 points, while the 10-session training improved the results by 0.6 point only. The score of the control group decreased by 0.95 point. According to Donoghue (2009), for a perceivable change an increase of min. 4 points is necessary in the baseline range of 45-56 points (confidence interval: 95%). In our study, we managed to reach this level. Based on the difference between the groups – including all components of the functional balance – we can conclude that sensorimotor training is capable of improving balance in women with decreased

bone density. Programs developed to prevent falls are similar to the ones that are meant for the elderly. Based on large-scale reviews, we can say that most exercise programs aim to increase muscle strength and aerob capacity, improve balance and the flexibility of lower limb muscles and joints (Turner, 2000; Brown, 1999).

## Conclusions

The investigations described in my doctoral thesis confirmed the direct effects and usefulness of exercise- and physiotherapy in the treatment of people suffering from decreased bone density and supported the influence of even one single session of intense physical activity on bone turnover by producing detectable changes in biochemical markers.

It is never too late to start physical exercise. Although many factors affect bone metabolism and we cannot influence all of them, presumably an exercise program started and continued in osteoporosis or osteopenia can prevent considerable bone loss and consequent bone fractures if applied together with medical therapy.

While at younger ages brisk walking performed in a vertical posture and providing axial load can stimulate bone turnover, those who already have decreased bone density benefit more from exercises that move large muscles and require a larger range of joint motion, as they have a more powerful effect on markers of bone turnover.

As regards modifiable lifestyle factors, smoking has a negative effect on bone formation even at a younger age, while regular physical activity has a positive effect on bone density even in such a small sample.

A progressive sensorimotor training that takes at least 3 months can improve functional balance significantly; however, a 10-session training cannot provide such benefits. A change in lifestyle and lifelong activity are necessary to prevent falls.

## **NEW FINDINGS**

In decreased bone density, comprehensive physiotherapy that moves large muscle groups and joints has a more beneficial effect on bone resorption markers than walking.

The 10-session physiotherapy which is routinely used in Hungary does not improve stabilometry indices or functional stability; to achieve a real improvement in balance targeted physiotherapy is necessary for a longer period of time.

A 3-month sensorimotor training can improve functional stability and lateral stabilometric indices, therefore it may be capable of decreasing the number of falls.

## **ACKNOWLEDGEMENTS**

I received a lot of support and assistance with my doctoral thesis.

I wish to thank, first and foremost, my supervisor, prof. János Kráncz for his support and assistance.

I would also like to show my gratitude to József Betlehem, dean of the faculty, for his understanding and encouragement.

I am indebted to Béla Schmidt, head of department, for his professional support and motivation.

This thesis would not have been possible without László Szekeres M.D., who put forward the original idea of the research and who was of great assistance during the laboratory investigations.

I must also acknowledge Judit Papp Gombos, and my previous students, Szandra Hauzer, Noémi Jéger, Kata Vass and Ágota Szántó for their active participation in the study.

Appreciation also goes out to my colleagues at the Education Centre of Zalaegerszeg for their encouragement and assistance.

I would also like to thank my family, husband, son and daughter for their understanding and patience.

## PUBLICATIONS

### Articles related to the Thesis

- Császárné Gombos G, Bajsz V, Sió E, Tóthné Steinhausz V, Schmidt B, Szekeres L, Kráncz J. The direct effect of specific training and walking on bone metabolic markers in young adults with peak bone mass. *Acta Physiol Hung.* 2014;101(2):205-215.
- Császárné Gombos G, Sió E, Bajsz V, Schmidt B, Kráncz J. A gyógytorna és a gyaloglás direkt hatása a csontanyagcsere-markerekre és a sclerostin-szintre csontritkulásban. *Egészségakadémia.* 2013;4(3):174-186.
- Császárné Gombos G, Fekete J, Tóthné Steinhausz V, Schmidt B, Szekeres L. Célrányos gyógytorna foglalkozás direkt hatása a csontanyagcsere-markerekre fiatal, csúcscsonttömegű felnőtteknél. *Magyar Reumatológia.* 2010;51(4):291-300.

### Main abstracts related to the Thesis

- Gombos G, Steinhausz V, Schmidt B, Szekeres L. The direct effect of moderate intensive physical activity on biomechanical markers of bone metabolism among healthy young people.. *Physiotherapy.* 2011;97(S1):eS415.
- Gombos G, Fekete J, Domján P, Schmidt B, Molics B, Boncz I. The effect of one-time physical therapy on biochemical markers of bone metabolism. *Value in Health.* 2011;14 (7): A303.

### Original articles

- Pek E, Fuge K, Marton J, Banfai B, Csaszarne Gombos G, Betlehem J. Cross-sectional survey on self-reported health of ambulance personnel. *Scand J Trauma Resusc Emerg Med.* 2015;23(14):1-9.
- Bajsz V, Sió E, Tóthné Steinhausz V, Karamánné Pakai A, Császárné Gombos G. Egy multinacionális cég egészségfelmérése a munkahelyi stressz tükrében. *Egészségfejlesztés.* 2014;54(5-6): 40-47.
- Sió E, Császárné Gombos G, Rashed A, Mazur M: Szív-műtéten átesett krónikus obstruktív tüdőbetegek perioperatív adatainak elemzése fizioterápiás szempontból. *Egészség-Akadémia.* 2013;3(3):194-202.
- Czompol O, Csaszarne Gombos G: Foglalkoztató-terapeuták nemzetközi képzése. *Mozgásterápia.* 2006; 1(1): 24-25.
- Gombos G, Czömpöl O. Inclusion in Zalaegerszeg, *Journal of the network for prevention of child maltreatment.* Timisoara. 2005;16:40-44.