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AN ASSESSMENT OF THE INFLUENCE OF FLUORIDE, MODIFIED TRANSDERMAL REPLACEMENT HORMONE THERAPY AND SUPPLEMENT HORMONE THERAPY ON UNMANAGEABLE OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

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Abstract

The study was conducted on 40 women in the early postmenopausal period, aged 52.3±3.1 years with primary osteoporosis unmanageable in treatment, divided into 2 groups based on a randomized list. Group I (*n*-20) was administered orally fluoride 0.25 mg kg^{-1} 24 h^{-1} with modified transdermal hormone therapy/HRT, and group II (*n*-20) was administered orally fluoride and supplement hormonal therapy(HST) in 21 therapeutic cycle. The serum concentrations of osteocalcin (OC), procollagen(PICP), insulin-like growth factor I (IGF-1), prolactin basic (PRL) and prolactin after metoclopramide (PRL/ MCP) 4 times by using radioimmunoassy methods, before treatment and after 1, 3, 12 months of treatment. Bone mineral density (BMD) L2 – L4 was determined before treatment and at 12 month with a dualenergy x-ray absorptiometry scanner (Lunar DPX-1Q). In group I women receiving fluoride and transdermal HRT IGF-1 increased significantly while the concentrations of OC and PICP significantly decreased after 3 and 12 months of treatment but no statistically significant changes in the PRL concentration occurred. In group II women receiving orally fluoride and HST, a significant decrease in the concentration of IGF-1, OC after 3 and 12 months and a significant increase in the concentration of PRL and PRL/ MCP after 1, 3 and 12 months of treatment compared with the baseline values appeared.

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The concentration of type I procolagen (PICP) showed no statistically significant changes. Increase in bone mineral density was statistically significant L1, L2 ($p < 0.05$), L3, L4 ($p < 0.01$) compared with the baseline in the group receiving transdermal HRT. In women receiving fluoride and orally HST increase in the bone mineral density for L1 and L2 was non-insignificant, whereas for L3 and L4 it was significantly higher compared with the baseline ($p < 0.05$).

Key words: osteoporosis, fluoride, osteocalcin, modified hormone replacement therapy, hormone supplement therapy.

OCENA WPŁYWU FLUORU, ZMODYFIKOWANEJ PRZEZSKÓRNEJ HORMONOTERAPII ZASTĘPCZEJ I DOUSTNEJ HORMONOTERAPII WSPOMAGANEJ W LECZENIU OSTEOPOROZY OPORNEJ U KOBIET W OKRESIE POMENOPAUZALNYM

Abstrakt

Badaniem objęto 40 kobiet we wczesnym okresie pomenopauzalnym, w wieku 52,3±3,1 lat, podzielonych wg listy randomizowanej na dwie grupy: grupę I. (*n*-20) otrzymującą doustnie fluor w dawce 0,25 mg kg^{-1} 24 h^{-1} oraz zmodyfikowaną przezskórną hormonoterapię zastępczą (HTZ), grupę II (*n*-20) otrzymującą doustnie fluor w dawce 0,25 mg kg^{-1} 24 h^{-1} i hormonoterapię wspomaganą (HTW) w postaci tabletek. Cykle terapeutyczne w obu grupach trwały 21 dni w miesiącu z następową przerwą 7 dni w celu wystąpienia krwawienia z odstawienia przez okres jednego roku. W surowicy oceniano stężenia osteokalcyny (OC), prokolagenu (PICP), insulinopodobnego czynnika wzrostu (IGF-1), podstawową prolaktynę (PRL) i po teście z metoklopramidem (PRL/MCP) radioimmunologicznie czterokrotnie: przed leczeniem oraz po 1. 3. i 12. miesiącu leczenia. Gęstość mineralną trzonów kręgów lędźwiowych L2 –L4 badano przed leczeniem i po 12 miesiącach leczenia densytometrem, firmy Luna (DPX-1Q), metodą DEXA. U kobiet z grupy I otrzymującej doustnie fluor i przezskórnie HTZ wystąpił znamienny wzrost stężenia IGF-1, znamienne obniżenie OC, PLCP po 3 i 12 miesiącach leczenia oraz brak statystycznych zmian w stężeniu prolaktyny. Natomiast u kobiet z grupy II otrzymującej w postaci tabletek doustnie fluor i hormonoterapię wspomaganą HTW wystąpiło znamienne obniżenie stężeń IGF-1, OC po 3 i 12 miesiącach leczenia oraz znamienny wzrost stężenia prolaktyny podstawowej i po teście z metoklopramidem po 1. 3. i 12. miesiącu leczenia w porównaniu z wartościami wstępnymi. Stężenia prokolagenu w czasie stosowania doustnie fluoru i HTW nie wykazywały znamiennych różnic. Gęstość mineralna L2-L4 wykazywała znamienne przyrosty u kobiet z grupy I. Natomiast u kobiet z grupy II gęstość mineralna L1, L2 nie wykazywała przyrostu znamiennego, a w kręgu L3, L4 występował znamienny przyrost w porównaniu z wartościami wyjściowymi ($p < 0,01$).

Słowa kluczowe: osteoporoza, fluor, osteokalcyna, zmodyfikowana hormonalna terapia zastępcza, hormonalna terapia wspomagana.

INTRODUCTION

Osteoporosis is one of the most important problems in developed societies. The deficiency of bone mass or skeletal osteopenia results in fractures

of the spine, the distal of the radius and ulna bones and the neck of the femoral bone (Okopień et al. 2005). Fluoride is an important element in the mineralization of bone and teeth (Sowers et al. 2005) The proper use of topical and systemic fluoride has resulted in major reductions in dental caries and associated disability (Palmer et al. 2005), although the therapeutic effect in osteoporosis depends on their dose (Yamaguchi 2007). High doses of fluorides applied in the treatment of osteoporosis reduce mineral part of the compact bone (Busse et al. 2006).During the long-term therapy with fluorides, it was established that an increase in the bone mineral density is accompanied by an increase in the bone fracture frequency (Giachini et al. 2004, Reid et al. 2007, Vestergaard et al. 2008).

It is the consequence of disturbances in bone architecture, expressed by the loss of connections between the thinned bone trabeculares which leads to a decrease in the bone mechanical endurance (Pepene et al. 2004, Ringe et al. 2005, Otsuka et al. 2008).

OBJECTIVE

The aim of the study was to assess the influence of two kinds of hormonal therapy and the minimal effective fluoride dose on concentrations of osteocalcin, procolagen, insulin-like growth factor I, prolactin basal and prolactin after metoclopramide in serum as well as the degree of mineralization of the lumbar spine of unmanageable osteoporosis in early postmenopausal women.

MATERIAL AND METHODS

The study was conducted on 40 women in the early postmenopausal period, aged 52.3 + 3.1 years with osteoporosis unmanageable in treatment and no history of general diseases; there were no significant differences between groups in terms of age, body mass index and parity. The women were divided into 2 groups based on a randomized list. Group I ($n = 20$) was treated fluoride (Fluossen, Polfa) 0.25 mg kg^{-1} 24 h^{-1} orally with modified transdermal hormone therapy (HTR) in the form of patches (Systen Janssen–Cilag), according to Stanosz et al. (1995). Group II ($n = 20$) was treated floride 0.25 mg kg^{-1} 24 h^{-1} orally and hormone supplement therapy orally, by taking Cyclomenorette (Wyeth, Munster). The therapeutic cycle in each group lasted 21 days, with a treatment free interval of 7 days. Estimation in serum concentrations of insulin-like growth factor I (IGF-1) was performed by using immunoenzymatic assay (Boldon IDS), propeptide of type I procol-

lagen (PICP), kit from Orion Diagnostica, osteocalcin (OC), by radioimmunoassay (a kit from DRG), basal prolactin (PRL) and prolactin after metoclopramide (PRL/MCP) radioimmunoassay kit from bioMerieux. In all women, concentrations in serum were measured 4 times, before treatment and after 1, 3, 12 months of treatment. Bone mineral density (BMD) L2 – L4 was determined before treatment and at 12 months with a dualenergy x-ray absorptiometry scanner (Lunar DPX – 1 Q).

Statistical calculations were performed using the Statistica 6.188 PL. package made by StaSoft (STANISZ 1998).

RESULTS

The results are shown in Tables 1 to 2. As shown in Table 1, after 3 and 12 month of treatment in group I. (modified transdermal HRT) and group II (orally administered HST) significant OC levels were found. The concentration of PICP in group I after 3 and 12 was significantly decreased ($p < 0.05$). In group II, receiving orally given HST, the concentration of PICP did not change significantly. In group I of women receiving modified transdermal HRT, increased IGF-1 concentrations were found during the whole therapy with a significant increase after 1 month ($p < 0.05$) and 3, 12 month ($p < 0.01$). In the women receiving oral HST, IGF-1 concentrations were significantly decreased after 3 and 12 months of therapy ($p < 0.05$). The concentration of prolactin in women receiving transdermal modified HRT (group I) during the period of our study, under basic condition (PRL) and after MCP stimulation test (PRL/MCP) no statistically significant changes were observed. In the group of women receiving orally HST (group II), the concentration of prolactin basal after 3 month ($p < 0.05$) and 12 months ($p < 0.001$) was significantly increased. Prolactin level after MCP stimulation test (PRL/MCP) was also increased significantly ($p < 0.001$) in group II during the entire course of treatment.

Table 1

Concentrations of osteocacin (OC), procolagen (PICP), insulin-like growth factor I (IGF-1), prolactin basal (PRL), prolactin after metoclopramide (PRL/MCP)

Group *n*	Time	OC μg L^{-1}	PICP ng L^{-1}	IGI-1 μg L^{-1}	PRL μg L^{-1}	PRL/MCP μg L^{-1}
I 20 Baseline 1	1 mo	8.4+3.5	155.+41.1	88.1+20.2	19.1+6.4	210.+79.2***
	3 mo	7.6+4.1*	161.2+55.3	81.3+19.2*	20.4+7. 1*	282.4+99.1***
	12 mo	7.2+3.1*	166.4+57.2	79.2+16.1*	26.3+8.3***	290.3+87.1***

Data are shown as mean + SD, p indicates level of significance, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 2

Bone mineral density of the lumbar spine (BMD) L2 – L4 g cm^{-2} in women in early postmenopausal period receiving fluoride, modified transdermal hormone therapy (HRT) and oral supplement hormone therapy (HST)

Group *n*	Time	L1	L2	L3	L4	BMD L2-L4	BMD L2-L4 (%)
I 20	Baseline	0.851	0.921	0.984	0.961	0.948	
		+0.075	+0.086	+0.087	+0.075	+0.075	
	12 mo	0.876*	0.955 *	1.019**	1.006**	0.993**	
		+0.038	+0.069	+0.099	+0.112	+0.098	4.7
II 20	Baseline	0.876	0.924	0.970	0.905	0.933	
		+0.071	+0.068	+0.087	+0.085	+0.080	
	12 mo	0.884	0.939	0.992*	0.933*	0.951*	1.02
		+0.080	+0.084	+0.077	+0.079	+0.083	

L1 indicates BMD of the first lumbar spine; L2 BMD of the second lumbar spine; L3 BMD of third lumbar spine, L4 BMD of the fourth lumbar spine; L1 – L4 mean values of BMD in grams per square centimeter; BMD L2 – L4, BMD of the lumbar spine L2 – L4

*$p < 0.05$; **$p < 0.01$ significance of differences in comparison with baseline results (Student t test for paired variables); $p < 0.01$ – significance of differences in comparison with control group (ANOVA + Tukey's post hoc test; Student t test)

The results of BMD L2-L4 of the lumbar spine of baseline and after 12 months of treatment are presented in Table 2. The increase in BMD L2-L4 was statistically significant ($p < 0.01$) in women receiving modified transdermal HRT (group I) and also in women (group II) undergoing orally given HST ($p < 0.05$) in comparison with the values before treatment. The mean increase in BMD after one year of treatment was 4.7% in group I women who received modified transdrmal HRT and 1.02% in group II women, administered orally given HST.

RESULTS AND DSCUSSION

Significantly elevated BMD L2-L4 ($p < 0.01$) after 12 months of modified transdrmal HRT may be caused by an elevated level of IGF-1 and decreased PRL level (Stanosz et al. 2009). In contrast, women receiving orally given HST for 12 months were observed not to experience any significant increase in BMD L2-L4, which may be associated not only with elevated PICP and PRL levels ($p < 0.001$) in serum. Significantly lower IGF-1 concentration after 3 and 12 months in group II ($p < 0.05$) may be an indication of diminishing bone mass and of the risk factor of osteoporotic fractures in postmeno-

pausal women. Despite the great progress in the field of recognizing the pathomechanisms responsible for the development of osteoporosis, the currently applied prophylaxis and treatments are still widely considered to be unsatisfactory. New combined therapy schemes are constantly being searched for and new medications are being developed. Currently employed treatment patterns use the bone resorption inhibitors or the bone formation stimulators. The former group of drugs consists of biphosphonians, estrogens, progestagens, calcitonin, vitamin D3, calcium derivates preparations, tiazides (GALUS 2005, MACLAUGHLIN et al. 2006, PALMER et al. 2005). The latter group is composed of fluorides, anabolic steroids, (OKOPIEŃ et al. 2005) parathormone and some of the growth stimulation factor (OHTA 2005).

Fluorides are considered to be the most powerful stimulators of bone formation, giving the possibility to achieve significant trabercular bone mass increase. Studies have showed that higher bone fracture frequency (arms and legs) was observed among patients given high doses of fluoride (VESTERGAARD et al. 2008). However, administration of small doses of fluoride combined with calcium resulted in significant increase of bone mass from 5 to 10% and decrease of bone fracture frequency. The authors' own studies on women treated for osteoporosis for one year with no fluorides applied revealed that the serum and urine concentrations of fluorides decreased significantly down to the trace values. The reason for such an evident drop in fluoride content seems to be their incorporation into the hydroxyapatite structure of bones (WHELAN et al. 2006) Fluorides are considered to diminish the dissolution of apatite crystals through the direct replacement of hydroxyl ions in the crystalline net. The results of the study presented prove that 0.25 mg kg^{-1} 24 h^{-1} is an optimum daily dose of fluoride and transdermal HRT in the osteoporosis treatment as it ensures the fluoride blood concentration to stabilize on the top level of the physiological range.Conclusions

1. Modified transdermal HRT and fluoride modify concentrations of prolactin, osteocalcin, insulin-like growth factor, procolagen and bone metabolism.

2. Lower albeit significant increase in BMD of lumbar spine in women receiving orally given HST may be a result of significantly lower concentration of IGF-1 and-significantly increased prolactin.

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