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ORIGINAL ARTICLE

Risk factors associated with peri- and postmenopausal bone loss: does HRT prevent weight loss-related bone loss?

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Abstract In the present study we evaluated the risk factors associated with peri- and postmenopausal bone loss and the effect of hormone replacement therapy (HRT) on weight-loss-related bone loss. The study population, 940 peri- and postmenopausal women, was selected from a random sample (n = 2025) of the OSTPRE study cohort (n = 13 100) in Kuopio, Finland. Bone mineral density (BMD; g/cm^2) at the lumbar spine and femoral neck, and body weight, were measured at baseline in 1989–91 and at 5-year follow-up in 1994–97 by trained personnel. Five hundred and forty-seven women had never used HRT and 393 women used part-time or continuous HRT during follow-up of 3.8–7.9 years (mean 5.8 years). Similarly, of the 172 weight losers, 97 had never used HRT while 75 used it during follow-up. According to multiple regression analysis on the total study population (n = 940), HRT use, years since menopause and weight increase significantly predicted lower annual bone loss at both the lumbar spine and femoral neck ($p < 0.005$). Low baseline weight and higher age predicted higher bone loss only at the lumbar spine ($p < 0.001$) and high grip strength predicted lower bone loss only at the femoral neck ($p = 0.021$). In a sub-analysis on weight losers, weight loss predicted greater bone loss in HRT non-users ($p < 0.05$), whereas this was not observed in HRT users. These results remained similar after adjustment for age, weight, height, calcium intake, duration of menopause, baseline BMD and bone-affecting diseases/medication. In conclusion, the transition to menopause, HRT and weight change are the most important determinants of bone loss at both the lumbar spine and femoral neck. Furthermore, HRT seems to be effective in prevention of weight loss related bone loss.

Keywords HRT · Osteoporosis · Postmenopausal bone loss · Risk factors · Weight change

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Introduction

Osteoporosis is a worldwide threat to well-being [1,2]. The most relevant features of the disease are fractures associated with reduced bone mineral density (BMD) [3–5], which is mainly determined by peak bone mass as well as age- and menopause-related bone loss [6–9]. In addition, a variety of other habitual and external factors have been suggested to contribute to bone loss [10,11].

Weight and hormone replacement therapy (HRT) have repeatedly been found to significantly predict BMD changes [12–15]. However, the magnitude of the effect of these factors in association with other putative bone-loss-modifying factors as regards peri- and postmenopausal bone loss has not been clarified. Furthermore, it is not known for certain whether HRT protects women from weight-loss-related marked bone loss. It has been suggested that low body mass index (BMI) associated with low bone mass could be effectively counteracted by HRT [16]. Long-term population-based studies primarily concerning the interactive effects of HRT and weight change on femoral neck and lumbar spine BMD changes have not been published.

The aim of the present study was to investigate the risk factors associated with peri- and postmenopausal bone loss and whether the use of HRT protects women from weight-loss-induced bone loss.

Subjects and Methods

Study population

The study population was formed from the prospective Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study cohort. The OSTPRE cohort was established in 1989 by selecting all women born in 1932–41 and resident in Kuopio Province, Finland (n = 14 220). The baseline postal inquiry, including questions about health disorders, medication, use of HRT, gynecologic history, nutritional habits, calcium intake, physical activity, alcohol consumption, smoking habits and anthropometric information, was sent to these women at baseline in 1989. The 5-year questionnaire was sent in 1994 to the 13 100 women who responded at baseline.

Of the respondents to the baseline inquiry, 11 055 (84.4%) were willing to undergo dual-energy X-ray absorptiometry (DXA). A random stratified sample of 2362 women was selected for densitometry, of whom 2025 actually underwent baseline densitometry during 1989–91. The questionnaire information was updated individually at the time of bone densitometry. A total of 1551 women of the 1873 who actually underwent both baseline (1989–91) and 5-year (1994–97) measurements had serial valid measurements for both the lumbar spine and femoral neck (no osteoarthritis, scoliosis or other bone deformities). For this study, the following groups were successively excluded: (1) hysterectomized women (for whom it was impossible to define menopausal status) and bilaterally ovariectomized women (n = 445), (2) premenopausal women (n = 152) and (3) women who had used HRT before baseline but not during follow-up (n = 14). Thus, the final study population consisted of 940 women (beginning of menopause either before (postmenopausal) or during (perimenopausal) the study) aged 48–59 years at baseline densitometry. The beginning of menopause was defined as 12 months' amenorrhea [17] and its duration varied from 1 week to 26 years among the 940 women at 5-year measurement. The duration of follow-up among these women varied from 3.8 to 7.9 years (mean 5.8 years).

For the study of HRT effects on bone loss, the women were divided into two groups according to use of HRT. The use of HRT was calculated based on the use of estrogen-containing tablets and plasters during the follow-up taken for menopausal symptoms. The most common hormonal products were estrogen/progesterone combinations followed by estrogen alone. Non-users (n = 547) had not used estrogen therapy either before baseline or during follow-up, whereas users (n = 393) had been on HRT continuously or occasionally during follow-up. Forty-five percent of HRT users had also used HRT prior to baseline. The duration of HRT was on average 51.3% of the follow-up time. Information about the use of hormonal products was obtained from the questionnaires by asking 'Have you used any hormonal products for prevention of menopausal symptoms?' Comparison between self-reported use of HRT and the national prescription records of The Social Insurance Institution, Finland (KELA), for the whole OSTPRE cohort in 1996—2001, revealed that 97.8% of those who had received an estrogen drug prescription reported HRT use in inquiries. On the other hand, in 25.5% of the self-reported non-users of HRT some estrogen use (short-term, median 6.0 months) was recorded (Sandini 2002; unpublished data).

Weight (kg) was measured at the baseline and 5-year densitometries. Simultaneously, grip strength was measured with a handheld dynamometer (Martin Vigorimeter, Germany) and taken to be the mean of three measurements. The calcium intake of each participant was calculated according to self-reported ingestion of dairy products and reported as the mean of two measurements (baseline, 5-year follow-up). The amount of nutritional calcium ingested was approximated at 120 mg/dl for fluid milk products (milk, sour milk, yoghurt, etc.) and 87 mg/slice for cheese.

Bone mass measurements

The BMD of lumbar spine (L2–L4), left femoral neck, Ward's triangle and trochanter major was determined using the same DXA equipment (Lunar DPX, Madison, WI, USA) at both baseline and 5-year follow-up. The measurements were carried out at Kuopio University Hospital by specially trained personnel. The long-term reproducibility (coefficient of variation) of the DXA instrument for BMD during the study period, as determined by regular phantom measurements, was 0.4%. The short-term reproducibility of this method has been shown to be 0.9% for lumbar spine and 1.5% for femoral neck BMD measurements [18].

Statistical methods

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS 9.0, SPSS, Chicago, IL) for Windows. The annual BMD changes at both measurement sites were calculated according to the following formula: [(BMD at the 5-year follow-up – BMD at baseline)/duration of follow-up] and reported as the percentage of baseline BMD. Similarly, weight change was taken to be a percentage of baseline weight. Putative risk factors were selected for the multiple regression model on the basis of their statistical significance in linear univariate regression models (inclusion criterion: $p < 0.2$) and additionally on the basis of being clinically applicable. Furthermore, the same variables were forced into both models regardless of significance $p < 0.2$ or $p > 0.2$ at the other site to obtain comparable analysis. The factors tested in the univariate model were (significance in univariate model lumbar spine/femoral neck): baseline weight ($p < 0.05/p = 0.220$), weight change (from baseline to 5-year measurement) ($p = 0.061/p < 0.001$), baseline height ($p = 0.472/p = 0.372$), age ($p < 0.001/p < 0.05$), time since menopause ($p < 0.001/p < 0.001$), grip strength ($p < 0.05/p = 0.072$), calcium intake ($p = 0.083/p = 0.074$), coffee intake ($p = 0.463/p = 0.296$), alcohol intake ($p = 0.870/p = 0.625$), smoking ($p = 0.359/p = 0.975$), age at menarche ($p = 0.774/p = 0.491$), and parity ($p = 0.736/p = 0.537$). In multiple regression, all variables were entered simultaneously into the model. In the analysis of HRT, factors affecting bone loss according to linear regression were used. Adjustment for age, baseline weight, baseline height, baseline BMD, calcium intake, duration of menopause and bone-affecting diseases/medication (yes/no) was used when appropriate. The selection of bone-affecting diseases/medication has been described previously by Kröger et al. [19]. Diseases were: renal disease, liver disease, insulin-dependent diabetes, malignancies, rheumatoid arthritis, endocrine abnormalities (parathyroid/thyroid glands, adrenals), malabsorption (including lactose malabsorption), total/partial gastrectomy, postovariectomy status, premenopausal amenorrhea, alcoholism and long-term immobilization. Medication included: corticosteroids, diuretics, cytotoxic drugs, anticonvulsive drugs, anabolic steroids, calcitonin, bisphosphonates and vitamin D.

Results

Table 1 shows the baseline and follow-up characteristics of the study groups. The duration of menopause, age at baseline, baseline weight, grip strength, mean annual BMD changes and prevalence of wrist fractures before the baseline differed significantly between HRT non-users and non-users in the total population. Table 1 also shows that HRT non-users were healthier in both the total population and weight-loser subgroup. In the

Table 1 Baseline and follow-up characteristics of the study groups

Characteristic	Study groups			
	No HRT (n = 547)	HRT (n = 393)	Total (n = 940)	Significance
Total population (n = 940)				
A. Means (SD) of continuous variables				
Duration of follow-up (years)	5.8 (0.5)	5.8 (0.4)	5.8 (0.5)	NS
Duration of menopause (months)[a]	101.6 (53.1)	82.7 (49.6)	93.9 (52.5)	$p < 0.001$
Proportion of HRT time in follow-up (%)	–	51.3 (36.0)	–	–
Baseline age (years)	53.9 (2.8)	53.2 (2.8)	53.6 (2.8)	$p < 0.001$
Baseline height (cm)	160.9 (5.2)	161.4 (5.1)	161.1 (5.2)	NS
Baseline weight (kg)	70.4 (12.5)	66.4 (9.6)	68.7 (11.5)	$p < 0.001$
Weight change (kg)	3.1 (5.3)	2.8 (4.8)	2.9 (5.1)	NS
Baseline grip strength (kPa)	61.2 (16.3)	64.0 (16.0)	62.4 (16.2)	$p = 0.010$
Mean calcium intake (mg/day)[b]	814 (378)	754 (358)	789 (371)	$p = 0.034$
Baseline lumbar BMD (mg/cm^2)	1.10 (0.15)	1.12 (0.16)	1.11 (0.16)	NS
Baseline femoral neck BMD (g/cm^2)	0.92 (0.12)	0.92 (0.13)	0.92 (0.12)	NS
Annual lumbar BMD change (%)	–0.61 (0.95)	–0.25 (1.14)	–0.46 (1.05)	$p < 0.001$
Annual femoral neck BMD change (%)	–0.69 (0.87)	–0.48 (0.90)	–0.60 (0.89)	$p < 0.001$
Distribution of category variables (%)				
Use of HRT during follow-up				
Occasional (<90%)	–	75.8	–	–
Continuous (≥90%)	–	24.2	–	–
Fracture history at baseline	23.0	18.8	21.3	NS
Previous wrist fracture at baseline	7.7	4.3	6.3	$p = 0.027$
Alcohol >1 drink/week at baseline	31.1	38.0	33.9	NS
Current smoker at baseline	8.7	10.7	9.5	NS
High overall physical activity level[c]	32.7	33.2	32.9	NS
No bone affecting disease/medication	72.2	50.1	63.1	$p < 0.001$
Weight-losers (n = 172)	(n = 97)	(n = 75)	(n = 172)	
Means (SD) of continuous variables				
Baseline age (years)	54.2 (2.7)	53.3 (2.7)	53.8 (2.7)	NS
Baseline height, (cm)	160.8 (5.3)	161.5 (5.3)	161.1 (5.2)	NS
Baseline weight (kg)	60.1 (15.2)	54.1 (2.7)	53.3 (2.7)	NS
Baseline grip strength (kPa)	60.1 (15.2)	62.6 (17.5)	61.2 (16.3)	NS
Mean calcium intake (mg/day)[b]	793 (306)	787 (331)	790 (316)	NS
Distribution of category variables (%)				
Fracture history at baseline	24.2	21.7	23.1	NS
Alcohol >1 drink/week at baseline	29.2	37.8	32.9	NS
Current smoker at baseline	8.2	13.3	10.4	NS
High overall physical activity level[c]	30.6	23.0	27.3	NS
No bone affecting disease/medication	71.4	48.0	61.3	$p = 0.001$

NS, non-significant ($p > 0.05$)
[a] At 5-year (second) measurement
[b] Mean of baseline and 5-year (second) measurements
[c] Women divided into three categories based on combined physical activity at work and leisure (low/moderate/high)

weight-loser subgroup no other differences were observed between study groups as regards these characteristics.

Table 2 presents the results of multiple regression analysis for the 940 women. Recent menopause, no use of HRT and weight loss predicted greater bone loss at both the lumbar spine and femoral neck. In contrast, high age and low weight at baseline were found to predict increased bone loss only at the lumbar spine, and high grip strength to predict lower bone loss only at the femoral neck. Prediction of bone loss at the femoral neck in relation to nutritional calcium intake was found to be of borderline significance ($p = 0.053$). The prediction of bone loss by the multivariate model in Table 2 explained 26.5% (crude/adjusted $R^2 = 0.272/0.265$ at the lumbar spine) and 13.6% (crude/adjusted $R^2 = 0.145/0.136$ at the femoral neck) of the observed bone mass changes in the present sample.

The effects of HRT on weight-loss-related bone loss were also studied. Figure 1 presents the effects of weight loss on mean annual BMD change (%) according to HRT use in a linear regression model. In all, 172 women (18.3%) lost weight during follow-up (mean –3.7 kg; –5.1% of baseline weight). In HRT non-users a statistically significant relationship was observed between weight loss and BMD decrease at both the femoral neck and lumbar spine. In HRT users weight loss did not have a statistically significant effect on bone loss at either measurement site. Accordingly, there was a considerable difference in bone loss rate between HRT users and non-users in women with a marked rate of weight loss (Fig. 1). Adjustment did not change these results.

Table 2 Effects of selected factors on annual BMD change (%) according to multiple regression analysis in peri- and postmenopausal women ($n = 940$)

Factor	Regression coefficient	Standard error	*T* ratio	Significance
Lumbar spine (adjusted R^2 = 0.265)				
(Constant)	–3.88	1.19	–3.26	0.001
Time since menopause (months)[a]	0.005	0.001	6.80	< 0.001
HRT use (% of follow-up time)	1.25	0.09	14.2	< 0.001
Weight (kg)	0.02	0.003	6.27	< 0.001
Age (years)	0.06	0.01	4.39	< 0.001
Weight change, baseline to 5 years (kg)	0.02	0.01	2.85	< 0.004
Height (cm)	–0.01	0.01	–1.59	0.112
Mean calcium intake (mg/day)	0.0001	0.0001	1.48	0.138
Grip strength (kPa)	–0.001	0.002	–0.48	0.629
Femoral neck (adjusted R^2 = 0.136)				
(Constant)	–0.47	1.09	–0.43	0.671
Time since menopause (months)[a]	0.003	0.001	4.33	< 0.001
HRT use (% of follow-up time)	0.68	0.08	8.36	< 0.001
Weight change, baseline to 5 years (kg)	0.03	0.01	5.23	< 0.001
Grip strength (kPa)	0.004	0.002	2.31	0.021
Mean calcium intake (mg/day)	0.0002	0.0001	1.94	0.053
Height (cm)	–0.01	0.01	–1.56	0.118
Weight (kg)	0.004	0.003	1.54	0.125
Age (years)	0.003	0.01	0.28	0.776

[a] At 5-year (second) densitometry

In Fig. 1 some observational data are also shown to provide more insight into the HRT effect on weight-loss-related bone loss.

In further analysis on other regions of femur the weight-loss-related bone loss seemed to be effectively counteracted by HRT at Ward's area. In contrast, weight-loss-related trochanteric bone loss seemed not to be counteracted by HRT (data not shown).

Discussion

In the present study we evaluated the risk factors associated with bone loss in peri- and postmenopausal women and the effect of HRT on weight-loss-induced bone loss in 940 peri- and postmenopausal women from the OSTPRE study cohort. Menopausal transition, no HRT use and weight loss were observed to be the most important determinants of postmenopausal bone loss. Furthermore, HRT seems to protect against weight-loss-related bone loss at both lumbar spine and femoral neck.

The strengths of our study were its prospective population-based nature, large base population and long-term follow-up. The follow-up interval was the same in the HRT users and non-users. In addition, the correlation between self-reported and observed use of HRT among this study population has been observed to be high (Sandini 2002; unpublished data). The study population was randomly selected, so that selection bias was unlikely to have occurred. Finally, comprehensive adjustment, including for a variety of bone-affecting diseases, was used in the analyses.

In epidemiologic studies the possibility of uncontrolled confounding is obvious. In our study the division of women into HRT users and non-users ('ever' and 'never' users) was straightforward. By this means we avoided the use of arbitrary cut-off points in self-reported HRT use, but the part-time HRT use may have distorted the results due to a non-steady bone metabolic state although the duration of HRT was on average half (51.3%) of the follow-up time in our study. We could have analyzed continuous HRT users (over 80–90% of follow-up) separately, but the number of women was too small for reliable analyses. Unfortunately, our inquiries did not provide any information on the main indication for HRT. In addition, the surprisingly poor validity of no use of HRT among non-users might have resulted in a slight underestimation of the true HRT effect. In all, although the part-time HRT may not reflect its true effect in our study, overestimation was certainly avoided. Another source of confounding may be that the majority of women lost less than 10% of their baseline weight, making it difficult to determine bone loss rate reliably in more significant weight-losers. Also, HRT non-users seemed to be healthier, which might modify the results, although the number of diseases and medications were used for adjustment. Furthermore, in the present study the initial reason for weight loss was not known, but the results were adjusted for bone-affecting diseases and medications making bias due to these factors unlikely. Finally, the study population, although randomly selected, represented a relatively small proportion of the original OSTPRE cohort. These limitations can only be avoided in randomized controlled trials.

To our knowledge, no previous studies have primarily been directed to the effects of HRT on weight-change-related bone loss in a longitudinal long-term population-based study. It has been reported that HRT counteracts thinness-associated bone loss [16]. However, it has been suggested that weight change may alter bone metabolism regardless of baseline weight [20]

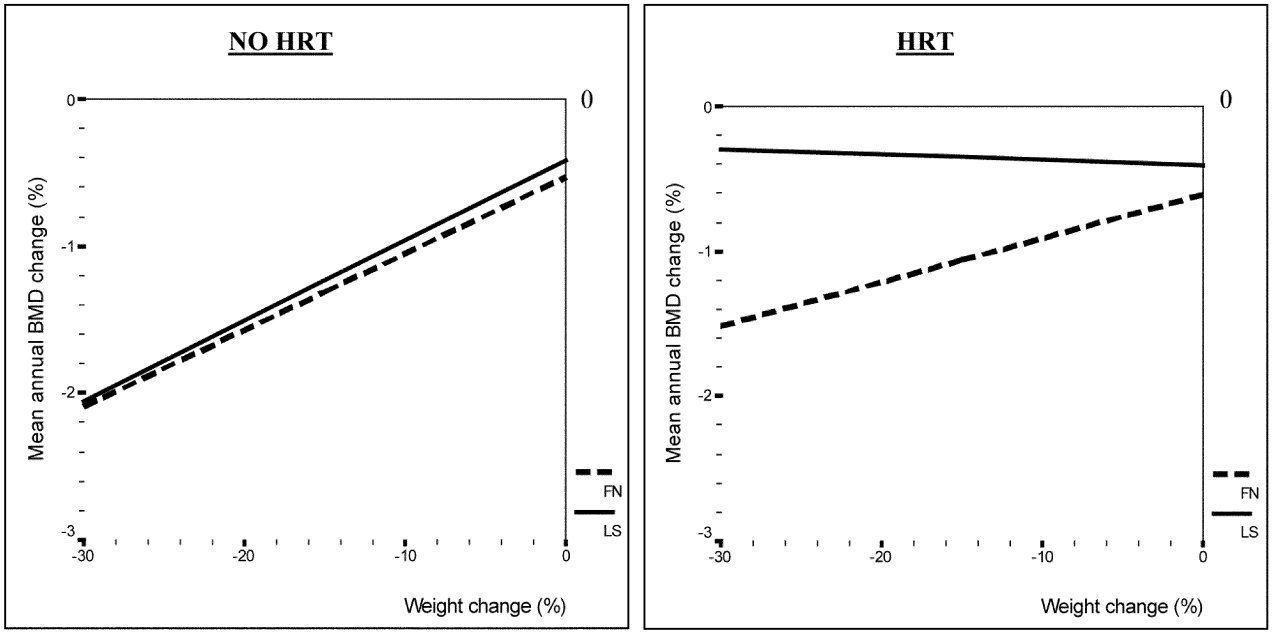

Fig. 1 Effects of weight change according to HRT use in peri- and postmenopausal weight-losers (n = 172). Linear regression model. FN, femoral neck; LS, lumbar spine

Equations predicting bone loss according to weight loss (%) (WL)

Model	Site	Mean annual BMD change (%) (ANN)	Significance (p-value)
No HRT (n = 97)			
Crude	Lumbar spine	ANN = –0.41 + 0.05*WL	0.032
	Femoral neck	ANN = –0.53 + 0.05*WL	0.011
Adjusted[a]	Lumbar spine	ANN = –6.54 + 0.09*WL	< 0.001
	Femoral neck	ANN = –1.50 + 0.05*WL	0.026
HRT (n = 75)			
Crude	Lumbar spine	ANN = –0.40 – 0.004*WL	0.914
	Femoral neck	ANN = –0.61 + 0.03 *WL	0.236
Adjusted[a]	Lumbar spine	ANN = –4.61 + 0.02 *WL	0.573
	Femoral neck	ANN = –0.14 + 0.04 *WL	0.166

[a] Adjusted for age, weight, height, time since menopause, calcium intake, baseline BMD, and bone-affecting diseases and medications (yes/no)

Observational effect of HRT on weight loss related bone loss[b]

	Weight loss group	n	Mean annual bone loss rate, % (SD)	
			Lumbar spine	Femoral neck
No HRT	< 5% of baseline weight	61	–0.51 (0.96)	–0.66 (0.78)
(n = 97)	> 5% of baseline weight	36	–1.00 (1.28)	–1.07 (1.03)
HRT	< 5% of baseline weight	49	–0.38 (1.09)	–0.65 (0.89)
(n = 75)	> 5% of baseline weight	26	–0.39 (1.24)	–0.96 (0.78)

[b] Observed; *not* based on the equations above

and, accordingly, weight change should be included as a variable in analyses. In addition, Komulainen et al. [21] have reported that thinness may result in no response to HRT, providing a totally opposite view to this interaction. In our study, however, the considerable difference between HRT users and non-users in bone loss rate among women with significant weight loss (e.g. –30% in Fig. 1) indicates a positive HRT effect and not the possibility that weight loss counteracts the effects of HRT. The results reported by Komulainen et al. may accordingly reflect an error in the interpretation of causality based on a single body weight measurement only. On the other hand, the surprisingly small difference between HRT users and

non-users in less significant weight-losers may reflect a degree of non-response. Only randomized trials can explain these differences.

The results of multivariate analysis indicated that factors significantly affecting bone loss are few: body weight and menopausal transition mainly determine the rate of postmenopausal bone loss. Other prospective studies have also shown similar results and the role of weight-loss-related bone loss is well establised [12,15,22,23]. Nevertheless, several other behavioral factors, such as smoking and alcohol consumption, have been found to predict BMD change [10,11,16] and smoking may also dampen the bone-protective effects of HRT [21]. However, because of poor reproducibility of significant results in longitudinal studies, these factors are likely to play a minor role in bone loss and indicate a need for more accurate research.

The pathophysiology of weight-change-related BMD changes is not fully understood. Different components of body mass, such as fat and muscle mass, may have different roles in bone mass changes while the relationship between fat and estrogen metabolism is well established. The increased estrogen production in fat tissue readily explains the results of the present study as well as the previous reports of an increase in BMD during weight gain and vice versa. Accordingly, weight-loss-induced fat tissue resorption and consequent estrogen depletion could be prevented by external estrogen, resulting in maintenance of bone mass. In addition the contribution of nutritional factors, most importantly calcium intake, to weight-loss-related bone loss remains unknown.

There may be several reasons for a clearer effect of HRT on weight-change-induced bone loss at the lumbar spine than at the femoral neck in the present study. The effects of menopause and HRT have been found to differ between skeletal sites [7,14] and, accordingly, HRT is more likely to affect trabecular (spinal) bone. In contrast, mechanical factors (body-weight-related, weight-bearing stress, exercise) are more likely to affect the femoral neck, where muscle strength seemed to protect against bone loss in the present study. In fact, the results of a previous study suggest that HRT and weight-bearing exercise have an additive effect on bone loss prevention [24]. It could be that exercise-induced weight loss could have a more significant effect on bone loss in contrast to purely restricting calorie intake. The differences in mechanical load could also partly explain our results that the trochanter major region lacked the protective effect of HRT. Another reason for this effect could be different responses of these regions to HRT and weight change. In addition, the part-time nature of HRT in our study may have caused different responses in cortical and trabecular bone as a result of a non-steady bone metabolic state.

The relationship between weight control and osteoporosis is problematic. Being overweight is a well-known risk factor as regards increased morbidity and mortality [25,26] and obviously weight loss should be encouraged in an overweight population regardless of the fact that it accelerates bone loss. Thus, the effective management of weight-loss-induced bone loss is important. Our study demonstrates the efficacy of even part-time HRT in solving this problem. The initiation of marked weight loss should be an indication to start HRT in peri- and postmenopausal women. In this way the same degree of prevention of osteoporosis might be achieved in both weight-losers and in women maintaining their body weight. Our results need confirmation by means of randomized trials and observational studies. In addition, the mechanisms underlying weight-loss-induced bone loss and its counteraction by HRT need further clarification.

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