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Bone loss and wrist fractures after withdrawal of hormone therapy: The 15-year follow-up of the OSTPRE cohort

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ABSTRACT

Context: Long-term bone mineral density (BMD) or fracture incidence changes after withdrawal of postmenopausal hormone therapy (HT) are not well known.
Objective: To study long-term postmenopausal bone loss and incidence of wrist fracture in respect to duration and withdrawal of self-reported HT.
Design/setting: A 15-year follow-up of the population-based prospective OSTPRE cohort in Kuopio, Finland.
Participants: Women (mean baseline age 53.4 years, range 48.1–59.6) were divided into four groups based on duration of HT: (1) never users (non-HT); (2) those who had used HT only throughout the 1st 5-year period (HT5); (3) throughout the first 10-years (HT10); (4) those who used HT throughout the entire 15-year follow-up (HT15).
Outcome measures: Femoral ($n = 857$) and spinal ($n = 599$) BMD measurements with dual X-ray absorptiometry (DXA) were carried out at 5-year intervals in 1989–2004. Wrist fracture incidence in 1989–2004 was studied in a population of 5119 women.
Results: The adjusted **spinal BMD** (L2–L4) changes by HT use during the entire 15-year follow-up were −4.8% for non-HT ($p < 0.0001$), −4.2% for HT5 ($p = 0.003$), +0.02% for HT10 ($p > 0.05$) and +3.2% for HT15 ($p < 0.0001$) groups. The respective **femoral** bone losses were -8.6% for non-HT ($p < 0.0001$), −7.9% for HT5 ($p < 0.0001$), −2.5% for HT10 ($p = 0.010$) and −0.2% for HT15 ($p > 0.05$) groups. Comparing to non-HT group the risk of **wrist fracture** was reduced by 33% ($p = 0.045$) in HT10 group and by 63% ($p < 0.0001$) in HT15 group during the 15-year follow-up.
Conclusion: Long-term HT-use protects from bone loss. Thus, it reduces the incidence of osteopenia, osteoporosis and wrist fractures. Still, HT-use of less than 5 years did not have long-term bone protective effects, but a larger sample size is needed to confirm this result.

1. Introduction

Behaviors and concerns related to hormone therapy (HT) as well as indications to start HT have changed among patients and health professionals [1,2] since the publication of the Women's Health Initiative (WHI) [3] and Million Women Study [4]. Postmenopausal HT in the form of combined estrogen & progestin therapy has been shown to prevent early postmenopausal bone loss and augment late postmenopausal bone mass as effectively as bisphosphonates [5]. Still, the risk or fear of adverse effects may have resulted in discontinuation of HT [1,6,7].

Thus far, the effect of HT withdrawal on bone loss rate remains controversial. The effect of discontinuation of short term HT on bone loss varies from long-term protection [8] to an efficacy equivalent to a placebo [9]. Most studies report that accelerated bone loss occurs soon after short-term HT withdrawal, but BMD values

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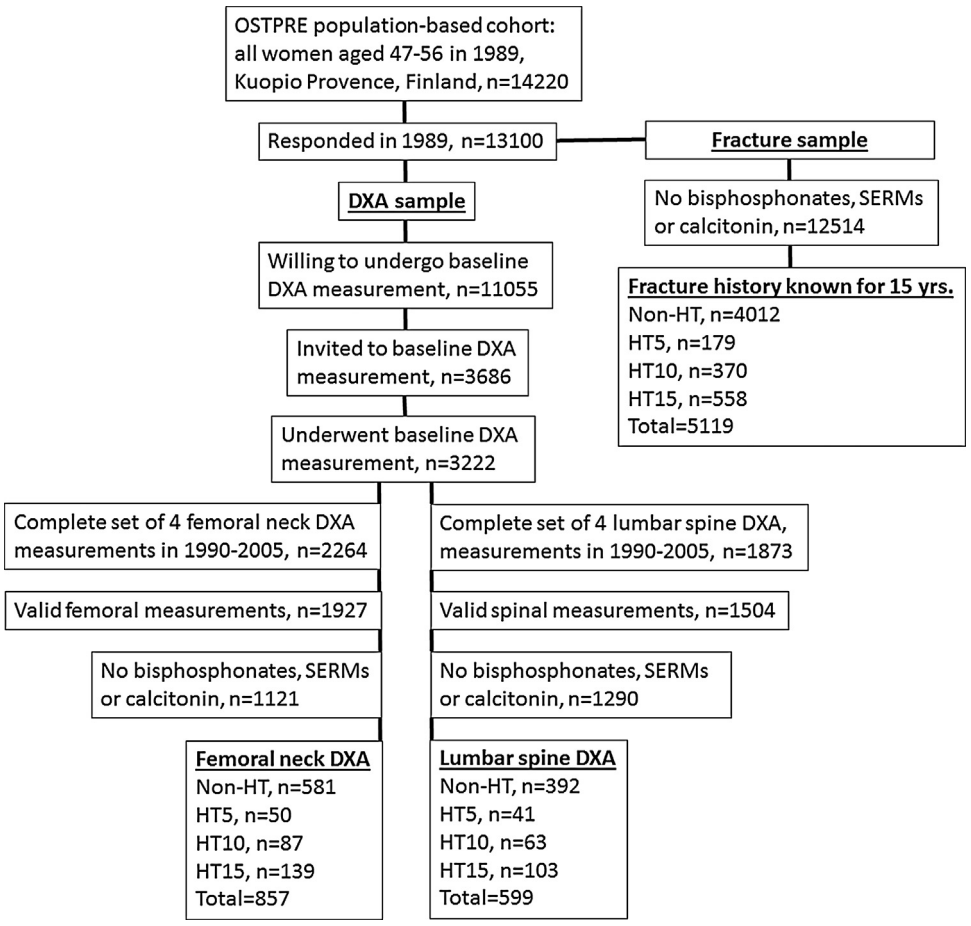

Fig. 1. The selection process of the final study populations as a part of the population-based Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study (SERMs = selective estrogen receptor modulators, DXA = dual X-ray absorptiometry, HT = hormone therapy). HT use denotes 80–100% of time used for a given 5-year period, categorized as follows: Non-HT = never used HT, HT5 = used HT throughout the 1st 5-year period of the follow-up but not thereafter, HT10 = used HT throughout the 1st and 2nd 5-year periods but not thereafter and HT15 = used HT throughout the total 15-year follow-up.

remain somewhat higher compared to those of users of placebo [5,10,11] or HT non-users [12]. Still, the number of long-term HT cessation studies is limited. Sornay-Rendu et al. report that the cessation of long-term HT does not accelerate bone loss [13], but according to Neele et al. rapid bone loss occurs thereafter [14]. Importantly, although postmenopausal HT confers protection from osteoporotic fractures, discontinuation of HT increases the likelihood of fractures [15–18]. Long-term studies addressing the issue of BMD changes following withdrawal of HT are needed. It is also unclear how discontinuation of HT affects the incidence of wrist fracture—the most common osteoporotic fracture. The aim of the present study was to compare the bone loss rate and the incidence of wrist fracture by duration of HT and to investigate how discontinuation of HT affects these outcomes during the 15-year follow-up of the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study.

2. Subjects and methods

2.1. Study participants

The OSTPRE Study in Kuopio, Eastern Finland is a population-based prospective cohort study. A postal enquiry [19] about health disorders, medications, use of HT, gynecological and fracture history, nutritional and lifestyle factors was mailed to the target population ($n = 14220$) in 1989, 1994, 1999 and 2004. The selection of the final study populations is depicted in Fig. 1. The number of study subjects was 857 for femoral BMD, 599 for spinal BMD and 5119 for the fracture sample.

At each densitometry, women with marked bone deformities (osteophytes, fractures, operations or scoliosis, hip prostheses), or otherwise non-valid measurements (spine, $n = 369$, hip, $n = 337$) were excluded. In the present study we excluded, in addition, users of selective estrogen receptor modulators (SERMs), bisphosphonates or calcitonin (spine, $n = 214$, hip, $n = 806$).

Participants were categorized according to HT use into following groups: never (non-HT), only for the first 5 years (HT5), only for the first 10 years (HT10) and finally for 15 years (HT15). Use of over 80% of time was accepted as use (c.f. sample size in tables for each analysis).

Written informed consent was obtained from participants and the OSTPRE design was approved by Ethics committee of Kuopio University Hospital throughout the entire study period.

2.2. Dual X-ray absorptiometry (DXA)

Anteroposterior lumbar spine (L2–L4) and left femoral neck BMD values were measured twice with the DPX during 1989–1991 [20] and after a mean (SD i.e., standard deviations) follow-up of 5.8 (0.5) years and once with the DPX-IQ at a mean follow-up of 10.6 (0.5) year by trained staff. Finally, BMD measurements were made at a mean follow-up of 15.5 (0.5) year with the Prodigy (GE Healthcare Lunar, Madison, Wisconsin-Illinois, USA). Cross-calibration studies were performed according to guidelines by the