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Original Article

Risk Factors for Perimenopausal Distal Forearm Fracture

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Abstract. This prospective population-based cohort study investigated factors predicting distal forearm fracture (DFF) in perimenopausal women. The study population consisted of 11 798 women from the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study in Finland. Mean baseline age of these women was 52.3 (SD 2.9) years (range 47–56 years) and 68% were postmenopausal. Three hundred and sixty-eight women (3.1%) had a validated DFF during the 5-year follow-up. Previous wrist fracture, postmenopausal state, age and nulliparity were independent predictors of DFF, while hormone replacement therapy (HRT), dairy calcium and overweight protected against it in multivariate Cox regression analysis: previous wrist fracture increased the DFF risk by 158% ($p<0.0001$), menopause by 69% ($p = 0.002$) and age by 6% per year ($p = 0.010$), whereas the continuous use of HRT decreased the risk by 63% ($p = 0.0001$), the use of dairy calcium at 1000–1499 mg/day (vs <500 mg/day) by 39% ($p = 0.004$), overweight (BMI >25 kg/m^2) by 36% ($p = 0.0002$) and parity by 29% ($p = 0.031$). Combining dichotomous low weight, low use of calcium, non-use of HRT and previous wrist fracture into a risk score gave a dose–response effect by score level: the presence (vs absence) of all four risk factors resulted in a 12-fold DFF risk. Nevertheless, the sensitivity and specificity of the score for detecting DFF remained low. It was concluded that HRT, high nutritional calcium intake and overweight protect against but a history of wrist fracture predisposes to perimenopausal distal forearm fracture. A simple risk factor inquiry would help to identify perimenopausal women at high risk of distal forearm fracture.

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Introduction

Distal forearm fracture (DFF) is the most common fracture of perimenopausal women. Risk factors for DFF have recently been investigated in several epidemiologic studies [1–7]. These studies have often been carried out in elderly women [3,6]. Some have been retrospective [1,5,7] and some have combined hip and forearm fractures into a single endpoint [2]. There are no prospective population-based studies of risk factors for DFF in perimenopausal women. It is well known that low bone mineral density (BMD) is associated with DFF [3,8–10], but other factors have not been found to be consistently related to it [1–7]. The risk factor profile of forearm fracture seems to differ from those of humerus, hip or ankle fracture [3,6,7]. Risk factor profiles may also vary with age. Therefore, it is important to determine risk factors for DFF in women from different age groups.

The purpose of this study was to examine prospectively which factors predict peri- and early postmenopausal DFF.

Subjects and Methods

Design and Study Population

This was a 5-year prospective population-based cohort study which used the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study data. The baseline postal inquiry was sent to all 14 220 women aged 47–56

years and resident in Kuopio Province, Finland in May 1989 [7]. A total of 13 100 (92%) women responded. The 5-year follow-up inquiry was carried out in May 1994. The present study population consisted of the 11 798 (83%) women who responded to both inquiries.

Variables

The baseline inquiry included questions about risk factors and the 5-year inquiry included information on fractures and HRT use during the follow-up.

Fracture History. Fracture history was elicited at baseline as follows: 'Have you sustained any bone fractures since the age of 15?' The participant was requested to list all fractures with bone sites and years of occurrence. The number of self-reported previous fractures at baseline was dichotomized: none versus 1+.

Follow-up Fractures. Reported follow-up fractures were validated against radiographic reports in the patient records. Only a validated follow-up fracture was used as an endpoint event.

Hormone Replacement Therapy (HRT). At baseline, the lifetime use of HRT in years was asked about. In the 5-year inquiry, the women were requested to list the number of months of HRT usage for each follow-up year separately. HRT was examined with three variables: (1) a dichotomous variable for HRT before baseline, (2) a dichotomous variable for HRT at baseline, and (3) a trichotomous variable for HRT during follow-up.

Menopause. A woman was regarded as postmenopausal if 6 months had elapsed since her last menstruation or if her history of HRT use was 6 months or more.

Anthropometry. Body mass index (BMI) was computed as the ratio of weight in kilograms to height in meters squared. BMI was categorized according to the international obesity classification [11]: <18.5 = thin, 18.5–24.9 = normal, 25.0–29.9 = overweight and 30.0+ = obese. Since there were few thin women (0.5%), thin and normal were combined into a single category. A dichotomous low-weight variable with a cutoff point of 22 kg/m^2, i.e., 1 SD below the study population mean, was also used.

Calcium Intake. Calcium intake from dairy products was used as the indicator of calcium intake. Information was obtained from two questions: (1) how many deciliters of milk and other liquid milk products do you consume daily on average? and (2) How many slices of cheese do you use daily on average? The daily calcium intake was the sum of that from liquid milk products (120 mg/dl) and cheese (87 mg/slice).

Physical Activity. Regular physical activity during leisure time was treated as a trichotomous variable: none, 1–3 h per week, or 4 h or more per week.

Health Status. The number of self-reported chronic health disorders diagnosed by a physician, and long-term work disability, were the health status variables. They were treated as dichotomous variables. The cutoff point in the former was none or one versus two or more health disorders.

Use of Drugs. The number of prescribed drugs in use at baseline was treated as a trichotomized variable: none, 1 or 2 drugs, 3 or more drugs.

Risk Score. The risk score was computed as the sum of the four following dichotomous variables: dairy calcium intake <500 mg = 1, else = 0; no HRT during follow-up = 1, else = 0; BMI <25 = 1, else = 0; and wrist fracture history positive = 1, else = 0. In an alternative computation HRT during follow-up was replaced by HRT use at baseline.

Statistical Methods

The chi-squared test was used to compare categorical variable distributions, and ANOVA to compare means of continuous variables. Relative risks (both uni- and multivariate) were estimated as hazard ratios (HR) with Cox regression. The nonlinear effect of continuous variables was examined by adding quadratic terms for those variables to the Cox model.

Results

A total of 382 validated distal forearm fractures were sustained by 368 women (3.1%) during the 5-year follow-up, corresponding to an annual incidence of 6.48/1000 persons. Ninety-three percent of these fractures were sustained in falls.

The mean baseline age for the entire study population was 52.3 (SD 2.9; range 47–56) years. Women with a DFF were older than those without one (Table 1). The menopausal status of 1178 (10.0%) women could not be defined due to hysterectomy before the menopause. Of the remaining 10 620 women, 7217 (68.0%) were postmenopausal at baseline. Table 1 shows that women with DFF had a lower body weight and calcium intake, used HRT at baseline and during follow-up less frequently but reported health disorders and past fractures more often than women without DFF. Past wrist fracture was strongly associated with DFF, but past nonwrist fracture was not. Regular physical activity during leisure time showed a trend toward increasing rather than decreasing the risk of DFF.

Table 2 presents univariate analyses using Cox regression, and Table 3 presents the final multivariate model with all independent variables simultaneously entered into the Cox regression model. Five percent of women reported a past wrist fracture, which was a strong predictor of subsequent DFF. Current HRT was the strongest preventive factor: the continuous use of HRT

Table 1. Baseline characteristics of the study population (n =11 798) according to the distal forearm fracture status: the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study

Characteristic	Fracture (n = 368)	No fracture (n = 11 430)	Total (n = 11 798)
Mean age, years	53.2 (2.9)***	52.3 (2.9)	52.3 (2.9)
Mean height, mm	1610 (54)	1612 (53)	1612 (53)
Mean weight, kg	66.3 (11.2)**	68.3 (11.7)	68.2 (11.7)
Mean BMI, kg/m^2	25.6 (3.9)**	26.3 (4.3)	26.2 (4.3)
Mean dairy calcium intake, mg/day	750 (359)***	833 (397)	830 (396)
Postmenopausal (%)	80.7***	67.5	68.0
Nulliparous (%)	16.2**	10.9	11.1
Bilateral oophorectomy (%)	3.9	5.8	5.7
Hysterectomy (%)[a]	10.9	10.9	10.9
HRT			
By baseline (%)	33.2	33.0	33.0
At baseline (%)	14.0**	21.1	20.9
During follow-up (%)	30.0***	41.4	41.0
Smoking (%)	9.5	11.1	11.0
Physical activity, regular leisure-time (%)	56.4	51.8	52.0
No. of health disorders, 2+ (%)	38.0**	31.3	31.5
Long-term work disability (%)	20.4	17.8	17.9
Fracture history			
Any (%)	26.9***	16.7	17.1
Wrist (%)	13.0***	4.8	5.1
Nonwrist (%)	13.9	11.9	12.0

Difference between fracture versus nonfracture cases: *p<0.05; **p<0.01; ***p<0.001.
[a] Without bilateral oophorectomy.

throughout the follow-up decreased the risk by 57%, while baseline use of HRT decreased the risk by 38% (Table 2). However, past use of HRT did not protect from DFF (Table 1). Replacing HRT during follow-up with HRT at baseline in the multivariate model (Table 3) did not affect the risks related to other variables. Higher calcium intake and overweight also protected from DFF. Low weight (BMI either <18.5 or <22.0 kg/m^2) did not predict DFF. The relations of DFF to HRT, BMI and calcium showed a dose–response effect or at least a trend. Baseline height, physical activity during leisure time, smoking, HRT before baseline, hysterectomy, bilateral oophorectomy, long-term work disability or number of prescribed drugs were not associated with DFF. The number of health disorders as a three-category variable was associated with DFF in univariate but not in multivariate analysis.

The effect of parity on DFF was slightly curvilinear: in the Cox model, which included a five-category (0, 1 or 2, 3 or 4, 5 or 6 and 7+ children) parity and its quadratic term, the quadratic term was statistically significant (p=0.01). The corresponding hazard ratios (HRs) without a quadratic term were: 1.0 (referent), 0.69 (0.51–0.93), 0.58 (0.42–0.79), 0.64 (0.41–1.01) and 0.71 (0.30–1.63), respectively. After adjusting for independent predictors of DFF, the parity category of 3 or 4 children still showed a lower DFF risk than the nulliparous category, with a HR of 0.69 (0.49–0.96).

The *joint effects* of the principal risk factors were additive (Table 4). The proportion of women with all four risk factors (no HRT during follow-up, calcium intake <500 mg/day, BMI <25 kg/m^2 and previous wrist fracture) in the total study population was small (0.6%). Replacing the HRT during follow-up with the HRT at baseline variable in the score resulted in slight (3–7%) decreases in the values of risk factor score categories 1–3, but decreased the category 4 value from 11.7 to 5.6 (Table 4). The sensitivity and specificity of the risk factor score for detecting DFF were 93% and 16%, respectively, if the cutoff point was between categories None and One (Table 4), but 15% and 94% if the cutoff point was set between categories Two and Three.

Sub-analyses

Analyses of the 7217 women (with 268 DFF) who were *postmenopausal* at baseline showed slight but statistically nonsignificant strengthening of the HRT, BMI and wrist fracture effects compared with the entire study population (data not shown). The risk factor score (Table 4) gave the following HR values for categories One to Four, respectively: 3.19 (95% CI 1.66–6.11); 5.35 (2.79–10.3); 10.5 (5.3–21.2) and 31.0 (9.7–98.9).

An analysis of the 5874 women (with 202 DFF) who had *never used HRT* produced the following univariate HR values for dichotomous variables: history of wrist fracture, 2.62 (95% CI 1.72–3.98); postmenopausal state, 2.27 (1.60–3.21); dairy calcium >499 mg/day, 0.66 (95% CI 0.47–0.92); and BMI >24.9 kg/m^2, 0.74 (0.56–0.98). The 2032 women who used HRT for >2.5 years during follow-up (36 DFF) showed a stronger calcium effect than the 3226 postmenopausal women who had never used HRT (141 DFF), with HRs of 0.44 (0.22–0.88) and 0.72 (0.48–1.10), respectively. No statistically signifi-

Table 2. Distal forearm fracture (DFF) risk related to selected baseline variables: univariate analysis

Variable (no. of women)	DFF	HR	95% CI	*p* value
Age, per year (11 798)	368	1.11	1.08–1.16	<0.0001
Menopausal status				
Pre (3403)	64	1.0		
Post (7217)	268	2.00	1.52–2.62	<0.0001
Dairy calcium intake, mg/day				
<500 (1997)	88	1.0		
500–999 (5877)	174	0.67	0.52–0.86	0.002
1000–1499 (2593)	66	0.57	0.42–0.79	0.0006
1500+ (586)	12	0.46	0.25–0.84	0.012
HRT at baseline				
No (9229)	312	1.0		
Yes (2433)	51	0.62	0.46–0.83	0.001
HRT during follow-up				
None (6880)	254	1.0		
Partly (3529)	89	0.68	0.53–0.86	0.0016
Throughout (1252)	20	0.43	0.27–0.67	0.0003
Body mass index, kg/m^2				
<25.0 (5213)	192	1.0		
25.0–29.9 (4510)	131	0.79	0.63–0.98	0.033
30.0+ (1968)	43	0.59	0.42–0.82	0.002
Low weight				
No (BMI 22+) (10 183)	314	1.0		
Yes (BMI <22) (1508)	52	1.12	0.83–1.50	0.450
Chronic health disorder				
None or one (8084)	140	1.0		
Two or more (3714)	228	1.35	1.09–1.66	0.006
Wrist fracture history				
No (11 201)	320	1.0		
Yes (597)	48	2.89	2.13–3.91	<0.0001
Nonwrist fracture history				
No (10 383)	317	1.0		
Yes (1415)	51	1.18	0.88-1.59	0.266
Parity				
Nulliparous (1304)	59	1.0		
Parous (10 434)	305	0.64	0.49–0.85	0.002

HR, hazard ratio.

cant differences in risk factor effects between subgroups were detected.

Discussion

The main findings of this study were that HRT, calcium and overweight protect from distal forearm fracture (DFF) and that a history of previous wrist fracture considerably elevates its risk.

This was a large-sample study with 368 women with endpoint events. Our target population consisted of all women aged 47–56 years resident in a defined geographic area. Since 83% of them responded to both baseline and 5-year inquiries (our study population), we can assume that our results represent well the Caucasian Finnish population. According to our validation study, the sensitivity of self-report for detecting distal forearm fracture is 95% [12]. The proportion (5%) of fractures which remained unreported is too small to have seriously biased the results. About 5% of self-reported wrist fractures were in fact soft tissue injuries which were reclassified into the non-DFF group during the fracture validation process.

The limitations of this study are that risk factor information was self-reported, HRT use during follow-up was retrospectively inquired about, and bone densitometry data were not available. It can be questioned whether differential recall of HRT biased the association between HRT and DFF. Fracture and HRT information were indeed collected with the same 5-year questionnaire, although they were asked in different sections of the large form. Therefore, we believe that recall bias was minimal.

We chose to use follow-up HRT as the main HRT indicator in this study, since it protected from fracture more effectively than did past or baseline use. Similar findings have been reported in the literature with regard

Table 3. Independent predictors of distal forearm fracture: the final multivariate Cox model with all the variables in the table simultaneously in the model

Predictor	HR	95% CI	*p* value
Age, years	1.06	1.01–1.11	0.010
Postmenopausal	1.69	1.22–2.35	0.002
Body mass index, kg/m^2			
<25.0	1.0		
25.0–29.9	0.73	0.57–0.93	0.012
30+	0.44	0.30–0.66	<0.0001
Dairy calcium intake, mg/day			
<500	1.0		
500–999	0.70	0.53–0.92	0.012
1000–1499	0.61	0.43–0.85	0.004
1500+	0.48	0.25–0.92	0.028
HRT during follow-up			
None	1.0		
Part of the time	0.64	0.48–0.84	0.002
Throughout	0.37	0.23–0.61	0.0001
Wrist fracture history			
None	1.0		
One or more	2.58	1.84–3.62	<0.0001
Parity			
Nulliparous	1.0		
Parous	0.71	0.52–0.97	0.031

HR, hazard ratio.

Table 4. Distal forearm fracture (DFF) risk related to the risk factor score[a] in perimenopausal women

No. of risk factors (no. of women)	DFF	HR	95% CI	*p* value
None (1729)	23	1.0		
One (5202)	135	1.96	1.26–3.06	0.003
Two (3280)	128	2.97	1.91–4.63	<0.0001
Three (622)	45	5.67	3.40–9.27	<0.0001
Four (28)	4	11.7	4.05–33.8	<0.0001

HR, hazard ratio.
[a] Sum of four dichotomous risk factors: calcium <500 mg/day, no HRT during follow-up, BMI <25 kg/m^2, positive wrist fracture history.

to both early postmenopausal bone loss [13] or hip fracture [14]. The distal end of the radius is mostly trabecular bone which shows rapid early postmenopausal bone loss without HRT [15]. Therefore, using information solely on baseline HRT use could not have been regarded as adequate for evaluating the effect of HRT on fracture risk.

Menopause and *age* were strongly associated with DFF in these perimenopausal women aged 48–61 years (mean age 55 years) at the midpoint of the 5-year follow-up period. This agrees well with the female incidence curves of DFF, which usually show a rapid increase at this age [16]. The DFF incidence in our study (6.5/1000 per year) was also the same as that of the women aged 50–59 years in that Swedish study [16]. Menopause remained a significant predictor after adjusting for age. It has been shown that DFF is a bone-density-dependent fracture and that the association between DFF and BMD is possibly even stronger than that between other fractures and BMD [8–10]. The distal end of the radius experiences rapid bone loss around menopause [15], which probably explains the major part of the menopause effect on the DFF risk.

Parity was related to DFF, nulliparous women being at a slightly increased risk. Similar findings have previously been reported for distal forearm [5] and hip fractures [17]. In their recent hip fracture study, Fujiwara et al. [17] found also that multiparous (>4 children) women were at a higher risk than women with 1 or 2 children. We noticed only a trend in this direction. It is not known whether the high risk in the nulliparous is due to genetic factors, low premenopausal estrogen levels or behavioral factors.

In our previous retrospective analysis on this same study population [7], we found that *height* was slightly related to premenopausal DFF. In this study, most of the fractures were postmenopausal and such a relationship was no longer detected. Some previous studies on osteoporotic fractures (hip and/or forearm) have indicated that low *weight* is also a risk factor for forearm fracture. In our study, low weight was not a risk factor, whereas overweight was a protecting factor.

The present finding that previous wrist *fracture history* strongly predicts DFF accords with observations that previous fragility fractures predict future ones [18–20]. The relationship is probably due to low (peak) BMD, since DFF is bone-density-dependent [3,8–10]. Wrist fracture in perimenopausal women appears to be strongly related to low BMD, whereas nonwrist fractures may have a more diverse background including higher trauma propensity [20].

This is one of the very few studies to show an inverse relationship between *calcium* intake and fracture risk [21], and the first to demonstrate it in perimenopausal women. Previous randomized clinical trials have usually failed to observe an association between calcium intake and early postmenopausal bone loss [22]. Our finding is thus important and supports the hypothesis that calcium may partially protect against bone loss even in acute estrogen deficiency of early postmenopausal years. This accords with our hypothesis [23] that the calcium effect can most easily be demonstrated in metabolically active bone sites such as the distal end of the radius in this phase of life [15]. Interestingly, fracture risk in this study showed a decreasing trend even when moving from sufficient intake (dairy milk 500–1499 mg/day) to the highest intake category of above 1499 mg/day. In Finland about 80% of calcium is obtained from milk products [24]. This suggests that a total calcium intake well in excess of 1000 mg/day may be beneficial in the prevention of early postmenopausal DFF. This is congruent with a recent finding that high daily calcium intake levels of 1500–2000 mg/day might give some additional protection against secondary hyperparathyroidism and bone loss in postmenopausal women compared with mean intakes of about 800–1000 mg/day [25].

However, it is possible that the full calcium effect can be achieved only with simultaneous HRT [26]. Accordingly, the calcium effect in our study lost part of its strength when HRT users were excluded, which suggests that HRT strengthens the calcium effect in early postmenopausal women.

The use of *HRT* during the follow-up was strongly associated with DFF. This supports the results of previous observational studies suggesting that HRT prevents hip and forearm fractures [14,27]. In addition, we have recently shown experimentally that HRT prevents early postmenopausal fractures in general [28].

Smoking and self-reported regular *physical activity* during leisure time were not related to DFF. Poor *health status* or use of prescribed drugs seemed not to be predictors of DFF either. These negative findings are in line with most previous studies and also with our retrospective analysis on these same women [1–7].

Combining several risk factors into a *score* improved the specificity of DFF prediction. However, since only a fraction of the population had three or four of the most potent risk factors, the sensitivity of such a combination to detect DFF was low. Previous attempts to use a different risk factor combination as a diagnostic test to detect osteoporotic fractures also produced unsatisfactory results [29]. However, the gradient of relative risk according to score level confirms the independence of risk factors and implies that calcium and/or HRT would benefit all, but particularly those who are not overweight and present a history of wrist fracture.

In conclusion, previous wrist fracture predicts and overweight protects against perimenopausal distal forearm fracture, whereas calcium and HRT seem to be effective in its prevention. Combining several risk factors into a risk score may help to identify perimenopausal women at high risk of distal forearm fracture.

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