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Use of Low Potency Estrogens Does Not Reduce the Risk of Hip Fracture

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High endogenous sexual hormone levels and use of medium potency estrogens are associated with a reduced risk of hip fracture in postmenopausal women. However, it is not clear if low potency estrogens confer the same benefits as the more widely used forms of menopausal hormone replacement. We examined the association between postmenopausal use of low potency estrogens, mainly estriol, and hip fracture risk in a population-based, case-control study. Using data from mailed questionnaires and telephone interviews, we analyzed the association between low potency estrogen use and hip fracture risk among 1327 cases, 50–81 years of age, and 3262 randomly selected age-matched controls. Ever use of low potency estrogens was reported by 19% of the cases and 23% of controls. Compared to with never users of any hormone replacement therapy, ever users of low potency estrogens had a multivariate odds ratio (OR) for hip fracture of 0.96 (95% confidence interval [CI] 0.67–1.39). Current use was also not associated with a reduction in risk: OR 0.94 (95% CI 0.58–1.53), and longer duration of use was also not associated with a risk reduction. Even current use of the highest dose of oral estriol (2 mg/day) conferred no risk reduction (OR 1.01, 95% CI 0.61–1.67) compared with never use of hormone replacement therapy. After exclusion of ever users of medium potency estrogens from the analyses, we found a risk reduction of fracture among current vaginal low potency estrogen users (multivariate OR 0.67, 95% CI 0.49–0.92). In contrast to medium potency estrogens, low potency estrogens did not confer a substantial overall reduction in hip fracture risk. (Bone 30:613–618; 2002)

Key Words: Hip fracture; Estrogen; Estriol; Hormone replacement therapy.

Introduction

Estrogen deficiency is recognized as a major factor in the pathogenesis of postmenopausal bone loss and of osteoporotic fractures. Whereas medium potency estrogens (such as conjugated estrogens, micronized estradiol, and ethinyl estradiol) can relieve climacteric symptoms and reduce the risk of bone loss, they also have the disadvantage of increasing the susceptibility to endometrial and possibly breast cancer.[15] Lower potency estrogens, such as estriol, can also relieve urogenital symptoms associated with estrogen deficiency and are commonly prescribed in Europe. Although estriol has considerably lower affinity for the estrogen receptor than medium potency estrogens, it can be an effective estrogen agonist with prolonged stimulation. Indeed, treatment with low potency estrogens may increase the risk of endometrial neoplasia.[44]

Data regarding the effects of low potency estrogens on bone density are conflicting. One study in Japan found that a combination of oral estriol (2 mg/day) and calcium (800 mg/day) retarded postmenopausal loss of bone density.[32] However, estriol alone in higher doses (4–12 mg/day) did not reduce bone loss in postmenopausal American women.[23] Whether low potency estrogen affects osteoporotic fracture risk is thus uncertain. We therefore examined the influence of low potency estrogen use on the risk of hip fracture in a population based case-control study among postmenopausal Swedish women. In an earlier analysis, using the same data, we showed that use of medium potency estrogens[30] or oral contraceptives[29] is associated with a reduction in the risk of hip fracture.

Subjects and Methods

Cases

The study took place in six counties of Sweden, comprising a largely urban area including nearly half of the inhabitants of the country. We aimed to ascertain all fractures of the proximal femur that occurred between October 1993 and February 1995 among women resident in the study area who were born after 1913. Using clinical records or operation registers in all 24 hospitals in the study area, we identified 2597 possible incident cases. Hospital records were scrutinized to confirm eligibility. We excluded those with a fracture due to malignancy (n = 26); high-energy trauma (n = 4); incorrect diagnosis (n = 51); blindness (n = 5); birth outside of Sweden (n = 202); severe alcoholic abuse, psychosis, or dementia (n = 576); or death within 3 months of the fracture (n = 123). There remained 1610 eligible cases, who were approached with a comprehensive questionnaire at a mean interval of 95 days (standard deviation 23 days) after the fracture. At the end of the recruitment period, we used the Swedish inpatient register to verify completeness of case ascertainment. We thus identified 34 additional cases, who were also asked to complete the questionnaire. The inpatient

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register has been validated with regard to hip fracture, and has been estimated to >99% complete.[34]

Controls

Controls were native-born women, residents of the study area, and randomly selected from the national, continuously updated population register the month before the start of the study. All Swedish citizens have a unique ten digit national registration number that permits identification of all selected controls and their addresses. Questionnaires were sent to controls on six occasions, evenly distributed throughout the study period (October 1993 to February 1995). Potential controls, aged 70–80 years, were frequency-matched (two controls to one case) to the expected hip fracture age distribution within the county of residence. Controls, aged 50–69 years, were also randomly selected from the population register, as part of a breast cancer study[26] being conducted at the same time with the same questionnaire. For these women, frequency matching to the expected number of breast cancer cases provided two to four times as many controls as hip fracture cases in each 5 year age group (50–69 years) and county of residence. Of the 4872 candidate controls in the hip fracture analysis, 4059 were eligible for the study, 610 were born outside of Sweden, 157 died before being approached, 44 had senility or psychosis, and 2 were blind.

Data Collection and Analysis

Data were collected through mailed questionnaires supported by telephone interviews requesting detailed information regarding use of hormone replacement therapy (HRT) including type of preparation, dose, and time of use.[30] Of those eligible, 1328 cases (82.5 percent) and 3312 controls (81.6%) answered the questionnaire. Approximately 50% of the participants were approached by telephone for completion of missing information. Two hundred two (15.2%) of the cases and 497 (15.0%) of the controls responded solely by telephone in a less extensive interview (omitting length and regularity of menstrual cycles at age 30 years, breastfeeding, menopausal symptoms, and alcohol consumption). Recall of hormone use was aided by a picture chart of all preparations commercially available in Sweden since 1950. No participant described taking low potency estrogens for the indication of preventing or treating osteoporosis. The questionnaire also included reproductive history, anthropometric measures, and lifestyle habits such as leisure physical activity, diet, and smoking. The women were also asked about medical history (stroke, diabetes mellitus, and cardiovascular and inflammatory bowel diseases). Previous occupational activity, socioeconomic class, and marital status were available through matching to national census databases for 1960, 1970, 1980, and 1990.

Participants claiming natural menses were classified as premenopausal (50 controls and 1 case) and were excluded from the analysis. We categorized as low potency estrogens the following drugs: oral estriol (normally prescribed 1–2 mg/day), vaginal dienoestrol (0.5 mg twice per week), vaginal estriol (0.5 mg twice a week), and vaginal estradiol (0.25 μg twice per week). Medium potency estrogens included use of the following preparations: oral, transdermal, or injected estradiol; ethinyl estradiol; or conjugated estrogens.

As measures of associations, odds ratios (ORs) and 95% confidence intervals (CIs) were computed by unconditional logistic regression. We estimated ORs for low potency estrogens both in an age-adjusted model, and in a multivariate model that included age in six classes (50–54, 55–59, 60–64, 65–69, 70–74, and 75–81 years), use of medium potency estrogens (never, former, or current), use of oral contraceptives (never or ever use), parity (zero, one, two, and three children or more), menopausal age (by quartiles among the controls), climacteric symptoms (having vs. not having experienced moderate to severe climacteric symptoms), current weight (by quintiles among the controls), smoking habits (never, former, or current cigarette smoking), and recent physical activity level (never, <1 h/week, 1–2 h/week, ≥3 h/week). Other potential covariates had only minimal impact on the estimates and were not included in the analysis. Never users of any postmenopausal estrogen or progestin were used as the reference category. We excluded from analysis subjects who had ever used medium potency estrogens, progestins only, or unknown HRT preparations if they did not also report use of low potency estrogens (118 cases and 451 controls). Interactions between low potency estrogen use and weight, body mass index, age, smoking status, or recent physical activity on hip fracture risk were considered through inclusion of product terms in the analysis and likelihood ratio tests.

Results

We obtained detailed information on exogenous estrogen use from 1327 cases (mean age 72.5 years) and 3262 randomly selected controls (mean age 70.5 years) (**Table 1**). Ever use of low potency estrogens was reported by 253 (19%) cases and 738 (22.6%) controls. Of the cases, 149 had used oral agents and 120 had used vaginal preparations; the corresponding numbers for controls were 397 and 417, respectively. Twenty cases and 77 controls had used both types of administration.

Compared with never users of any HRT, ever users of low potency estrogens had an age-adjusted OR for hip fracture of 0.75 (95% CI 0.64–0.88), but this risk reduction did not persist after multivariate adjustment (**Table 2**). The risk reduction seen in the age-adjusted model was largely due to confounding by use of medium potency estrogens and climacteric symptoms; after additional adjustment for these covariates, the OR for ever use of low potency estrogens was 0.90 (95% CI 0.64–1.28). Current use was also not associated with a reduction in risk after multivariate adjustment (multivariate OR 0.94, 95% CI 0.58–1.53). Duration of use was not associated with risk.

Oral treatment, both as ever use and as treatment for >5 years, was also associated with a relative risk near unity (**Table 3**). Even current use of the highest oral estriol dose (2 mg/day) conferred no risk reduction compared with never use of HRT (multivariate OR 1.01, 95% CI 0.61–1.67).

We also estimated hip fracture risk with low potency estrogen use after excluding from analysis ever users of medium potency estrogens. In this subgroup analysis, there was no reduction in risk with oral treatment (multivariate OR for current use was 1.11, 95% CI 0.85–1.46), but current vaginal treatment was associated with a multivariate OR of 0.67 (95% CI 0.49–0.92). There was an apparent trend of reduced hip fracture risk with longer duration of vaginal estrogen use, but this was not statistically significant; the multivariate OR per 5 year use among current users was 0.90 (95% CI 0.75–1.09).

In age-adjusted analyses, we found that current weight modified the effect of low potency estrogen use on hip fracture risk ($p < 0.05$ for interaction) with lower ORs for estriol use among lean women than among heavier women (data not shown). This effect modification did not persist after multivariate adjustment, even among women whose only HRT use was vaginal administration of low potency estrogens ($p > 0.1$ for interaction). Nevertheless, there was a tendency for lower multivariate risk estimates among women with a more slender body habitus in this subgroup (data not shown). We found similar risk estimates for estriol use within different categories of age, smoking status, and physical activity (data not shown).

Table 1. Descriptive characteristics of the participants and number of subjects providing information [values are means (SD) unless indicated otherwise]

Characteristic	Number of cases/controls	Cases	Controls
Age (years)	1327/3262	72.5 (6.8)	70.5 (7.7)
Age at menopause (years)	1327/3262	50.0 (4.4)	49.8 (4.2)
Weight (kg)	1308/3233	61.0 (11.1)	66.8 (11.8)
Height (cm)	1307/3235	164.1 (6.6)	163.3 (5.9)
Body mass index (kg/m^2)	1294/3216	22.2 (3.8)	24.6 (4.2)
		Percent	
Ever use of any postmenopausal estrogen[a]	371/1189	28.0	36.5
Ever use of low potency estrogen[b]	252/738	19.0	22.6
Ever use of medium potency estrogen[c]	120/456	9.0	14.0
Ever use of only low potency estrogen	221/641	16.7	19.7
Ever use of only medium potency estrogen	88/359	6.6	11.0
Ever use of both low and medium potency estrogen	32/97	2.4	3.0
Ever use of unspecified estrogens	30/92	2.3	2.8
Ever use of oral contraceptives	130/562	11.6	19.1
Climacteric symptoms[d]	1082/2707	59.4	52.5
Parity			
Nulliparous	274/518	20.6	15.9
One child	312/665	23.5	20.4
Two children	399/1123	30.1	34.4
Three children or more	334/951	25.2	29.2
Smoking status			
Never	719/1872	54.3	60.7
Former	260/619	19.6	20.0
Current	345/595	26.1	19.3

[a]Including medium, low potency, or unspecified estrogens.
[b]Low potency estrogens were oral estriol (normally prescribed 1–2 mg/day), vaginal dienoestrol (0.5 mg twice per week), vaginal estriol (0.5 mg twice a week), and vaginal estradiol (0.25 μg twice per week).
[c]Medium potency estrogens were oral or transdermal treatment with estradiol compounds (normally 1–2 mg estradiol, 5–10 μg ethinyl estradiol, or 25–50 μg transdermal estradiol) or conjugated oestrogens (normally 0.325–0.625 mg/day orally).
[d]Moderate to severe vasomotor symptoms such as hot flushes, sweating, and palpitations of the heart.

Discussion

In this large, population-based case-control study, we found low potency estrogens, in doses normally prescribed, generally do not substantially influence hip fracture risk. A reduction in risk in age-adjusted analyses was explained by a tendency for low potency estrogen users to also use medium potency estrogens and to have a relatively high prevalence of estrogen deficiency (as reflected in menopausal symptoms).[36] Current vaginal treatment was inversely related to risk, although without a statistically significant trend over duration of use.

It has been estimated that a large proportion, approximately 60%, of all hip fractures among women ≥65 years of age is attributable to low levels of endogenous sex hormones, that is,

Table 2. Association of low potency estrogen use with hip fracture risk

Low potency estrogen	Cases (n)	Controls (N)	Age-adjusted model odds ratio (95% CI)	Multivariate model odds ratio[a] (95% CI)
Never use	956	2073	1.0 (ref)	1.0 (ref)
Ever use	253	738	0.75 (0.64–0.88)	0.96 (0.67–1.39)
Per year of use			0.97 (0.71–1.32)	0.99 (0.72–1.37)
Use >5 years	82	244	0.72 (0.56–0.94)	1.07 (0.47–2.41)
Current use	183	545	0.74 (0.61–0.89)	0.94 (0.58–1.53)
Per year of use			0.93 (0.66–1.32)	0.98 (0.67–1.42)
Use >5 years	68	215	0.68 (0.51–0.90)	0.93 (0.80–2.17)
Former use	70	193	0.79 (0.60–1.05)	1.01 (0.61–1.69)
Per year of use			1.39 (0.65–2.99)	1.34 (0.56–3.22)
Use >5 years	14	29	1.05 (0.55–2.00)	1.58 (0.59–4.18)

[a]Multivariate model including age (<60, 60–64, 65–69, 70–74, 75–81 years), current weight (by quintiles), physical activity at leisure time in recent years (never, < 1 h/week, 1–2 h/week, ≥3 h/week), smoking (never, former, current), parity (0, 1, 2, or ≥3 children), menopausal age (by quartiles), climacteric symptoms (yes/no), oral contraceptive use (ever, never), and use of medium potency estrogens (never, former, current use). CI, confidence interval.

Table 3. Association of low potency estrogen by type of administration and hip fracture risk

Low potency estrogen	Cases (n)	Controls (N)	Age-adjusted model odds ratio (95% CI)	Multivariate model odds ratio[a] (95% CI)
Never use	956	2073	1.0 (ref)	1.0 (ref)
Oral treatment	129	320	0.87 (0.70–1.08)	1.02 (0.62–1.66)
Use >5 years	34	94	0.77 (0.52–1.15)	1.07 (0.46–2.53)
Vaginal treatment	100	340	0.66 (0.52–0.83)	0.82 (0.50–1.36)
Use >5 years	37	115	0.70 (0.48–1.03)	1.08 (0.45–2.57)

[a]Multivariate model including age (<60, 60–64, 65–69, 70–74, 75–81 years), current weight (by quintiles), physical activity at leisure time in recent years (never, <1 h/week, 1–2 h/week, ≥3 h/week), smoking (never, former, current), parity (0, 1, 2, or ≥3 children), menopausal age (by quartiles), climacteric symptoms (yes/no), oral contraceptive use (ever, never), and use of medium potency estrogens (never, former, current use). CI, confidence interval.

the combination of low estradiol and high sex hormone-binding globulin values.[11] The low levels of biologically available serum estradiol in hip fracture cases may be explained in part by the lower body weight of cases,[12] and leanness is associated with low endogenous serum levels of estrogen.[4,14,43] In our previous study,[31] as well as in others,[10] medium potency estrogens have been most strongly associated with hip fracture and breast cancer among relatively lean women. In the present analysis, we found suggestions that the effect of low potency estrogens is more apparent among lean women, but these trends were consistent with chance in multivariate analyses.

Our relative risk estimates for vaginal low potency estrogen treatment depended on the analyses applied. Exclusion of medium potency estrogen users from the analyses revealed a significant risk reduction with current vaginal low potency estrogen. This subgroup finding could be due to chance. However, it is also possible that use of medium potency estrogens could mask an effect of low potency estrogens. If the drugs were taken simultaneously, which was reported by some (20%, 24 of 129 subjects) of both the medium and low potency estrogen users, there may have been competition for binding to the estrogen receptor. The trend with duration of use of vaginal preparations was compatible with chance, even among current users.

Several randomized studies have shown that medium potency estrogens can reduce postmenopausal bone loss[8,22,40,42] and reduce risk of osteoporotic fracture.[5,15,16,25,30] Even ultra-low doses of estradiol (parenteral use of 7.5 μg/day) might preserve bone in women ≥60 years of age.[33] However, the lowest dose of estrogen that can prevent hip fracture remains to be clarified.

The affinity of estriol to the estrogen receptor is considerably weaker than that of medium potency estrogens such as estradiol (approximately 5%–10%).[3,13] Indeed, estriol appears potentially able to produce both agonistic and antagonistic estrogenic effects. The antagonistic effects have been observed when estriol was given in conjunction with estradiol and independently when given as a short-burst bolus.[9,27] In vitro studies have found that estriol competes with estradiol in binding to the estrogen receptor, a balance that probably explains its antagonistic effects.[2] However, estriol has lower affinity for binding to sex hormone-binding globulin than estradiol, and thus a greater proportion of circulating estriol is biologically active.[24] Orally administrated estriol is, however, largely conjugated and inactivated by first pass in the liver, and thus only a small percentage enters the circulation in bioactive form.[19,21,39]

In view of these considerations, it is not surprising that 0.5–1.0 mg intravaginal estriol provides serum levels equivalent to that of approximately 10 mg of oral treatment.[19,21] This implies that the doses of vaginal low potency estrogens used by the participants in our study should have systemic effects similar to, or even greater than, those for the higher dose oral preparations. The impact on endogenous production and local effects on target organs of estrone, estradiol, and sex hormone-binding globulin after exogenous low potency estrogen administration has not been thoroughly investigated.

Despite a lack of convincing evidence for a bone-sparing effect of estriol from studies among white women,[23,28] some Japanese and Chinese investigators have displayed the potential for low potency estrogens to provide protection against bone loss.[6,7,17,20,32,41] The differences in apparent response might theoretically be attributable to genetic differences in estrogen uptake, conjugation, sensitivity, degradation, or even associated dietary differences. It has been speculated that phytooestrogens from soybeans, in refined form from an often-used dietary compound in Japan, may act synergistically with estriol to provide protection against bone loss.[18]

We are aware of only one previous study examining osteoporotic fracture risk after use of low potency estrogens.[35] This prescription-based cohort study showed no independent effect of use of low potency estrogens and hip fracture risk. However, the small number of exposed cases limited the statistical power of the analyses.

Although potentially limited by the case-control design, our study size enabled us to detect even moderately weak associations; the confidence limits around our relative risk estimates are not wide. We were also able to consider duration, recency, and dose of low potency estrogen use, and to examine the influence of several potential covariates.[38] Further strengths of our investigation include the population-based design, the high response rates, and the thorough ascertainment of covariates. We did not, however, include subjects with known senility, alcoholism, and psychosis, mainly because of the likelihood of inadequate recollection of previous medications. The subjects' actual estrogen intakes were not measured, and thus measurement error is a potential issue. However, the concordance between self-reports of type of preparation, dose, and duration of hormone intake and data from pharmacy records has been found to be high,[37] and recall of our subjects was aided by picture charts of hormone preparations.[1]

Our data demonstrate the dissimilarity between low and medium potency estrogens in effects on hip fracture risk, a result unlikely to be explained by selection mechanisms. Aside from a younger average age for users of medium potency estrogens compared with those who used low potency preparations, we found only small differences in their covariate profiles. More than 80% of the low potency estrogen (LPE) users in our study, however, reported that they used these drugs for the relief of

Table 4. Association between low potency estrogen and hip fracture risk after exclusion from the analyses of ever users of medium potency estrogen

Low potency estrogen	Cases (n)	Controls (N)	Age-adjusted model odds ratio (95% CI)	Multivariate model odds ratio[a] (95% CI)
Never use	956	2073	1.0 (ref)	1.0 (ref)
Ever use	221	641	0.75 (0.63–0.89)	0.88 (0.73–1.05)
Oral use	116	273	0.91 (0.72–1.15)	1.02 (0.80–1.30)
Vaginal use	84	298	0.63 (0.48–0.81)	0.75 (0.57–0.98)
Oral and vaginal use	17	65	0.56 (0.32–0.95)	0.67 (0.39–1.17)
Current use	164	487	0.74 (0.61–0.89)	0.86 (0.70–1.06)
Oral use	94	203	1.00 (0.77–1.29)	1.11 (0.85–1.46)
Vaginal use	55	222	0.55 (0.41–0.75)	0.67 (0.49–0.92)
Oral and vaginal use	11	57	0.41 (0.21–0.79)	0.50 (0.25–0.96)
Former use	57	154	0.80 (0.58–1.09)	0.93 (0.67–1.29)
Oral use	22	70	0.67 (0.41–1.09)	0.76 (0.46–1.27)
Vaginal use	29	76	0.82 (0.53–1.27)	0.97 (0.61–1.54)
Oral and vaginal use	6	8	1.61 (0.56–4.67)	1.90 (0.65–5.61)

[a]Multivariate model including age (<60, 60–64, 65–69, 70–74, 75–81 years), current weight (by quintiles), physical activity at leisure time in recent years (never, <1 h/week, 1–2 h/week, ≥3 h/week), smoking (never, former, current), parity (0, 1, 2, or ≥3 children), menopausal age (by quartiles), climacteric symptoms (yes/no), and oral contraceptive use (ever, never). CI, confidence interval.

local urogenital symptoms. Among users of medium potency estrogen (MPE), the corresponding proportion was about 20%. In contrast, 60% of MPE users reported that the drug was given to reduce climacteric symptoms, whereas <10% of LPE users reported this indication. Although it is difficult to disentangle the separate associations for medium and low potency estrogen on hip fracture risk with an observational design, we conclude that low potency estrogens do not substantially reduce hip fracture risk in white women. It is possible that vaginal treatment might offer some protection. However, our subgroup findings regarding this issue should be interpreted with caution unless there is further supporting data.

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