Original Article

Increase in Fracture Risk Following Unintentional Weight Loss in Postmenopausal Women: The Global Longitudinal Study of Osteoporosis in Women[†]

Running title: Unintentional weight loss and fracture in postmenopausal women

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ABSTRACT

Increased fracture risk has been associated with weight loss in postmenopausal women but the time course over which this occurs has not been established. The aim of this study was to examine the effects of unintentional weight loss of ≥10 lb (4.5 kg) in postmenopausal women on fracture risk at multiple sites up to 5 years following weight loss. Using data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) we analyzed the relationships between self-reported unintentional weight loss of ≥10 lb at baseline, year 2, or year 3 and incident clinical fracture in the years following weight loss. Complete data were available in 40,179 women (mean age ± SD 68 ± 8.3 years). Five-year cumulative fracture rate was estimated using the Kaplan-Meier method, and adjusted hazard ratios for weight loss as a time-varying covariate were calculated from Cox multiple regression models. Unintentional weight loss at baseline was associated with a significantly increased risk of fracture of the clavicle, wrist, spine, rib, hip, and pelvis for up to 5 years following weight loss. Adjusted hazard ratios showed a significant association between unintentional weight loss and fracture of the hip, spine, and clavicle within 1 year of weight loss, and these associations were still present at 5 years. These findings demonstrate increased fracture risk at several sites after unintentional weight loss in postmenopausal women. This increase is seen as early as 1 year following weight loss, emphasizing the need for prompt fracture risk assessment and appropriate management to reduce fracture risk in this population.

KEYWORDS: WEIGHT LOSS, FRACTURE, POSTMENOPAUSAL WOMEN

Introduction

Body mass index (BMI) is a major determinant of bone mineral density (BMD) and low BMI is a well-recognized risk factor for fragility fracture.[1] Weight loss is associated with accelerated bone loss and increased risk of fracture in postmenopausal women. In women enrolled in the Study of Osteoporotic Fractures, weight loss of ≥10% was associated with a 68% increase in the risk of non-spine fracture (defined as hip, pelvis, and humerus) over an average follow-up of 19.5 months.[2] In a subsequent study with longer follow-up in the same cohort, a two-fold increase in the risk of hip fracture was demonstrated.[3] Increased risk of hip fracture associated with weight loss has also been reported in other US populations (relative risks 2.9 and 2.37)[4,5]; and in a prospective population-based study from Norway, weight loss of ≥5% was associated with a significant increase of 33% in the risk of distal radius fracture.[6] In a recent post-hoc analysis from the Women's Health Initiative Observational Study and Clinical Trials with a mean follow-up period of 11 years, weight loss of ≥5% was associated with increased risk of fracture of the hip (65%), upper limb (9%), and central body (hip, spine, or pelvis) (30%). When women with unintentional versus intentional weight loss were considered separately, significantly higher incidence rates of both hip (33%) and vertebral (16%) fracture were demonstrated in the former group.[7] The association of weight loss with hip, wrist, and vertebral fractures in these studies is consistent with the inverse correlation between BMI and fracture at these sites.[8]

These studies provide a growing body of evidence that weight loss after the menopause is associated with increased fracture risk, particularly at the hip but also at other sites. However, the follow-up period of these studies has ranged from 19.5 months to 11 years and the time course over which fractures occur in relation to weight loss has not been clearly established; in particular, it is uncertain how rapidly fracture risk increases following weight loss. The aim of the present study was to investigate the effects of unintentional weight loss in postmenopausal women on the incidence and time course of clinical fractures at multiple sites in the 5 years following self-reported weight loss.

Materials and Methods

GLOW is a prospective cohort study involving 723 physician practices at 17 sites in 10 countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK, and USA). The study methods have been reported.[9] In brief, practices typical of each region were recruited through primary care networks organized for administrative, research, or educational purposes, or by identifying all physicians in a geographic area. Each site obtained local ethics committee approval to participate in the study. The practices provided the names of women aged ≥55 years who had been seen by their physician in the past 24 months. After exclusion of women due to cognitive impairment, language barriers, institutionalization, or who were too ill, 60,393 women agreed to participate in the study.

Data collection

All data for the study were self-reported, using self-administered questionnaires mailed at baseline and years 1, 2, 3, and 5 and covered domains that included patient characteristics and risk factors for fracture, fracture history, current medication use, and other medical diagnoses.

Information was collected at baseline on history of previous fractures (that had occurred since the age of 45 years), and incident fractures were assessed during the 1-, 2-, 3-, and 5-year follow-up surveys. All surveys included details of fracture location, including spine, hip, wrist, clavicle, upper arm/shoulder, rib, pelvis, ankle, upper leg, and lower leg.

Unintentional weight loss was defined as a "yes" response to the question: "In the last 12 months, have you lost 10 or more pounds without trying?" This question appeared on the baseline and the year 2 and year 3 follow-up surveys. Incident fracture data were collected on all follow-up GLOW surveys, including the fracture site and date. A fracture was considered associated with unintentional weight loss if it occurred at any time after the survey date when weight loss was reported, with a separate analysis for fracture within 365 days after the weight loss survey (if fracture occurred >365 days after weight loss, the fracture was not considered to be associated with weight loss).

Subjects were considered to be taking anti-osteoporosis medication if they reported current use of alendronate, calcitonin, estrogen, etidronate, ibandronate, pamidronate, recombinant human parathyroid hormone (1–84), raloxifene, risedronate, strontium ranelate, teriparatide, tibolone or zoledronic acid. Information was also obtained about comorbid conditions including asthma, emphysema, osteoarthritis,

rheumatoid arthritis, colitis, stroke, high cholesterol, hypertension, Parkinson's disease, multiple sclerosis, cancer, and type 1 diabetes. Health-related quality of life and functional status were assessed using the EuroQoL EQ-5D tool[10] and the vitality and physical function sections of the SF-36 health survey.[11] Mortality data were not obtained in GLOW participants and it was therefore not possible to distinguish between loss to follow-up and death.

Statistical Analysis

Weight loss of ≥10 lb (4.5 kg) was assessed at baseline and follow-up years 2 and 3. Fracture was assessed at all surveys (baseline and follow-up years 1, 2, 3, and 5, where year 5 included fracture in years 4 and 5). The primary endpoint was time to first fracture between 0 and 5 years after baseline, for each of 10 bone sites and their composite (denoted 'any fracture'). A secondary endpoint was time to first fracture within 1 year of weight loss.

Baseline characteristics of women with involuntary weight loss ≥10 lb at any of the three surveys were compared to those with no weight loss, using the chi-square test for discrete, and Wilcoxon rank sum test for continuous variables.

Three sets of unadjusted and two sets of adjusted analyses were performed. Unadjusted analyses: (1) rates of 5-year fracture were computed using the Kaplan-Meier method, for women with and without baseline weight loss. Rates in the two groups were compared using the log-rank test; (2) hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for 5-year fracture and the covariate of baseline weight loss, using the Cox model; (3) as in (2), for weight loss at any time treated as a time-varying covariate (TVC). Adjusted analyses: (4) using the Cox model, HRs and 95% CIs were calculated for 5-year fracture and the TVC of weight loss at any time, adjusted for any Table 1 factors which changed unadjusted weight loss HRs (on the log scale) by ≥10%. Backwards elimination of covariates was performed until only covariates whose p-value was ≤0.20 remained. Covariate elimination was performed independently for each of the 11 fracture outcomes; (5) HRs and 95% CIs for 1-year fracture and the TVC of weight loss at any time, adjusted as in (4).

Analyses were performed using the SAS software package, version 9.2 (SAS Institute, Cary, NC, USA).

Results

The numbers of women who completed the baseline and follow-up surveys at years 1, 2, 3, and 5 were 60,393, 51,490, 48,750, 45,490, and 38,411, respectively. Complete data on weight loss at baseline and years 2 and 3 and on fracture through to year 3 were available in 40,179 women aged 68 ± 8.3 (mean ± SD) years. Of these, 33,471 women also had year 5 fracture information. Median follow-up time for the 3897 women with any fracture was 713 days (2.0 years). Median follow-up for the women with no fracture was 1685 days (4.6 years). Unintentional weight loss of ≥10 lb was reported by 3124 (7.8%) women at baseline, 3149 (7.8%) in year 2, and 3070 (7.6%) in year 3. Baseline characteristics of women according to weight loss are shown in Table 1. Women with unintentional weight loss were significantly older, with poorer physical function and quality-of-life indices, and greater frequency of falls. They were also more likely to have a history of fracture, to use anti-osteoporosis medication or glucocorticoids, and to have comorbid conditions.

Cumulative 5-year fracture rate estimates according to baseline weight loss are shown for all fracture sites in Table 2 and for hip and spine in Figure 1. Significant increases were seen in women with unintentional weight loss versus women without weight loss for any fracture and for fracture of the clavicle, wrist, spine, rib, hip and pelvis. The association between weight loss and subsequent fracture was proportional over the study period in all cases except for spine fracture, where the association was stronger in the first year after weight loss (p=0.02; proportional hazards assumption test).

Unadjusted and adjusted HRs between unintentional weight loss and fracture are shown in Table 3. Details of the adjusted models are shown in Supplementary Tables 1–11. After adjustment, a significant increase in risk of fracture was seen for any fracture, clavicle, hip, and spine fracture both at 5 years and within 1 year of unintentional weight loss.

Discussion

Our results confirm previous reports of an association between weight loss and increased fracture risk in postmenopausal women[2-7] and add novel information about the time frame in which fracture occurs relative to weight loss. We have shown for the first time that fracture risk at the hip, spine, and clavicle increases significantly within 1 year following the year in which unintentional weight loss was reported and that the cumulative risk of these fractures, as well as those of the wrist, rib, and pelvis is significantly increased at 5 years of follow-up.

Previous studies of the effects of weight loss on fracture risk have differed in their time frame of weight loss and of follow-up, and have also varied in their definition of weight loss.[2-7] All have included women with a history of weight loss over a number of years, ranging from 3 to 20 or more, and the average duration of follow-up has ranged from 19.5 months to 22 years. Our study is unique in that we could assess the time course of the effect of unintentional weight loss on fracture rate over a 5-year period. Most other studies defined weight loss in percentage rather than in absolute terms, some using a criterion of ≥5% and others ≥10% of baseline body weight. All of these studies used measured weight rather than self-reported weight as in our study. Notwithstanding these differences, our results are consistent with those previously reported, with increased risk of hip fracture,[3-5,7] and of non-spine,[2,7] spine,[7] and wrist fracture[6] in association with unintentional weight loss. An association between unintentional weight loss and fracture of the clavicle has not been previously reported.

In our questionnaire we included information only about unintentional, not intentional, weight loss. The distinction is important because unintentional weight loss is often associated with coexisting conditions that may independently cause increased bone loss and fracture risk. In addition, whereas unintentional weight loss may start from any baseline weight, intentional weight loss is more likely to be seen in overweight or obese women. In the study of Crandall et al,[7] different fracture site profiles were seen in women with unintentional and intentional weight loss, the former being associated with increased risk of hip and spine fracture and the latter with increased risk of ankle fracture but decreased risk of hip fracture. As expected, in the present study lower baseline BMI was a significant independent contributor to fracture risk at most sites, although for upper arm and lower limb fractures there was a positive association between baseline BMI and fracture risk. Both sets of results are consistent with the known site-specificity of the relationship between BMI and fracture risk,[8] low BMI being a strong risk factor for hip and spine fracture and obesity being associated with decreased risk of hip fracture and increased risk of ankle and upper arm fractures.[8,12-16] However, in the study of Ensrud et al. both intentional and unintentional weight loss were associated with increased risk of hip fracture.[3] The adverse effects of intentional weight loss on BMD in obese adults can be attenuated by exercise-training programs, but the feasibility and effectiveness of this approach in older adults with unintentional weight loss has not been investigated.[17]

A number of mechanisms may underlie the association between unintentional weight loss and increased fracture risk. Weight loss, whether unintentional or intentional, is associated with increased rates of bone loss, particularly at the hip[18-21] and reflects, at least in part, a physiological response to decreased mechanical loading. Co-morbid conditions may contribute as a result of decreased mobility, medications such as aromatase inhibitors and glucocorticoids, and increased production of pro-inflammatory, pro-resorptive cytokines. Co-morbidities that were significant on a univariate level were included in the multivariable analysis. Weight loss is also associated with reduced muscle mass and strength, resulting in increased risk of falling, reduced protective responses to falling, and reduced padding from subcutaneous tissue.

Our study has several strengths, including the large sample size, prospective design, and international representation. There are also some limitations. GLOW is a practice- based rather than a population- based study and is therefore subject to bias both in the selection of physicians and in the sampling and recruitment of patients. All data were collected by patient self- report and may be limited by recall inaccuracies and measurement error with regard to reported weight loss. Studies that have examined the validity of self- reported fractures have shown reasonable accuracy for fractures of the hip, wrist, and humerus but lower sensitivity for rib, ankle, and clinical vertebral fractures [22-25]; however, in addition, subclinical vertebral fractures are likely to be under-reported. We believe that the generalizability of our findings to clinical practice in the general population is likely to be good, but cannot exclude possible effects of sampling bias and inaccuracies resulting from self- report of fractures and weight loss. As data on mortality were not available in GLOW, higher mortality rates in women with unintentional weight loss may have resulted in underestimation of fracture risk. Finally, only women were included in the study.

In conclusion, the results of our study indicate that unintentional weight loss in postmenopausal women is associated with increased fracture risk at several sites. The increased fracture risk in the hip, spine, and clavicle was independent of underlying diseases included in the questionnaire, as well as other risk factors associated with fracture at different sites. Finally, an increase in fracture risk is seen within the year following weight loss and persists for at least 5 years. Our findings emphasize the need for prompt assessment and appropriate management strategies in such women in order to reduce the risk of fracture.

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Figure legend

Fig. 1. Kaplan-Meier curves showing cumulative (A) hip and (B) spine fracture rates over 5 years, by baseline weight loss in postmenopausal women.

Table 1. Baseline Characteristics of GLOW Women by Unintentional Weight Loss

Variable	Unintentional loss of ≥10 lb (4.5 kg) (at baseline, year 2, or year 3 survey)		
	No (*n*=32,886)	Yes (*n*=7293)	*p Value*
Age, years	66 (60–73)	69 (62–76)	<0.0001
Body mass index, kg/m^2	26 (23–29)	27 (23–31)	<0.0001
SF-36 physical function	85 (70–95)	70 (44–90)	<0.0001
SF-36 vitality	63 (50–75)	56 (44–69)	<0.0001
EQ-5D index	0.83 (0.76–1.00)	0.79 (0.68–0.83)	<0.0001
Medical history			
Fracture since age 45 years	6757 (21)	1931 (27)	<0.0001
Early menopause	4253 (13)	1388 (19)	<0.0001
Maternal history of hip fracture	4224 (13)	913 (13)	0.91
Current smoker	2387 (7.3)	844 (12)	<0.0001
Alcohol (≥21 drinks/week)	170 (0.5)	32 (0.4)	0.46
Falls in past 12 months			<0.0001
0	21173 (65)	4029 (56)	
1	7447 (23)	1752 (24)	
≥2	4030 (12)	1427 (20)	
Medication use			
Anti-osteoporosis medication	6174 (19)	1442 (21)	0.01
Estrogen	3044 (9.3)	619 (8.6)	0.05
Calcium	14755 (45)	3083 (43)	0.0001
Cortisone or prednisone	737 (2.3)	345 (4.8)	<0.0001
Vitamin D	14410 (45)	3141 (44)	0.39
Co-existing condition			
Asthma	3340 (10)	1079 (15)	<0.0001
Cancer	4382 (13)	1208 (17)	<0.0001
Celiac disease	202 (0.6)	49 (0.7)	0.51
Chronic bronchitis or emphysema	2104 (6.5)	866 (12)	<0.0001
Diabetes (type 1)	756 (2.3)	412 (5.7)	<0.0001
Heart disease	3733 (12)	1414 (20)	<0.0001
High cholesterol	16156 (50)	3829 (53)	<0.0001
Hypertension	15289 (47)	4168 (58)	<0.0001
Multiple sclerosis	182 (0.6)	63 (0.9)	0.003
Osteopenia	5973 (19)	1023 (15)	<0.0001
Osteoporosis	6083 (19)	1777 (26)	<0.0001
Parkinson's disease	85 (0.3)	86 (1.2)	<0.0001
Rheumatoid arthritis	221 (0.7)	93 (1.3)	<0.0001
Stroke	892 (2.7)	407 (5.7)	<0.0001
Ulcerative colitis or Crohn's disease	524 (1.6)	229 (3.2)	<0.0001
Geographic region			<0.0001
Canada/Australia	4543 (13)	1057 (14)	
Europe	13,298 (40)	2413 (33)	
USA	15,045 (46)	3823 (52)	
Physical function			
General health fair or poor	5234 (16)	2123 (29)	<0.0001
Need arms to assist in standing	8544 (26)	3304 (46)	<0.0001

Data are medians (25th and 75th percentiles) or frequency (percentage).

Table 2. Cumulative 5-Year Fracture Rate Estimates according to Baseline Weight Loss (Unintentional Weight Loss Versus no Unintentional Weight Loss)

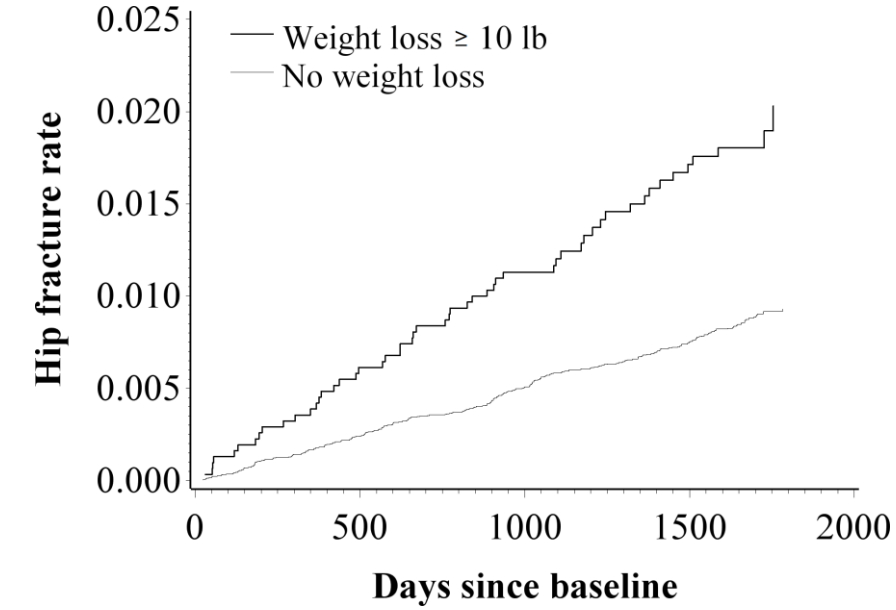
Fracture location	# of fractures	5-year cumulative estimate (%) (Kaplan-Meier)		Log-rank *p*-value
		Weight loss (*n*=3124)	No weight loss (*n*=37,055)	
Any fracture	3897	15	10	<0.0001
Clavicle	161	1.3	0.4	<0.0001
Upper arm	404	1.4	1.1	0.11
Wrist	1130	3.9	3.1	0.03
Spine	521	2.5	1.4	<0.0001
Rib	705	3.0	2.0	<0.0001
Hip	350	2.0	0.9	<0.0001
Pelvis	206	2.4	1.4	0.01
Ankle	670	2.3	1.9	0.07
Upper leg	180	0.6	0.5	0.22
Lower leg	287	0.8	0.8	0.78

Table 3. Unadjusted and Adjusted Associations between Unintentional Weight Loss and Fracture (hazard ratio and 95% confidence interval for weight loss)

Fracture site	Weight loss at baseline only (unadjusted), and fracture within 5 years	Weight loss at baseline, year 2, or year 3* (unadjusted), and fracture within 5 years	Weight loss at baseline, year 2, or year 3* (adjusted†), and fracture within 5 years	Weight loss at baseline, year 2, or year 3* (adjusted†), and fracture within 1 year
Any fracture of the 10 listed bones	1.49 (1.34–1.65)	1.45 (1.33–1.58)	1.15 (1.05–1.27)	1.15 (1.00–1.33)
Clavicle	3.07 (2.08–4.52)	2.70 (1.89–3.86)	1.81 (1.22–2.70)	1.72 (1.00–2.96)
Upper arm	1.31 (0.94–1.82)	1.31 (0.99–1.73)	0.97 (0.72–1.32)	1.24 (0.84–1.85)
Wrist	1.24 (1.02–1.52)	1.16 (0.97–1.38)	0.98 (0.80–1.20)	0.97 (0.72–1.31)
Spine	1.99 (1.55–2.55)	2.08 (1.69–2.57)	1.41 (1.13–1.77)	1.63 (1.19–2.23)
Rib	1.59 (1.26–2.00)	1.53 (1.25–1.86)	1.05 (0.84–1.32)	1.14 (0.82–1.59)
Hip	2.13 (1.59–2.85)	2.32 (1.82–2.97)	1.57 (1.21–2.05)	1.59 (1.09–2.33)
Pelvis	1.55 (1.00–2.39)	1.47 (1.02–2.14)	0.93 (0.61–1.41)	0.85 (0.45–1.59)
Ankle	1.28 (0.98–1.65)	1.31 (1.05–1.63)	1.10 (0.87–1.40)	1.03 (0.72–1.47)
Upper leg	1.35 (0.83–2.20)	1.49 (0.99–2.24)	0.90 (0.58–1.39)	1.19 (0.68–2.07)
Lower leg	1.06 (0.70–1.63)	1.00 (0.69–1.45)	0.77 (0.52–1.14)	0.78 (0.43–1.42)

*Weight loss treated as a time-varying covariate.

†Adjusted for set of all Table 1 factors which, individually, change weight loss estimate ≥10%, and which, after backwards elimination, have $p \leq 0.20$ in adjusted final model.



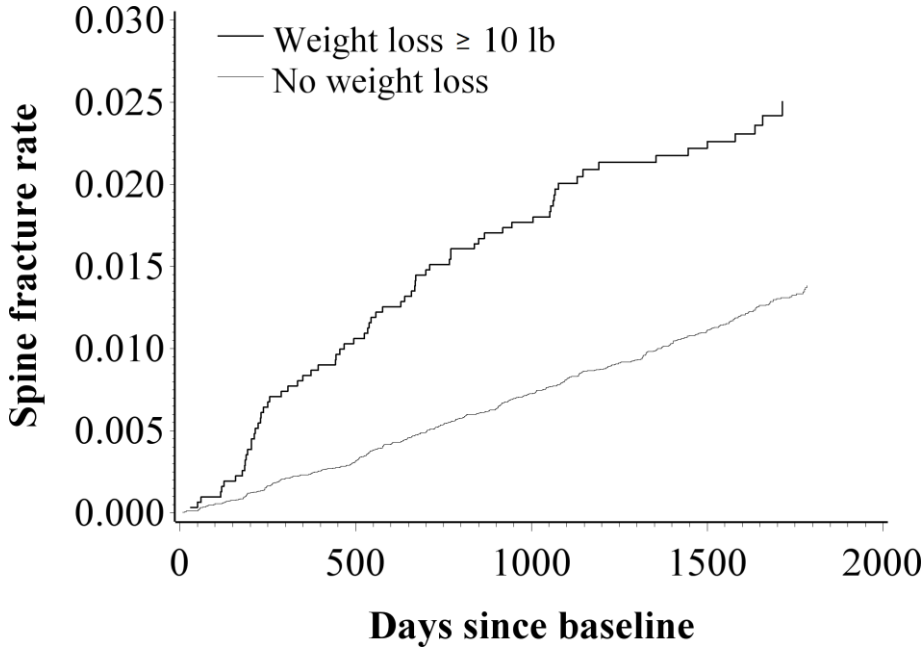


Figure 1