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ORIGINAL ARTICLE

The effect of cyclooxygenase-2 inhibitors on bone mineral density: results from the Canadian Multicentre Osteoporosis Study

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For the Canadian Multicentre Osteoporosis Study (CaMos)

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Abstract
Introduction The use of cyclooxygenase-2 (COX-2) inhibitors has been demonstrated to not only impair load-induced bone formation but also prevent menopause-associated bone loss. We hypothesized that COX-2 inhibitor use would be associated with increased bone mineral density (BMD) in postmenopausal women not using estrogen therapy and, conversely, with decreased BMD in men.
Methods The Canadian Multicentre Osteoporosis Study is a longitudinal, randomly selected, population-based community cohort. We present data from men (n=2,004) and postmenopausal women age 65 and older (n=2,776) who underwent a BMD measurement and structured interview in the 5th year of the study. The outcome measure was percent difference in BMD (g/cm^2).
Results Daily COX-2 inhibitor use was reported by 394 subjects. In men, daily use of COX-2 inhibitors was associated with a lower BMD at all hip sites, with a percent difference of −3.1% [95% confidence interval (CI), −6.0, −0.3] between users and nonusers at total hip. In postmenopausal women not using estrogen replacement therapy, daily COX-2 inhibitor use was associated with higher BMD at most sites [percent difference at total hip: +3.0% (95% CI, 0.3, 5.8)]. These effects appeared to be dose-dependent.
Conclusion COX-2 inhibitor use was associated with a lower BMD in men and, on the other hand, with a higher BMD in postmenopausal women not using estrogen replacement therapy. Men who have used COX-2 inhibitors may wish to seek BMD measurement to assess their fracture risk. However, COX-2 inhibitors may have utility in postmenopausal women if bone-selective analogs can be developed.

Keywords Bone mineral density · Cyclooxygenase-2 inhibitors · Inflammation · Osteoporosis

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Introduction

Bone is a dynamic tissue, constantly remodeling to accommodate mechanical stress and hormonal influences. Prostaglandin production is central to the processes of load-induced bone formation and menopause-associated bone loss [1, 2]. Celecoxib and rofecoxib are both cyclooxygenase-2 (COX-2) inhibitors that prevent prostaglandin production, and they were widely used for arthritic

disorders prior to their association with increased risk of cardiovascular events [3, 4]. Rofecoxib has been withdrawn from most Western markets, whereas celecoxib currently remains available by prescription in many countries. Although osteoporosis is frequently observed in the same age groups in which COX-2 inhibitors have been most widely employed, no reports have described the effect of daily use of these agents on human bone mineral density (BMD).

Both in humans and in rodent models, repeated mechanical trauma has been demonstrated to increase prostaglandin-E_2 (PGE_2) production [5–8]. PGE_2 is produced constitutively by the COX-1 enzyme, but during mechanical stimulation, the inducible COX-2 enzyme appears to be responsible for PGE_2 production [7]. Inhibition of COX-2 has been shown to lead to decreased load-induced bone formation in rodents [9].

In contrast to the bone-forming properties of PGE_2, the withdrawal of estrogen, through natural or surgical menopause, appears to lead to a PGE_2-dependent pro-inflammatory state characterized by bone loss [10–13]. In vivo and in vitro models have indicated that after menopause, T-cells secrete pro-inflammatory cytokines that enhance osteoblast production of a potent stimulus of bone resorption, the receptor activator of nuclear factor kappa B ligand (RANKL) [14, 15]. This cytokine-dependent production of RANKL can be decreased by the use of COX-2 inhibitors [10]. Consequently, inhibition of the COX-2 enzyme in postmenopausal women may prevent menopausal bone loss.

Previous epidemiologic studies involving predominantly postmenopausal women have shown that non-selective inhibition of prostaglandin production through the use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a small increase in BMD compared with non-users [16–18]. However, a cross-sectional study found no association between markers of bone turnover and NSAID use [19].

We hypothesized that the use of COX-2 inhibitors would be associated with a lower BMD in men, reflecting an inhibition of load-induced bone gain, but might conversely be associated with a higher BMD in postmenopausal women not using estrogen supplementation. Because aspirin (ASA) is a known irreversible inhibitor of the COX-1 enzyme [20], we also assessed the combined effects of the COX-2 inhibitors and ASA to determine their impact on BMD. We estimated the magnitudes of these effects using data from a multi-center, randomly selected population-based cohort.

Materials and methods

Study design and population

The Canadian Multicentre Osteoporosis Study (CaMos) has prospectively followed a randomly selected, population-based community cohort of noninstitutionalized men and women over the age of 25 living within 50 km of one of nine regional centers. Details of the purpose and methodology of the CaMos cohort have been reported elsewhere [21]. Briefly, recruitment for the cohort began in February 1996 and ended in September 1997. At the time of recruitment, BMD was measured in all available subjects, and participants were interviewed by a trained interviewer to assess for osteoporosis and fracture-related risk factors. A second intensive interview was conducted 5 years after enrollment to reassess these risk factors and remeasure BMD. These repeat BMD measurements were conducted between July 2000 and January 2003. The female population in this current study was restricted to those 65 years and older to permit the analysis of a postmenopausal female population and to allow for direct comparison with previous studies analyzing the effect of NSAID use on BMD [16, 18]. The study was approved by regional institutional ethics review boards; all participants provided written informed consent; and these research activities are in compliance with the Helsinki Declaration.

Assessment of medication use

Interviewers collected detailed drug information, including type of medication, dose, delivery route, and frequency of use. When interviews were conducted in the homes of participants, all contents of their medicine cabinets were assessed. For all other interviews, subjects were instructed to bring all of the contents of their medicine cabinets to the interview site. All medications reported are those at the 5th-year interview. The COX-2 inhibitors assessed in this study were celecoxib and rofecoxib, the only two COX-2 inhibitors available for use at the time of the patient interviews. Rofecoxib and celecoxib were released onto the Canadian market in 1999.

To assess dose effects, rofecoxib and celecoxib doses were standardized such that starting daily doses for osteoarthritis (12.5 mg for rofecoxib and 200 mg for celecoxib) were considered equivalent [22]. For patients taking higher doses of these medications, their dose was considered as a multiple of these starting doses. For purposes of analysis we categorized each subject into nonuser, low-dose daily user (25-mg equivalent dose), and high-dose daily user (50-mg equivalent dose) and assessed the relationship between dose and BMD. Persons were considered daily users of rofecoxib or celecoxib if they reported taking the medication every day. Persons were considered daily users of ASA or low-dose acetaminophen if they took at least 80 mg and less than 1 g of these medications, respectively, every day. Women were considered nonusers of estrogen therapy if they did not report previous estrogen therapy use. In light of our study

Table 1 Selected characteristics of study population after 5 years of follow-up (*BMI* body mass index, *OA* osteoarthritis, *RA* rheumatoid arthritis, *ASA* aspirin)

Variable	Men		Women not using estrogen therapy		Women using estrogen therapy	
	COX-2 daily users (*n*=108)	Nonusers (*n*=1896)	COX-2 daily users (*n*=145)	Nonusers (*n*=1392)	COX-2 daily users (*n*=141)	Nonusers (*n*=1098)
Age	70.4 (11.8)	63.3 (13.2)	76.6 (5.6)	75.2 (6.2)	73.8 (5.4)	73.4 (5.5)
BMI	28.6 (4.1)	27.4 (3.9)	28.9 (5.3)	27.3 (5.1)	27.8 (5.0)	26.7 (4.6)
Calcium intake (mg/day previous 12 months)	913.3 (608.9)	880.8 (573.4)	885.0 (474.8)	878.9 (502.5)	925.7 (558.0)	897.6 (504.4)
Vitamin D intake (mg/day previous 12 months)	143.8 (277.2)	160.7 (651.6)	233.3 (306)	276.7 (590)	410.0 (919.6)	340 (714.5)
OA	79 (73.2%)	389 (20.5%)	114 (78.6%)	512 (36.8%)	118 (83.7%)	499 (45.5%)
RA	10 (9.3%)	46 (2.4%)	13 (9.0%)	68 (4.9%)	7 (5.0%)	61 (5.6%)
Lupus	0 (0%)	0 (0%)	0 (0%)	5 (0.4%)	1 (0.7%)	8 (0.7%)
Number of inactive hours per day (previous 12 months)	7.0 (2.5)	7.4 (3.0)	6.6 (2.3)	6.7 (2.4)	6.7 (2.2)	6.5 (2.4)
Number of lifetime ovulatory cycles	–	–	425.9 (84.3)	444.9 (78.1)	419.3 (79.0)	430.8 (85.3)
Daily low-dose acetaminophen users[a]	9 (8.3%)	21 (1.1%)	10 (6.9%)	36 (2.6%)	10 (7.1%)	40 (3.6%)
Daily ASA users[b]	31 (28%)	410 (21.6%)	25 (17.2%)	326 (23.4%)	29 (20.6%)	288 (26.2%)

Mean and (SD) or count and (%)
[a] Daily acetaminophen use < 1 g each day
[b] Daily ASA use ≥80 mg each day

hypotheses, women were stratified a priori by estrogen use.

Bone mineral density

Seven of the nine centers measured BMD of the lumbar spine (L1–L4) and hip using dual energy x-ray absorptiometry with the Hologic QDR 1,000, 2,000, and 4,500, and two centers used Lunar DPX densitometers. All BMD results were converted to a Hologic standard using the method described by Genant et al. [23]. Each month a European spine phantom was measured systematically at each site for standardization purposes [24]. BMD results reported are those at the 5th-year assessment.

Other measures

Baseline demographic information was recorded during the initial patient interview. The weight and height of each participant were measured, and body mass index (BMI) was calculated by dividing the weight of the subject in kilograms by the square of his or her height in meters. Physical inactivity was assessed by recording the average number of sedentary hours per day in the previous year. Calcium and vitamin D intake were recorded—both supplementation and dietary intake from calcium- and vitamin D-rich foods—using a standardized calcium- and vitamin D-specific diet questionnaire. All comorbidities, including osteoarthritis and rheumatoid arthritis, were based on subjects' reports of diagnoses made by their treating physicians. This was done to ensure that the presence of these diseases was confirmed by a physician and was not based on the patient's self-diagnosis.

Statistical methods

Descriptive statistics—including means and standard deviations for continuous variables, and percentages in each category for binary and categorical variables—were calculated. The effect of COX-2 inhibition on BMD was examined using both univariate and multivariate linear regression (SAS Institute, Cary, NC, USA). The relationships between the dependent and independent variables were assessed for nonlinear trends. Various curves were fit to examine the relationship between age and BMD, including logarithmic transformations and quadratic fits. Because we found that a simple linear relationship fit the model well, only these results were reported for all variables except calcium intake over the previous 12 months. Calcium intake was subsequently log-transformed. The residual plots for all

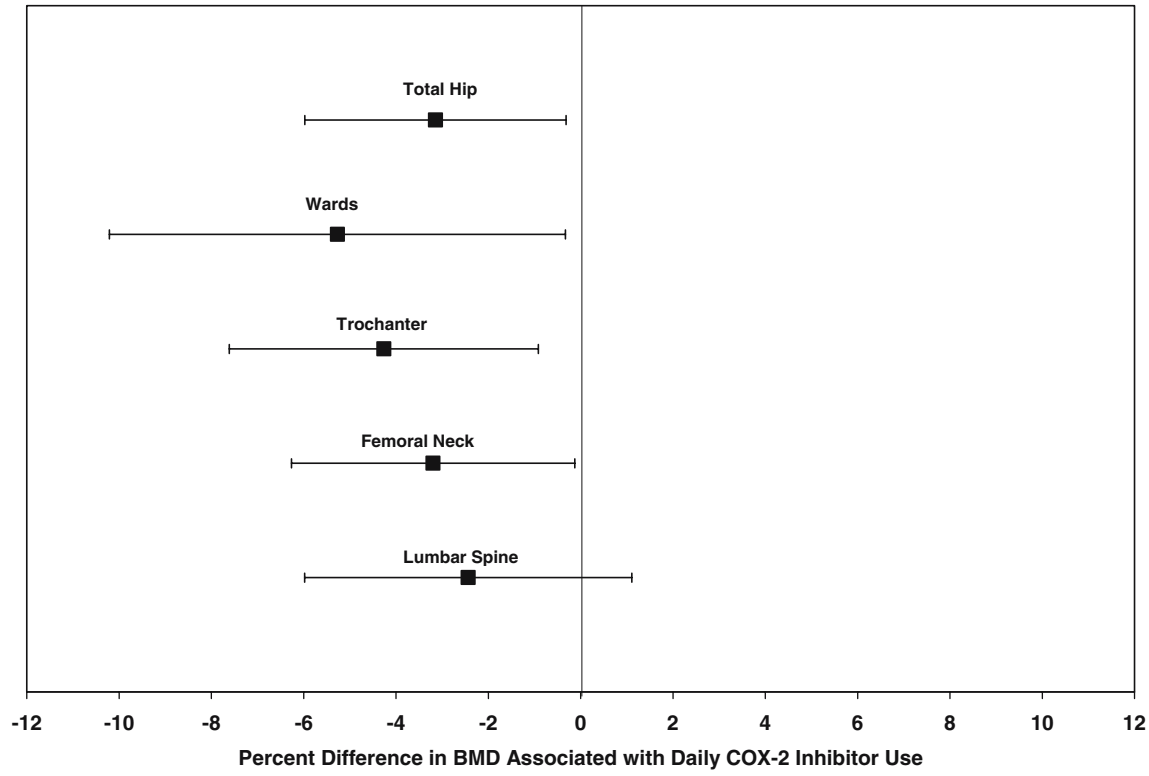

Fig. 1 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with COX-2 inhibitor use in men (95% CI). Users vs. nonusers; adjusted for age, body mass index, physical activity, calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

covariates were assessed. Predictors of BMD and fracture were considered as potential confounders (age, BMI, estimated number of ovulatory cycles in females, physical activity, calcium and vitamin D intake over the previous 12 months, previous fragility fracture, education level, and center) and added to the models. Comorbidities (osteoarthritis, rheumatoid arthritis, and lupus) that are medical indications for COX-2 inhibitor use were also included as potential confounders. Interaction terms between estrogen and medications (COX-2 inhibitors, ASA, and acetaminophen) were considered. The difference in BMD associated with the use of COX-2 inhibitors is expressed throughout as percent difference, derived from the regression coefficients using the following formula: 100% × beta/mean BMD for nonusers at year 5 [25]. Thus, all differences in BMD attributed to medication use are derived from a cross-sectional analysis of data at year 5.

Results

In total, 9,423 subjects were enrolled at baseline in the CaMos cohort. We restricted our analysis to men of all ages and women 65 years and older who had completed a year-5 interview and BMD measurement. After 5 years of follow-up our sample included 2,004 men and 2,776 women, of whom 394 (8.2%) subjects used COX-2 inhibitors (either rofecoxib or celecoxib) daily (Table 1). Users of COX-2 inhibitors were older, were more likely to self-report osteoarthritis or rheumatoid arthritis, and had a slightly higher BMI. Daily use of ASA was reported by 1,109 subjects (23%) in the population studied, and the frequency of its use was not different between COX-2 daily users and non-users. Low-dose acetaminophen daily use was also common; 126 (2.6%) subjects reported daily use, and they were more likely to also use COX-2 inhibitors daily. All analyses reported are adjusted for previously described confounders and predictors of BMD.

Effect of COX-2 inhibitor use on BMD

In men, daily COX-2 inhibitor use was associated with lower BMD at all hip sites and with a similar effect at the lumbar spine, although at the lumbar spine the 95% confidence interval (CI) crossed the null value (Fig. 1). For example, the adjusted effect of COX-2 inhibitor daily use on total hip BMD in men was −3.1% (95% CI: −6.0, −0.3). In contrast, among postmenopausal women not using estrogen replacement therapy, COX-2 inhibitor daily use was associated with a higher BMD (Fig. 2). For example,

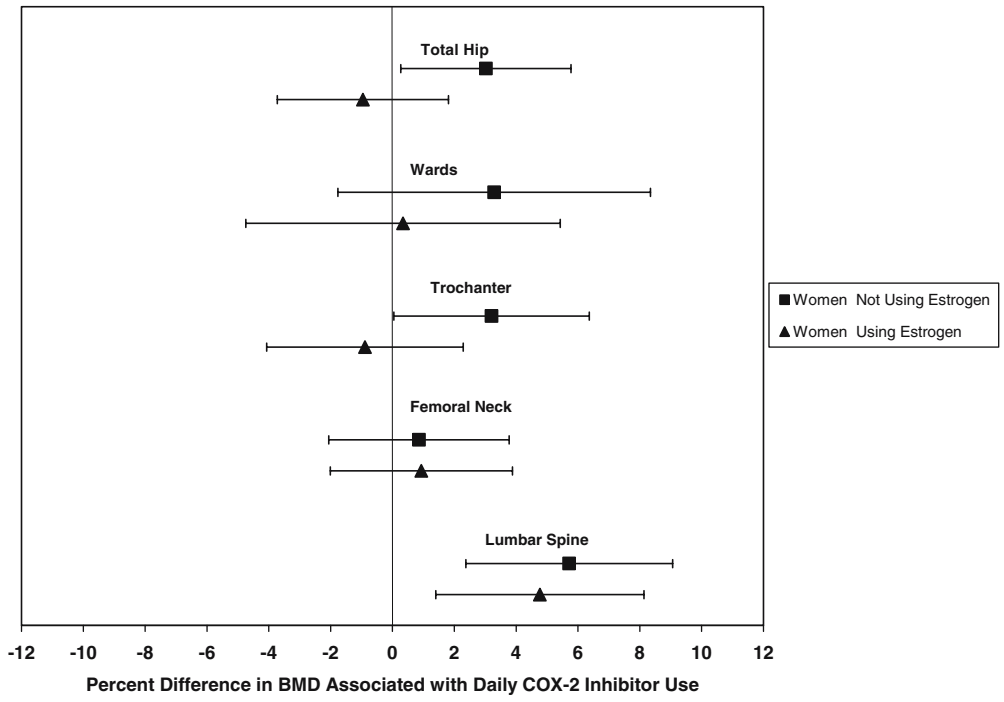

Fig. 2 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with COX-2 inhibitor use in women ≥65 years (95% CI). Users vs. nonusers; adjusted for age, body mass index, physical activity, number of ovulatory cycles, calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

daily COX-2 inhibitor use was associated with a 3.0% (95% CI: 0.3, 5.8) higher value for BMD at the total hip compared with nonusers. A greater difference in BMD was observed at the lumbar spine. When women *using* estrogen were analyzed, BMD in COX-2 users was no longer seen to be increased at all sites except for the lumbar spine (Fig. 2). Interestingly, the COX-2-associated lower BMD in men and the COX-2-associated higher BMD in women exhibited more profound effects at higher doses of these medications, although there was overlap in the CIs between the two different dose categories (Table 2). In contrast, again there was no consistent association between BMD and COX-2 inhibitor dose in women using estrogen therapy and COX-2 inhibitors (data not shown).

Daily acetaminophen is commonly prescribed to treat osteoarthritis, but at low doses it is not known to profoundly influence the COX-2 pathway [26]. To evaluate whether the described relationship between COX-2 inhibitors and BMD was due to confounding by indication, we assessed the effect of daily low-dose acetaminophen use on BMD. Daily low-dose acetaminophen use was not associated with a consistent difference in BMD in either men or women in this cohort (Table 3).

Effect of COX-2 inhibitor and ASA use on BMD

In total, only 31 male (1.5%) and 54 female (1.9%) subjects of the total study population reported using both COX-2 inhibitors

Table 2 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with low-dose (25 mg) and high-dose (50 mg) standardized daily dose of COX-2 inhibitor (95% CI); users vs. nonusers

Site	Men (*n*=2,004)		Women ≥65 years not using estrogen (*n*=1,537)	
	Low-dose	High-dose	Low-dose	High-dose
Total hip	**−4.3 (−7.6, −1.0)**	−8.6 (−15.1, −2.0)	**3.5 (0.2, 6.8)**	**7.0 (0.4, 13.6)**
Wards	**−7.3 (−13.1, −1.6)**	**−14.7 (−26.2, −3.2)**	3.5 (−2.5, 9.6)	7.0 (−5.0, 19.1)
Trochanter	**−5.3 (−9.2, −1.5)**	**−10.7 (−18.3, −3.0)**	3.1 (−0.7, 6.9)	6.2 (−1.3, 13.8)
Femoral neck	**−4.3 (−7.9, −0.7)**	**−8.6 (−15.8, −1.4)**	1.5 (−2.0, 5.0)	3.0 (−4.0, 9.9)
Lumbar spine	−3.5 (−7.6, 0.7)	−6.9 (−15.3, 1.4)	**6.0 (2.1, 10.0)**	**12.1 (4.1, 20.0)**

Differences with confidence intervals that exclude the null value are shown in bold type. Adjusted for age, body mass index, physical activity, number of ovulatory cycles (in females), calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

Table 3 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with low-dose acetaminophen daily use[a] (95% CI); users vs. nonusers

Site	Men (n=2,004)	Women ≥65 years not using estrogen (n=1,537)	Women ≥65 years using estrogen (n=1,239)
Total hip	−4.5 (−9.4, 0.5)	2.7 (−1.8, 7.2)	1.9 (−2.4, 6.3)
Wards	−6.2 (−14.8, 2.5)	5.1 (−3.1, 13.4)	1.7 (−6.3, 9.8)
Trochanter	−5.3 (−11.1, 0.4)	4.2 (−0.9, 9.4)	1.9 (−3.2, 6.9)
Femoral neck	−4.6 (−10.0, 0.8)	0.1 (−4.7, 4.9)	3.1 (−1.6, 7.7)
Lumbar spine	−3.4 (−9.7, 2.8)	2.7 (−2.9, 8.3)	0.0 (−14.6, 14.6)

[a]Acetaminophen daily use <1 g per day

Adjusted for age, body mass index, physical activity, number of ovulatory cycles in females, calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

and ASA daily. Generally, the combined adjusted effect of COX-2 inhibition and ASA use exaggerated the aforementioned relationship between COX-2 inhibition and BMD. In men, the use of both daily ASA and COX-2 inhibitors was associated with a markedly lower BMD at all hip sites and with a possible reduction in BMD at the lumbar spine, although the 95% CI crossed the null value at the lumbar site (Fig. 3). On average, the effect of daily ASA and COX-2 inhibitor use was associated with a 2.4-fold (range 2.1–2.8) greater difference in BMD compared with the difference attributed to COX-2 inhibitor use alone. In women not using estrogen, a similar exaggeration of the effect of COX-2 inhibitors was seen when daily ASA and COX-2 users were analyzed (Fig. 4). Again, on average the addition of daily ASA further *increased* the effect of COX-2 inhibition on BMD by a factor of 2.4 (range 1.4–4.0). Daily ASA and COX-2 inhibitor use had no discernible effect on BMD at any site in women using estrogen replacement therapy (data not shown).

Effect of COX-2 inhibitor use in patients who reported osteoarthritis

Most of the daily users of COX-2 inhibitors self-reported a physician-made diagnosis of osteoarthritis (men, 73%; women not using estrogen therapy, 78%). To control for confounding by indication, we repeated our analyses using only those subjects who reported a diagnosis of osteoarthritis. This reduced our sample size by 64% (468 men and 1,243 women). While CIs were wide in this restriction analysis, the point estimates were similar to those from the analyses of COX-2 inhibitors for the total study population (Table 4).

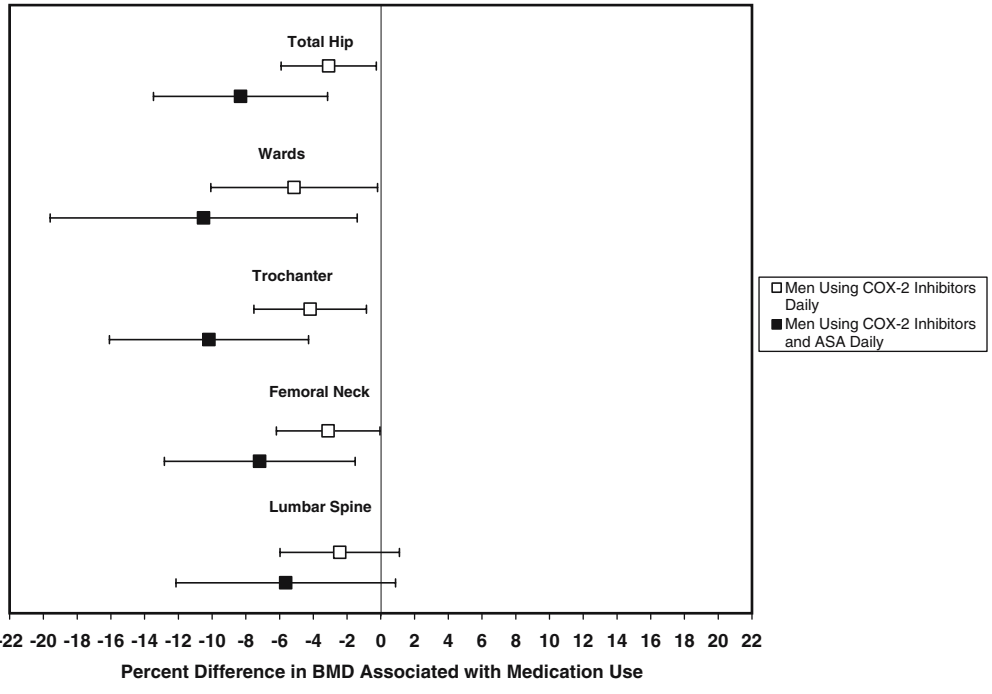

Fig. 3 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with both COX-2 inhibitor and ASA daily use (95% CI) in men. Users of both medications vs. nonusers of either medication; adjusted for age, body mass index, physical activity, calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

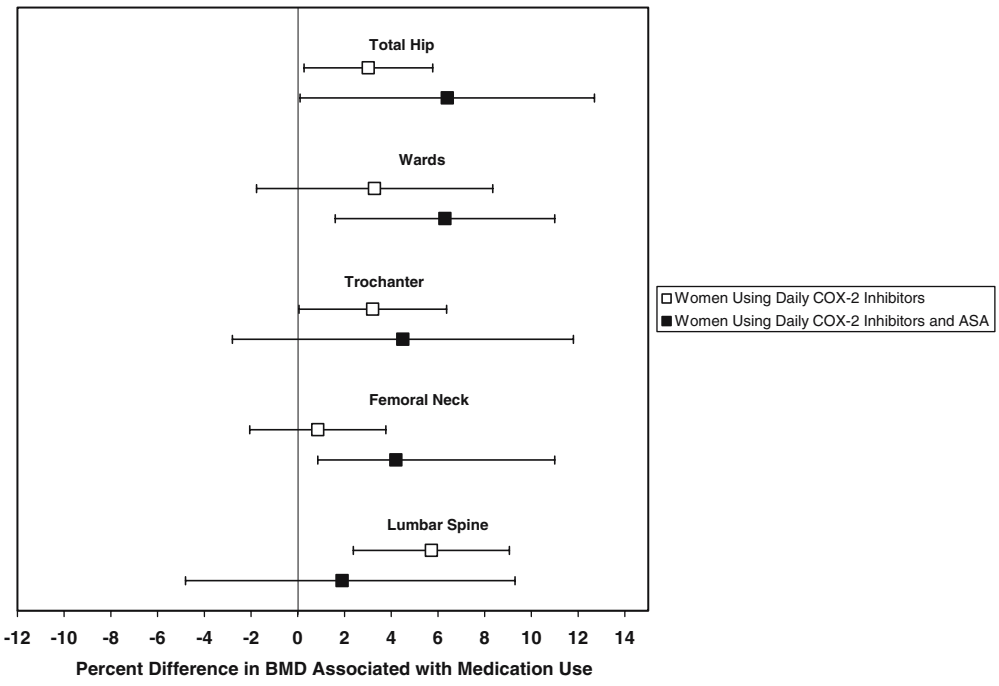

Fig. 4 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with both COX-2 inhibitor and ASA daily use (95% CI) in women ≥65 years not using estrogen therapy. Users of both medications vs. nonusers of either medication; adjusted for age, body mass index, physical activity, number of ovulatory cycles, calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

Discussion

In this population-based study of randomly selected community dwellers, the daily use of COX-2 inhibitors was associated with a 2.4–5.3% lower BMD across hip and spine in men, after statistical adjustment for possible confounders. In postmenopausal women not using estrogen replacement therapy, daily use of COX-2 inhibitors was associated with a 0.9–5.7% higher BMD at hip and spine sites after statistical adjustment for confounders. Importantly, these changes were generally consistent across multiple anatomic sites. Prostaglandins may have complex effects in bone, and our findings support the hypotheses that inhibition of the COX-2 pathway and resultant reductions in PGE_2 may prevent the pro-inflammatory state associated with postmenopausal bone loss. However, PGE_2 may also exert beneficial skeletal effects by mediating mechanical load-induced bone formation, and our findings of reduced BMD in men taking COX-2 inhibitors is consistent with interference with load-induced bone gain.

In postmenopausal women using estrogen replacement therapy, we observed no consistent effect of COX-2 inhibitor daily use on BMD. Recent randomized controlled trial data indicate that estrogen replacement therapy is unable to fully return women to a biological premenopausal state [27–29]. Thus, postmenopausal women using estrogen replacement therapy may have only a partial reversal of the pro-inflammatory menopausal state. Hence in this population, the lack of effect of COX-2 inhibition may represent both a partial suppression of this residual inflammation and concomitant interference with load-induced bone gain, resulting in no appreciable net change in BMD.

Although COX-2 inhibitors reversibly inhibit the COX-2 enzyme, ASA irreversibly inhibits COX-1 [30]. Thus, the combined use of COX-2 inhibitors and ASA may potentiate the effect of COX-2 inhibitors alone. We found that the

Table 4 Multiply-adjusted percent difference in bone mineral density (g/cm^2) associated with COX-2 inhibitor daily use, in only subjects with osteoarthritis (95% CI); users vs. nonusers

Measurement site	Men (*n*=468)	Women ≥65 years not using estrogen (*n*=626)	Women ≥65 years using estrogen (*n*=617)
Total hip	−2.1 (−5.6, 1.5)	2.8 (−0.5, 6.1)	−0.6 (−3.8, 2.6)
Wards	−5.4 (−11.8, 0.9)	1.5 (−4.6, 7.6)	0.7 (−5.2, 6.6)
Trochanter	−2.6 (−6.7, 1.5)	3.4 (−0.4, 7.1)	−0.4 (−4.0, 3.3)
Femoral neck	−3.3 (−7.2, 0.6)	0.1 (−3.5, 3.4)	1.4 (−2.0, 4.8)
Lumbar spine	−3.2 (−7.7, 1.3)	**6.1 (2.0, 10.2)**	4.9 (0.9, 8.9)

Differences with confidence intervals that exclude the null value are shown in bold type. Adjusted for age, body mass index, physical activity, number of ovulatory cycles in females, calcium and vitamin D intake, previous fragility fracture, osteoarthritis, rheumatoid arthritis, lupus, education level, and center

combined use of daily COX-2 inhibitors and daily ASA had an exaggerated effect on BMD compared with use of COX-2 inhibitors alone in both men and postmenopausal women not using estrogen replacement therapy.

A large proportion of daily COX-2 inhibitor users reported a physician-made diagnosis of osteoarthritis (men, 73%; women not using estrogen therapy, 78%). Hence, osteoarthritis was considered a potential confounder by indication. Osteoarthritis has been reported to be associated with an increased BMD at the hip and lumbar spine; however, this relationship is stronger at the lumbar spine than at hip sites, likely due to degenerative changes [31]. Indeed, osteoarthritis may have contributed to observed differences in lumbar spine BMD in all treatment categories, despite statistical adjustment for self-reported osteoarthritis using multiple linear regression.

Yet it is unlikely that our findings can be explained entirely by this potential confounder, for several reasons. First, in our study population and in other cohorts, osteoarthritis was associated with an *increased* BMD at total hip and spine, while in men our results indicate that COX-2 inhibitor use is associated with a *lower* BMD. Second, daily acetaminophen is also a medication commonly used to treat osteoarthritis, and at low doses it is not known to markedly influence the COX-2 pathway [26, 32, 33]. Thus, if the described relationship between BMD and COX-2 inhibitor use was due to confounding by indication, we would expect a similar relationship between daily low-dose acetaminophen use and BMD. However, low-dose acetaminophen use demonstrated no relationship with BMD. Third, when we restricted our study population to only those subjects with osteoarthritis, daily COX-2 inhibitor use was still associated with a similarly decreased BMD in men and a similarly increased BMD in postmenopausal women not using estrogen therapy. The resultant CIs in this restriction analysis were wide and in most cases include 0, likely reflecting the fact that by limiting the analysis to only those subjects with osteoarthritis, the sample size was reduced by 64%. Finally, osteoarthritis was controlled for in our analysis using multiple linear regression.

Our study has several limitations. First, the duration of medication use was not known, and consequently we cannot assess the cumulative dose effect of COX-2 inhibitors on BMD. However, rofecoxib and celecoxib were released onto the Canadian market in 1999. Hence, we do know that no subjects could have used these medications for more than 4 years. Other reports of the effect of NSAIDs on BMD have described little effect of the duration of medication use on BMD [16]. Second, we used the subjects' reports of physician-made diagnoses of osteoarthritis, which may be prone to misclassification error. However, other large osteoporosis studies have used self-reported diagnoses of osteoarthritis and found these self-reports to be valid and reliable [16, 17, 34]. If misclassification error is present in our study, then it is highly likely that this is a random classification error, as the subjects and interviewers were unaware of our study hypotheses. Any such random misclassification would tend to dilute any underlying associations, not create or amplify them. Finally, as in all observational studies, it is possible that COX-2 inhibitor use may be associated with an unknown confounder, which was therefore not controlled for.

In a previous study of postmenopausal women, the multiply adjusted effect of daily use of ASA or NSAIDs was associated with a 1.0–3.1% increase in BMD of the hip and spine [16]. During the course of our study, COX-2 inhibitors were thought to have an improved safety profile over traditional NSAIDs, and consequently, many fewer subjects in our study reported daily use of traditional NSAIDs compared with daily use of COX-2 inhibitors. Indeed, there were 40% fewer daily NSAID users compared with daily COX-2 inhibitor users. Although it would have been interesting to examine the relationship between traditional NSAIDs and BMD, we were unable to offer further insight into this relationship due to the small number of subjects using these medications.

Another study stratified the relative COX-1 and COX-2 selectivity of traditional NSAIDs and compared their effect on BMD in men and women [18]. Relative COX-2 inhibitors were found to increase BMD at whole body, total hip, and cortical spine only when used in combination with ASA. The investigators found no effect of relatively COX-2-selective NSAIDs alone. Importantly, there was only one subject in that study using a specific COX-2 inhibitor. Cauley et al. [34] conducted a cross-sectional study of predictors of BMD in a cohort of men over the age of 65. The authors found no multiply adjusted association between COX-2 inhibitor use and femoral neck BMD but found an increased lumbar spine BMD in elderly males using COX-2 inhibitors. Our study differs in several respects. Their cohort was recruited from clinical settings and not from the general community, and subjects with osteoporosis were excluded. In addition, while we analyzed daily COX-2 inhibitor use, Cauley et al. included all subjects who used this medication, however infrequent. These methodological differences may at least in part explain the contrasting results between those reported by Cauley et al. and those reported here.

Although there were insufficient incident clinical fractures in our study to describe the effect of COX-2 inhibitors on clinical fracture risk, many recent randomized controlled studies of fracture have indicated that small changes in BMD (less than 5%) predict large changes in fracture rate [35–38]. In addition, each standard deviation decrease in BMD increased the age-adjusted risk of hip fracture 2.6-

fold in a longitudinal study of fractures in postmenopausal women [39]. Thus, the differences in BMD associated with COX-2 inhibitor use described in our study indeed have relevance to the eventual development of fractures.

In conclusion, our study suggests that the daily use of COX-2 inhibitors is associated with a potentially clinically relevant higher BMD in postmenopausal females not using estrogen and with a lower BMD in men across most sites. Given these results, men currently, or previously, using COX-2 inhibitors may wish to evaluate their BMD to assess their future fracture risk. On the other hand, the demonstrated effect of COX-2 inhibitors on BMD in postmenopausal women underscores the importance of inflammation in postmenopausal bone loss.

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