Menopause: The Journal of The North American Menopause Society
Vol. 11, No. 2, pp. 138–143
DOI: 10.1097/01.GME.0000087983.28957.5D

Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies

Olivier Bruyere, MSc,[1,2,3] Karel Pavelka, MD, PhD,[4,5] Lucio C. Rovati, MD, [6] Rita Deroisy, MSc,[3] Marta Olejarova, MD, PhD,[5] Jindriska Gatterova, MD,[5] Giampaolo Giacovelli, PhD,[6] and Jean-Yves Reginster, MD, PhD[1,2,3,7]

ABSTRACT

Objective: To investigate the effect of glucosamine sulfate on long-term symptoms and structure progression in postmenopausal women with knee osteoarthritis (OA).

Design: This study consisted of a preplanned combination of two three-year, randomized, placebo-controlled, prospective, independent studies evaluating the effect of glucosamine sulfate on symptoms and structure modification in OA and post-hoc analysis of the results obtained in postmenopausal women with knee OA. Minimal joint space width was assessed at baseline and after 3 years from standing anteroposterior knee radiographs. Symptoms were scored by the algofunctional WOMAC index at baseline and after 3 years. All primary statistical analyses were performed in intention-to-treat, comparing joint space width and WOMAC changes between groups by ANOVA.

Results: Of 414 participants randomized in the two studies, 319 were postmenopausal women. At baseline, glucosamine sulfate and placebo groups were comparable for demographic and disease characteristics, both in the general population and in the postmenopausal women subset. After 3 years, postmenopausal participants in the glucosamine sulfate group showed no joint space narrowing [joint space change of +0.003 mm (95% CI, −0.09 to 0.11)], whereas participants in the placebo group experienced a narrowing of −0.33 mm (95% CI, −0.44 to −0.22; $P < 0.0001$ between the two groups). Percent changes after 3 years in the WOMAC index showed an improvement in the glucosamine sulfate group [−14.1% (95%, −22.2 to −5.9)] and a trend for worsening in the placebo group (5.4% (95% CI, −4.9 to 15.7) ($P = 0.003$ between the two groups).

Conclusion: This analysis, focusing on a large cohort of postmenopausal women, demonstrated for the first time that a pharmacological intervention for OA has a disease-modifying effect in this particular population, the most frequently affected by knee OA.

Key Words: Osteoarthritis – Glucosamine sulfate – Women – Menopause – Joint structure.

Received February 28, 2003; revised and accepted July 2, 2003.

From the [1]WHO Collaborating Center for Public Health Aspect of Osteoarticular Disorders, Liege, Belgium; the [2]Department of Public Health and Epidemiology and the [3]Bone and Cartilage Research Unit, University of Liege, Liege, Belgium; the [4]Department of Medicine and Rheumatology, Charles University, Prague, Czech Republic; the [5]Institute of Rheumatology, Prague, Czech Republic; the [6]Department of Clinical Pharmacology, Rotta Research Laboratorium, Monza, Italy; and the [7]Georgetown University Medical Center, Washington, DC, USA.

Address correspondence to: Prof. Jean-Yves Reginster, Bone and Cartilage Metabolism Unit, Quai G. Kurth 45, 4000 Liege, Belgium. E-mail: jyreginster@ulg.ac.be.

Osteoarthritis (OA) is a major cause of pain and physical disability in older people.[1] However, the older population is more and more demanding of therapeutic interventions that allow a pain-free, active lifestyle. Therefore, the management of knee OA, recognized as responsible for consistent pain and disability, is a major social and economic target in health management.[2] Before the age of 50 years, knee OA is more frequent in men, but later in life, the incidence increases more rapidly in

women.[3-5] These epidemiologic observations suggest a possible role for postmenopausal hormone deficiency as a risk factor for knee OA and knee pain in women. However, no randomized, prospective, controlled trials have been designed to specifically assess the impact of hormone therapy (HT) on symptomatic or structural progression of OA. Moreover, a recent review taking into account preclinical as well as observational and clinical studies, concluded that, at the current level of evidence, HT could not be recommended as a specific treatment to prevent progression of osteoarthritis.[6]

For a few years, glucosamine sulfate has been considered a potential disease-modifying drug for OA. Two recent, long-term, prospective, placebo-controlled studies have shown an improvement in symptoms and a stabilization of radiographic joint space width (JSW) in people treated with glucosamine sulfate compared with placebo.[7,8] The aim of the present study was to investigate whether the structural and symptomatic effects of glucosamine sulfate were also observed in a specific subset of postmenopausal women with knee OA.

METHODS

Participants and treatments

The study population consisted of 319 postmenopausal women, older than 45 years and with primary knee OA. They all had taken part in two randomized, double-blind, placebo-controlled studies evaluating, over a period of three years, the symptomatic and structural effects of glucosamine sulfate in OA.[7,8] Knee OA was diagnosed according to the clinical and radiological criteria of the American College of Rheumatology,[9] which include the presence of pain and of radiographic osteophytes. Women were considered as postmenopausal when the time of amenorrhea was at least 1 year: no misclassifications occurred in this respect due to possible hysterectomy, endometrial ablation, or hormonal interventions promoting amenorrhea. In both trials, crystalline glucosamine sulfate was used, ie the original glucosamine sulfate described in the vast majority of clinical studies and available as a prescription drug for osteoarthritis in several European and other countries and as a single nutritional supplement brand in the United States (Dona, Viartril-S, or Xicil; Rottapharm Group, Monza, Italy, and Rotta Pharmaceuticals, Wall, NJ, USA). The product was used in its once-a-day formulation (packets of powder for oral solution), with a net content equivalent to 1500 mg of glucosamine sulfate. Participants were randomized to double-blind, continuous, daily treatment for 3 years with the active formulation or identical placebo. As described in details in the original study reports,[7,8] acetaminophen 500 mg tablets in the Pavelka study, or the same and selected NSAIDs in the Reginster study, were provided for rescue analgesia as needed, with use recorded in participants' daily diaries. Because of its possible confounding effect on the progression of OA, HT was prohibited in both studies. In addition, no other cointerventions for OA were allowed during the study, with the exception of physical therapies (namely hydrotherapy, exercise, and ultrasound) that were allowed in the Pavelka study if participants were following a stable regimen.[8]

X-ray acquisition

Standard radiographs were taken for each knee at baseline and after 3 years, using the state-of-the-art technique at the time of the trial, as recommended by the guidelines of the Osteoarthritis Research Society International.[10] The radiographic protocols were remarkably similar, as described in the two original reports.[7,8] In particular, the focus-to-film distance was fixed as well as all other radiographic parameters and settings (ie, kilovolts, milliamperes, and milliseconds). In addition, the posterior aspect of the knee was in contact with the x-ray cassette to avoid variations in the distance between the knee and the cassette throughout the study. Finally, fluoroscopy was used to correct lower limb positioning and x-ray beam alignment. In both trials, participant repositioning was guided by the baseline film and aided by foot map in the Reginster study and by placing the feet together in the Pavelka study.

Joint space width measurement

Minimal JSW—ie, at the narrowest point of the medial compartment of the femorotibial joint—was assessed by visual determination using a 0.1-mm graduated magnifying lens according to a validated method.[11] Reproducibility of JSW measurement was high in both studies.[7,8] The primary efficacy endpoint, for the structure modification, was joint space narrowing as recommended by current guidelines.[10,12] As a secondary analysis, we looked at the number of participants who experienced a relevant joint space narrowing over a 3-year period. Based on the literature, any loss greater than 0.5 mm was considered relevant.[13] This arbitrary cutoff of 0.5 mm in JSW was based on the paper by Lequesne et al[13] in which a difference of 0.5 mm in joint space narrowing between an active drug and a comparator was suggested to be a relevant primary endpoint in a study assessing disease-modifying drugs in OA, as more recently confirmed by other validation studies. [14]

TABLE 1. *Baseline characteristics of all randomized women participants in the placebo and glucosamine sulfate group*

Characteristics	Glucosamine sulfate[a]	Placebo[b]	*P*
Age (y)	63.2 (8.1)	64.8 (7.3)	0.07
Body mass index (kg/m^2)	26.5 (2.6)	26.4 (2.6)	0.86
Minimum joint space width (mm)	3.86 (1.31)	3.77 (1.39)	0.54
WOMAC total, VAS scales (mm)	1.04 (480)	959 (490)	0.28
WOMAC pain, VAS scales (mm)	194 (107)	176 (105)	0.27
WOMAC function, VAS scales (mm)	751 (361)	687 (367)	0.26
WOMAC stiffness, VAS scales (mm)	94 (56)	95 (57)	0.91
WOMAC total, Likert scales (point)	31.7 (14.6)	31.7 (14.3)	0.99
WOMAC pain, Likert scales (point)	6.8 (3.4)	6.5 (3.2)	0.48
WOMAC function, Likert sales (point)	22.5 (10.9)	23.0 (10.9)	0.79
WOMAC stiffness, Likert scales (point)	2.3 (1.5)	2.2 (1.4)	0.69

WOMAC, Western Ontario and McMaster Universities Osteoarthritis index; VAS, visual analogue scale version of index.
All values expressed as mean (SD).
[a] $n = 159$ for age, body mass index, and minimum joint space; $n = 79$ for WOMAC assessed by VAS; $n = 80$ for WOMAC assessed by Likert.
[b] $n = 160$ for age, body mass index, and minimum joint space; $n = 83$ for WOMAC assessed by VAS; $n = 77$ for WOMAC assessed by Likert.

Symptom measurement

Symptoms of OA were evaluated, at baseline and after 3 years, by a validated, disease-specific questionnaire, the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis index, addressing severity of joint pain (5 questions), stiffness (2 questions) and limitation of physical function (17 questions), and referring to the 48 hours before assessment.[15] In the first study, the visual analogue scale version (VAS) of the index was used, ie, with the participant assessing each question by a 100-mm VAS and the total index score being represented by the sum of the 24 component item scores.[7] In the second study, the Likert scale version of the index was used, with each question scored on a scale of 0 to 5, with 0 indicating none and 5 indicating extreme.[8] The primary efficacy endpoint for the symptom modification was change in WOMAC score; this is a recommended and valid outcome in OA drug trials.[10,12]

Statistical analysis

Quantitative variables were expressed as mean ± SD or with the 95% CI of the mean, and qualitative variables were reported as absolute or relative frequencies. The primary efficacy endpoint, for the structure modification, was the change in JSW, ie, a possible joint space narrowing. Changes in WOMAC score were taken for the primary assessment of symptom modification. Because WOMAC score was assessed by two different scales in the two studies, percentage changes but not absolute changes were used in the analysis. Comparisons in WOMAC changes or joint space width changes between the placebo and the treated groups were assessed by ANOVA. All analyses were performed in intention-to-treat according to the worst-case scenario: participants who did not complete the treatment course were assigned a poor outcome, corresponding to the final average change recorded in the per-protocol completer population in the placebo group. However, we also performed the analysis on participants who completed the 3-year observation period. The proportion of all randomized participants reaching the clinically relevant, predefined cutoff of 0.5 mm was compared between groups by the χ^2 test. We eventually calculated the relative risk (RR, 95% CI) of having a joint space narrowing over 3 years greater than 0.5 mm in the placebo and the treated group. The results were considered significant at the 5% level ($P < 0.05$).

RESULTS

Of 414 participants randomized in the two studies initially published, 319 were postmenopausal women (162 in the Reginster study[7] and 157 in the Pavelka study).[8] Mean age of all randomized, postmenopausal women was (mean ± SD) 64.0 ± 7.7 years, BMI was 26.4 ± 2.6 kg/m^2, and minimal JSW was 3.8 ± 1.4 mm. At baseline, glucosamine sulfate and placebo groups were comparable for demographic and disease characteristics (Table 1). Only a small proportion of postmenopausal participants (between 20% and 30%) used any of the physical treatments allowed throughout the Pavelka study, without any difference between groups.

All participants could be included in the intention-to-treat analysis. The pattern of dropouts in these post-

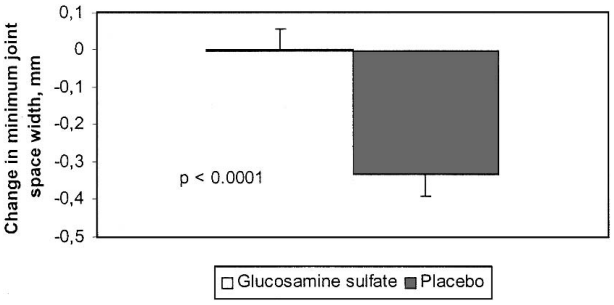

FIG. 1. Mean (SE) change in minimal joint space width after 3 years.

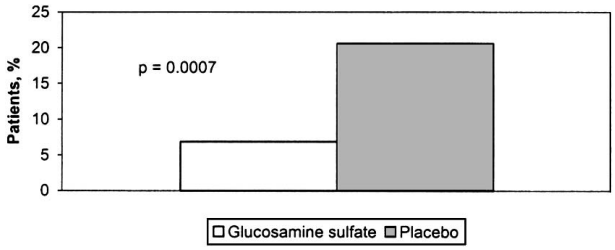

FIG. 2. Proportion of participants with a joint space narrowing greater than 0.5 mm throughout the study.

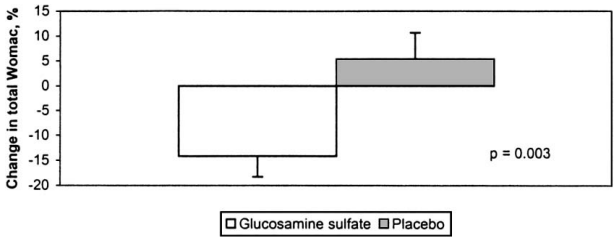

FIG. 3. Mean (SE) change in total WOMAC after 3 years.

menopausal women subsets was quantitatively and qualitatively similar to that observed in the two respective studies for the complete population. In the pooled analysis, there were more postmenopausal women not completing the study with placebo (71 participants, 44%) compared with those receiving glucosamine sulfate (55 participants, 35%). The reasons for dropout were similar between groups, with adverse events being the main cause in 15% of the participants taking placebo and 13% on glucosamine sulfate, loss to follow-up in 22% and 16%, and lack of efficacy in 7% and 6%, always in placebo and glucosamine sulfate groups, respectively.

After 3 years, the intention-to-treat analysis revealed that the participants in the glucosamine sulfate group did not experience any joint space narrowing [JSW changes: + 0.003 mm (95% CI, −0.09 to 0.11)], whereas participants in the placebo group showed a JSW narrowing of −0.33 mm (95% CI, −0.44 to −0.22; $P < 0.0001$ between the two groups) (Fig. 1). In the glucosamine sulfate group, 11 of 159 (6.9%) women experienced a clinically relevant joint space narrowing (> 0.5 mm over 3 years) compared with 33 of 160 (20.6%) in the placebo group ($P = 0.0007$) (Fig. 2). The relative risk of having a joint space loss greater than 0.5 mm in women treated with glucosamine sulfate was significantly reduced, to 0.33 (95% CI, 0.17 to 0.64) compared with women treated with placebo. In participants who completed the 3-year study, JSW increased by 0.17 mm (95% CI, 0.02 to 0.31) in the glucosamine sulfate group compared with a decrease of −0.37 mm (95% CI, −0.56 to −0.18) in the placebo group ($P <$ 0.0001 between the two groups).

Percent changes after 3 years in the WOMAC index showed a significant improvement in the glucosamine sulfate group [−14.1% (95% CI, −22.2 to −5.9)] and a trend for worsening in the placebo group [5.4% (95% CI, −4.9 to 15.7)] ($P = 0.003$ between the two groups) (Fig. 3). Although the WOMAC index was assessed by different scales in the two studies (VAS in the Reginster study and Likert scale in the Pavelka study), the percent improvement with glucosamine sulfate was virtually identical [−14.1% (95% CI, −23.2 to −5.1) in the Reginster trial and −14.1% (95% CI, −27.9 to −0.4) in the Pavelka trial], thus outlining a consistent drug effect in the two independent observations. Conversely, the trend for worsening with placebo was more evident in the former [14.2% (95% CI, −4.7 to 33.1)] than in the latter study, in which no relevant change occurred in the control group [−4.1% (95% CI, −11.2 to 3.0)].

When considering the subscales of the WOMAC index, a statistical improvement was shown in the glucosamine sulfate group, compared with placebo, for pain ($P = 0.02$) and function ($P = 0.004$) (Fig. 4) but not for stiffness ($P = 0.27$). Within the 3-year valid completers, the results are similar, with a statistical difference for the total WOMAC ($P = 0.005$) and for the pain ($P =$ 0.02) and function subscales ($P = 0.006$) but not for stiffness ($P = 0.29$) (data not shown).

There were no statistically or clinically significant differences between treatment groups in the consumption of the rescue medications, which was minor and variable in most participants (data not shown).

DISCUSSION

Results of the present study suggest that long-term oral administration of glucosamine sulfate for 3 years can delay the natural symptomatic and structural course of knee osteoarthritis in postmenopausal women.

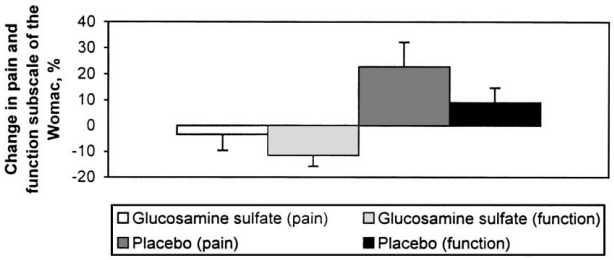

FIG. 4. Mean (SE) change in pain and function subscale of the WOMAC after 3 years.

Before the age of 50 years, OA of the knee is more prevalent in men, but after this age it becomes more common in women.[3-5] In the Bristol "OA500" study,[16] the 3-year clinical progression of OA, defined as a self-reported worsening of the overall condition, was more severe in women, in older people, and in those with severe pain at entry. In a cohort of 508 people between 50 and 75 years of age,[17] the better predictors of radiological progression observed in hip OA (ie, a change of a least 0.6 mm in JSW after 1 year) included severe symptoms, age greater than 65 years, and gender, with women having an odds ratio for progression of 2.51. Based on these results, suggesting that postmenopausal women might be the group with the highest needs in OA management, there is a real need to demonstrate the efficacy of pharmacological interventions in this particular population.

Estrogen deficiency after menopause has been linked to an increase of several chronic diseases, including cardiovascular disorders, osteoporosis, Alzheimer's disease, and osteoarthritis.[18-20] It has been suggested that HT could be appropriate for prevention or treatment of osteoarthritis in postmenopausal women. However, no randomized, prospective, controlled trial has been conducted to specifically assess the impact of HT on symptomatic or structural progression of OA. For this reason, HT cannot be currently recommended as a first-line treatment against OA.

To the best of our knowledge, none of the drugs currently available to improve OA symptoms (NSAIDs, paracetamol, etc) has been specifically tested in a cohort of postmenopausal women with OA of the lower limbs, nor in long-term studies on disease progression. Drugs currently investigated for their potential disease-modifying effects (chondroitin sulfate, diacerein, etc) are most frequently tested in cohorts that include participants of both genders, and no data are available for a population restricted to women. In the present study, the pooled analysis of two independent, long-term studies demonstrated for the first time that a pharmacological intervention might induce a disease-modifying effect in postmenopausal, osteoarthritic women, concomitantly to a significant improvement of the symptoms. Glucosamine sulfate, therefore, is the first agent that meets the current requirements to be classified as a symptom- and structure-modifying drug in women with knee OA.

These results are in accordance with the effects of glucosamine sulfate reported in the general population. In 212 men and women with knee OA,[7] people on glucosamine sulfate had no significant joint space loss over 3 years compared with a progressive joint space narrowing in the placebo group ($P = 0.003$ between the two groups). A second independent study[8] confirmed these results with, after 3 years, a joint space narrowing in the placebo group and no change in the glucosamine sulfate group ($P = 0.001$ between the two groups). More recently, the results of a meta-analysis[21] demonstrated a highly significant efficacy of glucosamine sulfate on all treatment outcomes, including joint space narrowing and WOMAC index. With regard to the latter, our analysis pointed out a significant effect in the pain and function subscales of the index, whereas the changes in the stiffness subscale were not statistically significant; this may be due to the possibility that it is hardest to detect changes in the stiffness subscale as it is composed of fewer items than the other two subscales.

In prospective studies, a criticism previously raised against the choice of conventional standing radiographs is related to the changes in people's positioning caused by symptom modification. Recent results[22] suggest that other radiographic views may improve precision and avoid underestimation of joint space narrowing. Indeed, an improvement in pain could result in a better extension of the joint and, subsequently, the JSW changes observed in such people could be artefactual and driven by the symptom modification. However, it is most unlikely that in our studies the symptom changes observed in the two groups might have affected the results, given the mild to moderate symptomatic conditions reported at baseline and in the two initial studies. Furthermore, the relationship between symptom and structure modification in our study was of poor magnitude and marginal clinical relevance.[23] Eventually, we recently demonstrated that,[24] when we considered only participants from both groups with a significant symptomatic improvement, the placebo participants nevertheless underwent a definite joint space narrowing that was not observed with glucosamine sulfate, excluding the hypothesis that pain improvement would prevent observation of negative changes in JSW in the glucosamine sulfate group.

CONCLUSION

The analysis of two long-term studies demonstrated, for the first time, that a pharmacological intervention might improve symptoms and reduce the structural progression of knee OA in postmenopausal women.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778-799.
2. Kirwan JR, Elson CJ. Is the progression of osteoarthritis phasic? Evidence and implication. *J Rheumatol* 2000;27:834-836.
3. Van Saase JLCM. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271-280.
4. Oliviera SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum* 1995;38:1134-1141.
5. Felson DT, Naimark A, Anderson J, Kazis L, Castilli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis study. *Arthritis Rheum* 1987;30:914-918.
6. Reginster JY, Kvasz A, Bruyere O, Henrotin Y. Is there any rationale for prescribing hormone replacement therapy (HRT) to prevent or to treat osteoarthritis. *Osteoarthritis Cartilage* 2003;11:87-91.
7. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulfate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet* 2001;357:251-256.
8. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis. A 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002;162:2113-2123.
9. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. *Arthritis Rheum* 1986; 29:1039-1049.
10. Altman R, Brandt K, Hochberg M, Moskowitz R. Design and conduct of clinical trials of patients with osteoarthritis: Recommendations from a task force of the Osteoarthritis Research Society. *Osteoarthritis Cartilage* 1996;4:217-243.
11. Lequesne M. Quantitative measurement of joint space during progression of osteoarthritis: chondrometry. In: Kuettner KE, Goldberg V, eds. *Osteoarthritis Disorders*. Rosemont, IL: American Academy of Orthopaedic Surgery; 1995:424-444.
12. Dougados M, for the Group for the Respect of Ethics and Excellence in Science. Recommendations for the registration of drugs used in the treatment of osteoarthritis. *Ann Rheum Dis* 1996;55:552-557.
13. Lequesne M, Brandt K, Bellamy N, et al. Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol* 1994;21(Suppl Dec):65-73.
14. Ravaud P, Girardeau B, Auleley GR, et al. Variability in knee radiographing: implication for definition of radiological progression in medial knee osteoarthritis. *Ann Rheum Dis* 1998;57:624-629.
15. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-1840.
16. Dieppe PA, Cushnaghan J, Shepstone L. The Bristol "OA500" study: progression of osteoarthritis (OA) aver 3 years and the relationship between clinical and radiographic changes at the knee joint. *Osteoarthritis Cartilage* 1997;5:87-57.
17. Dougados M, Gueguen A, Nguyen M, et al. Radiological progression of hip osteoarthritis: definition, risk factors and correlations with clinical status. *Ann Rheum Dis* 1996;55:356-362.
18. Riggs BL, Melton LJ III. The prevention and treatment of osteoporosis. *N Engl J Med* 1992;327:620-627.
19. Grodstein F, Stampfer MJ, Manson JE. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-461.
20. Sherwin BA. Hormones, mood, and cognitive functioning in postmenopausal women. *Obstet Gynecol* 1996;87:20-26.
21. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin sulfate in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003;163:1514-1522.
22. Mazzuca SA, Brandt KD, Lane KA, Katz BP. Knee pain reduces joint space width in conventional standing anteroposterior radiographs of osteoarthritic knees. *Arthritis Rheum* 2002;46:1223-1227.
23. Bruyere O, Honore A, Rovati LC, Giacovelli G, Henrotin YE, Reginster J-YL. Radiologic features poorly predict clinical outcomes in knee osteoarthritis. *Scand J Rheumatol* 2002;31:13-16.
24. Pavelka K, Bruyere O, Rovati LC, et al. Relief in mild-to-moderate pain is not a confounder in joint space marrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. Osteoarthritis Cartilage 2003;11:730-737.