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Effectiveness of Glucosamine and Chondroitin Sulfate Combination in Patients with Primary Osteoarthritis

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Abstract

Purpose: Studying the effectiveness of chondroprotective agents for patients with primary knee arthritis or primary generalized osteoarthritis, according to the American College of Rheumatology 2000 criteria. *Material and Methods*: comparative study, the groups were constituted out of 25 patients in the study group and 15 patients in the control group. The patients were evaluated with the WOMAC test, Lequesne, cross-linked C-terminal (CTX) telopeptide of type I collagen on inclusion, at 6 and 12 months and through bilateral- knee radiography, using the Kellgren-Lawrence classification on inclusion and 12 months later. Patients from the study group received a chondroprotectiv agent orally for 12 months. *Results*: WOMAC score was improved in the study group at 6 and 12 months -4.1 (CI -6.1 to -2.1) and -5.9 (CI -8 to -3.8) compared to the control group 1.5 (CI -0.7 to 3.7) and 2 (CI -0.2 to 4.2), with a statistical significance p=0.02. There has also been an amelioration of the Lequesne score in the study group at 6 and 12 months -3.8 (CI -6.3 to -1.3) and -6.2 (CI -9.1 to -3.3), and the control group 1.3 (CI -1.5 to 4.1) to 6 months and 1.9 (CI -0.8 to 4.6) to 12 months, with a statistical significance p=0.03. No adverse reactions were registered. *Conclusions*: The chondroprotective agent was effective in improving the function of patients with osteoarthritis, the studied marker cannot be used to monitor the treatment effectiveness, and the radiological modifications in the knee are statistically insignificant after 12 months of monitoring.

Keywords: Osteoarthritis; Chondroprotective agent; Glucosamine; Chondroitin sulfate.

Introduction

Arthritis represents a group of chronic, degenerative disorders that mainly affects the joint cartilage with later involvement of other joint structures.

The joint cartilage is normally consisting of chondrocytes in proportion of 5% and extracellular matrix in proportion of 95%.

The chondrocytes synthesize and maintain the matrix and the matrix confers to the chondrocytes a resistance environment to the continuous mechanical stress.

Depending on the thickness of the cartilage, they differ in terms of cellular and fibrillar content and matrix [1].

The matrix contains water in proportion of 70% and collagen (with type 2 being the predominant type-50%). Other collagen types are represented by types 3, 5, 6, 9, 11. All these form a fibrillary network that confers resistance to the cartilage and prevents the expansion of the proteoglycans by retaining them [2].

Proteoglycans are derived from glycosaminoglycans (formerly called mucopolyssacharides) being attached in a circle by a proteic core. This structure resembles a bottle brusher. Few of the most important glycosaminoglycans are 4 and 6 chondroitin –sulfate and keratan-sufate.

Inside the matrix numerous proteoglycans are attached by a molecule called hyaluronate forming a proteoglycan aggregate.

Due to the fact that glycosaminoglycans are negatively charged molecules they reject one another, but attract polar molecules. Thus, these molecules are highly hydrophilic. This is one of the reasons why the matrix contains a lot of water.

The cartilage has no intrinsic blood supply, the nutrients being transported by electrostatic diffusion, pump-like compression and by active transfer (only at the level of the chondrocytes). It is important to emphasize that the nutrition takes place both at the subchondral level and towards the synovium [3].

Treatment of Osteoarthritis

In treating these patients 3 main objectives are followed:

1) Improving of the symptoms
2) Stopping the progression of the disease
3) Increasing the functionality

Treatment modalities are multiple: drugs, physiotherapy, balneotherapy, surgery and lifestyle changes.

Surgery is used for improving the symptoms and the sequelae of the disease with little if any change at the molecular level.

Changes in lifestyle include weight loss, dietary changes, and controlled exercise therapy, reducing the stress and home environment modifications to the infirmity caused by the disease. Although all of these methods can be very helpful they are very hard to put in practice due to the reduced patient compliance.

Physiotherapy, balneotherapy and drug treatment all represent effective treatment modalities [4].

Research in recent decades has focused on reducing osteoarthritis process and stimulating the matrix synthesis. This research has identified substances such as the chondroprotective agents. These are defined as compounds that: 1) stimulate chondrocyte synthesis of collagen and proteoglycans as well as hyaluronate production at synoviocytes level. 2) inhibit joint degradation 3) prevent fibrin formation at the level of subchondral and synovial blood vessels.

Examples of compounds that meet some of the above characteristics are endogenous molecules of the joint cartilage, including hyaluronic acid, glucosamine and chondroitin sulfate.

Hyaluronic acid disadvantage is represented by the sole intraarticular administration which makes treating only one joint at the time.

Chondroitin sulfate is the predominant glycosaminoglycan in the joint cartilage. It consists of repetitive dissacharides units of glucuronic acid and galactosamine sulfate.

Chondroitin sulfate it is found in the body in the joints, tendons, intervertebral disks, bones, cornea, skin, blood vessel walls and cardiac valves. As a chondroprotector, besides the metabolic affect at the joint level it also has an inhibitory competitive action with the degradative enzymes on the matrix and synovial fluid [5-7].

An additional action is prevention of fibrin thrombi formation in the synovial and subchondral micro-circulation.

Absorption of 70% after oral administration was proved by radiotracing so as the tropism for synovial fluid and cartilage.

In multiple clinical studies where chondroitin sulfate was administered 1200 mg/day for 3 years there were no major local or systemic side effects registered, most of the side effects being similar to placebo.

Glycosaminoglycans have been studied in intramuscular, intravenous or oral administration. Absorption of the radiotraced glucosamine has proved the tropism of the agent for the joint structures. When orally given, the absorption of glucosamine is approximately 87%. Metabolite's excretion is mainly through the kidneys with only one small unmodified amount eliminated through stool.

Recent year's research has showed that no single component has met the characteristics of one agent, but the combination has a synergistic effect (proved by the GAIT study) [8].

Thus, the 2 components in combination: 1. stimulate the synoviocite and chondrocyte metabolism; 2. inhibit the enzymatic degradation and reduce the fibrin thrombi in the periarticular microcirculation.

There are studies as well that show that this combination can regulate the genetic expression and the synthesis of nitric oxide and PGE2, thus explaining the antiinflammatory properties.

Purpose of Study

Our purpose was to study the effectiveness of glucosamine and chondroitin combination on a clinical and functional level, as well as on a laboratory and radiological level.

Material and Method

The study was performed in a period of June 2005 and September 2007, in Rehabilitation Hospital, Cluj-Napoca.

The study was conducted on 40 patients with primary knee arthritis, clinically and radiologically diagnosed, according to the American College of Rheumatology 2000 criteria (the ARA criteria). The inclusion criteria consisted of: primary, uni- or bilateral knee osteoarthritis, generalized primary osteoarthritis. The criteria for osteoarthritis has been supported by the criteria of the American College of Rheumatology 2000 and the criteria for knee arthritis consisted in the presence of: pain and three of the following elements: patient over 50 years of age, morning stiffness under 30 minutes, crepitus when moving, pain on palpation, the knee does not feel warmer to touch. The patients were randomly distributed in two groups: the study group included 25 patients, to whom chondroprotective treatment had been administered for 12 months, and the control group was represented by the rest of 15 patients, who were only observed during the study. The evaluation of the patients from the two groups has been done in parallel and through the same methods. So, when included in the study, as well as 12 months from recruitment, the following evaluations were done: complete clinical examination, specific functional tests (WOMAC, Lequesne) for knee arthritis, determining biological markers that measure the degradation of the joint cartilage and standard radiological examination. In addition, there has also been an intermediary evaluation 6 months from the initial moment, which consisted of the same methods, except for the radiological examination.

In the second stage of the study the administering of chondroprotective treatment has been continued for the patients in the study group for 12 months from the initial moment.

It is important to point out that the tolerability of the drug has been remarkably good, so no case of abandonment has been registered throughout the study. A contribution to that was the fact that the administering of the drug had been done without any kind of personal expense on behalf of the patients. Another important element that has contributed to a good compliance was the absence of adverse reactions.

The chondroprotective agent has been administered orally, as tablets, in two daily equal doses. The daily total dosage has been 1500 mg glucosamine chlorhydrate and 1060 mg chondroitin sulfate.

Both groups have been motivated and supervised at the same time and throughout during the whole process by the authors.

After the final evaluation the comparative statistical analysis has been applied.

Clinical Examination

All patients were examined by one doctor, participant to the study, who had also done the functional studies.

All the systems have been examined (cardio-vascular, respiratory, digestive, renal) and all the modifications were written down for every patient on the personal chart.

During the examination of the muscular-skeletal system the accent was placed on examining the joints and muscles. The inspection pointed out all the changes in shape, color, vicious attitudes, and muscular hypotrophy. Palpation pointed out crepitus, painful muscle or ligament insertion points, muscle force for muscle groups. Percussion was done for the hip and spine joints.

All the joints have been mobilized, both passively as well as actively.

Evaluations and Clinical Tests

For appreciating pain The Visual Analog Pain Scale was used, which represents a scale of 11 units, where 0 represents no pain and 10 is maximum pain.

Other tests that were used were the functional ones: the Lequesne and the WOMAC (Western Ontario McMaster Universities Index of Osteoarthritis). Both are internationally validated for the evaluation and observing the evolution of patients suffering from osteoarthritis.

We used the Romanian version of WOMAC and Lequesne tests from Popescu et al. [9].

These tests were performed at the inclusion, at 6 months and at the end at 12 months.

Biological Analysis

The seric biologic markers determinations were represented by determining the cross-linked C-terminal (CTX) telopeptide of the type I collagen (beta-cross laps).

Imagistic Explorations

The radiological evaluation was represented by bilateral knee radiographies, antero-posterior position for knee osteoarthritis and bilateral hand radiographies, antero-posterior position for primitive generalized osteoarthritis. Gradating the level of osteoarthritis has been done according to the Kellgren-Lawrence Scale.

Statistical Analysis

Statistical analysis was performed using Excel (Microsoft Office 2003) and EpiInfo (3.4.3. version). Results were expressed as mean and 95% confidence interval. Student's t-test was used to compare the quantitative continuous variables and the differences between their means.
The level of statistical significance was considered at $p \leq 0.05$.

Results

Out of the 40 patients included in the study, with ages ranging from 50 and 77 years old (average age of 54.7 years), 29 were females and 11 were males. Regarding the place of origin 25 of the patients reside in the rural area and 15 in the urban area. (The study group was composed out of 18 females and 7 males, and the control group- out of 11 females and 4 males).

Certain correlations have been noticed: between the severity of the symptoms and of the clinical signs, the importance of the radiological modifications and the scores to the two functional tests. Although none of the groups has been denied the consumption of NSAIDs, mild painkillers, pain relief ointments and physiotherapy procedures, a reduction in the frequency of antiinflammatory and painkiller self-administering has been noticed in patients who had already begun the treatment with chondroprotective agents (the study group).

No adverse reactions to the medication were noted.

For the functional tests the variation of the score from one evaluation to the other has been considered, a much more important fact than the absolute value of the score that cannot even be interpreted independently.

In the WOMAC test that consists of two domains, with a total of 24 items, the following results have been obtained (Tabel 1, Figure 1).

Table 1. WOMAC test results

WOMAC score	At 6 months	At 12 months
Study group	-4.1 (CI -6.1 to -2.1)	-5.9 (CI -8 to -3.8)
Control group	1.5 (CI -0.7 to 3.7)	2 (CI -0.2 to 4.2)

An improvement in the WOMAC score has been noted in the study group compared to the control group, with a statistical significance in 6 months ($p= 0.03$) as well as in 12 months ($p= 0.02$). Analyzing the WOMAC score we can conclude that the administered medication has proven effective on all the components of the score, meaning pain, functionality (activities) and stiffness.

In the Lequesne test, that consists of three domains, with a total of 11 items, the following results were obtained (Table 2, Figure 2).

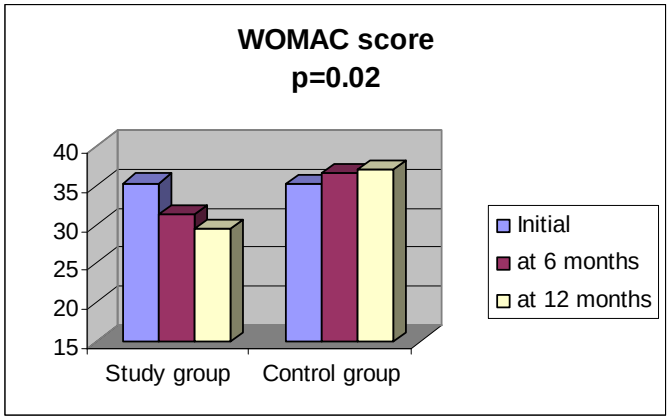

Figure 1. Changes in WOMAC score

Table 2. Lequesne test results

Lequesne score	At 6 months	At 12 months
Study group	-3.8 (CI -6.3 to -1.3)	-6.2 (CI -9.1 to -3.3)
Control group	1.3 (CI -1.5 to 4.1)	1.9 (CI -0.8 to 4.6)

Similar results have been obtained for the Lequesne score in all three of the analyzed domains, meaning pain, walking perimeter and activities. The diminishment of the score in the study group has been more obvious in the first 6 months, with a significant difference between the two groups (p=0.02), which corresponds to a significant functional improvement. The improvement and the diminishment of the score has continued nonetheless until the end of the study in the group taking chondroprotective medication, while in the control group a slight functional deterioration has been noted, deterioration that was pointed out by the growth of the Lequesne score. Thus, after 12 months, the difference between the two groups is p= 0.03.

For the radiological examination, done comparatively for the knees from a postero- anterior position, on inclusion and 12 months after, in all the patients from the two groups, the intraarticular femuro-tibial space was measured, with the following results (Table 3, Figure 3).

In what the radiologic evolution is concerned in the case of the studied patients we can state that the intraarticular space has not suffered significant changes in the study group and a slight diminishment of the intraarticular space has been noted in the control group. However, the difference between the two groups carries no statistical significance (p= 0.2).

In what the seric markers are concerned, CTX, that have been determined on 6 month intervals, it has been noted (Table 4, Figure 4).

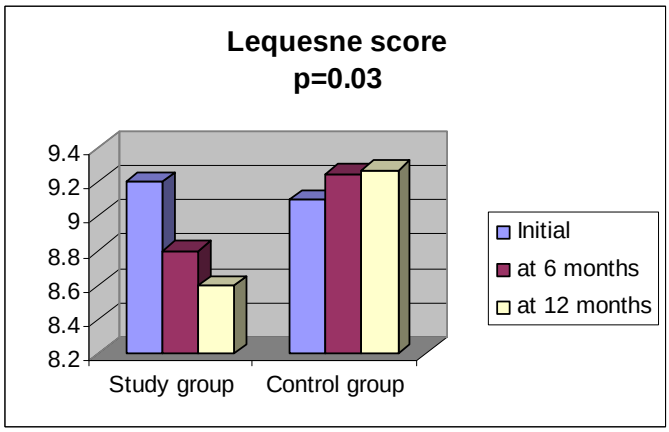

Figure 2. Changes in Lequesne score

Table 3. Femurotibial joint space change

Variation of femorotibial joint space	0 - 12 months
Study	0.008 (CI -0.069 to 0.085)
Control	-0.12 (CI -0.189 to -0.050)

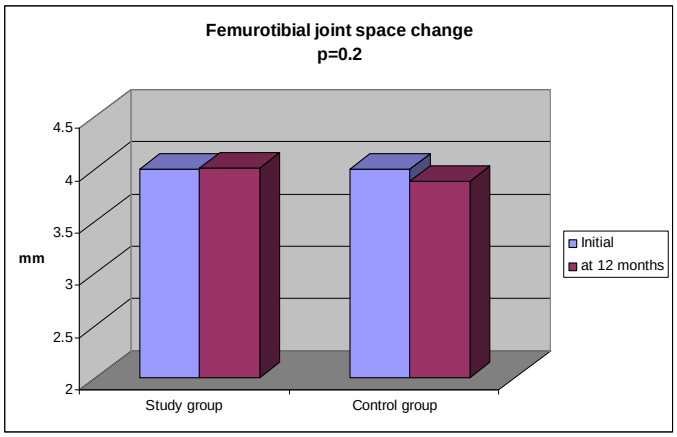

Figure 3. Femurotibial joint space change in one year

Table 4. Changes in CTX

CTX (ng/ml)	0 - 6 months	0 - 12 months
Study	0.126(CI -0.124 to 0.376)	-0.0279(CI-0.4032 to 0.3474)
Control	0.026 (CI-0.114 to 0.166)	-0.022 (CI -0.242 to 0.198)

In this context we can state that the CTX used in the present study does not appear to be relevant for following the efficiency of the condroprotective treatment in patients suffering from primary osteoarthritis. The variations were not significant 6 months nor 12 months after the initial moment, but had more of a random evolution (in 6 months p=0.07, in 12 months p=0.8). We are also considering the fact that monitoring patients who undergo treatment for longer term duration would not bring a higher degree of significance, keeping in mind that the registered values were random and had a non systematic evolution, both in the study group as well as in the control group. Also, considering the fact that the variations in the control group were also insignificant and just as random, we can conclude that this marker cannot be used for monitoring osteoarthritis.

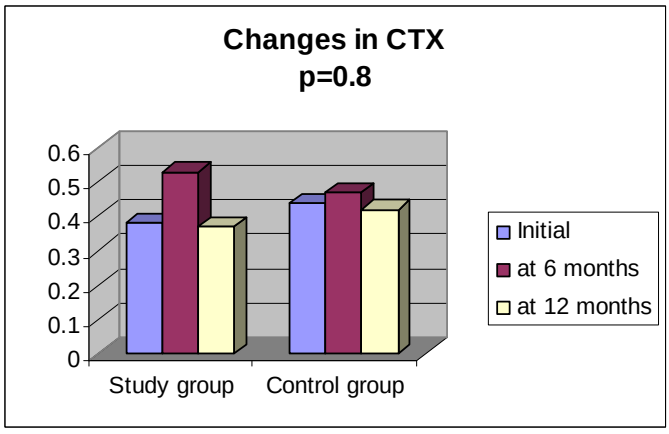

Figure 4. Changes in CTX

Discussion

In this comparative monitoring study a condroprotector agent with the chondroitine-glucosamine combination has been administered on a daily basis to a group of patients for 12 months. This combination has proven to be effective in reducing the intensity of the pain and improving the joint function, fact demonstrated through the WOMAC and Lequesne tests. The same thing cannot be said about the control group. Thus, after 6 months, the improvement in the study group has been 4.1 points (CI -6.1 to -2.1), as opposed to the deterioration in the control group: 1.5 points (CI -0.7 to 3.7), the difference being statistically significant for the WOMAC (p= 0.03) For the same test, 12 months after inclusion, a 5.9 points amelioration has been recorded (CI -8 to -3.8) in the study group, as opposed to a deterioration of 5.9 points (CI -0.2 to 4.2) in the control group, with p= 0.02). Similar results have been obtained by other authors, but on a monitoring interval of 3 years.

In what the Lequesne test is concerned, we have noticed that, after 6 months, the improvement of the score in the study group by 3.8 points (CI -6.3 to -1.3) and the deterioration by 1.3 points of the same score in the control group (CI -1.5 to 4.1), with statistical significance between the two groups (p= 0.04). 12 months after inclusion, the improvement in the study group has been 6.2 points (CI -9.1 at -3.3), while a deterioration of 1.9 points has been noted (CI -0.8 to 4.6) (p= 0.03 between the two groups).

Most studies in the field were conducted over a period of three years and not one year such as the present study and that is why comparing it with other studies may be misinterpreted. However, similar data were obtained by other authors for these two tests [10-13].

From a radiologic perspective, no significant variation in the intraarticular space has been noted in the study group (0.008 mm, CI -0.069 to 0.085), while in the control group the tendency was of diminishing the intraarticular space (-0.12 mm, CI -0.189 to -0.050), without any significant statistic difference between the two groups (p= 0.2).

In the specialty literature the studies on this parameter have been conducted on a time frame of a minimum of 3 years, time frame in which maintaining the joint space has had a statistic significance in patients undergoing condroprotective treatment as opposed to the deterioration noted in the patients who did not benefit from the treatment [11,14,15] .

Determining the biologic marker (seric CTX) has not proven useful for monitoring the efficiency of the chondroprotective treatment nor for the monitoring the evolution of the osteoarthritis. Thus, 6 months after inclusion, the variation in the study group was 0.126 ng/ml (CI -0.124 to 0.376), and in control group 0.026 (CI -0.114 to 0.166), p=0.7. At 12 months the variation in the study group was -0.0279 ng/ml (CI -0.4032 to 0.3474) and in control group -0.022 (CI -0.242 to 0.198), p=0.8.

A common point in similar studies is represented by the results of the variations of the biological markers, meaning the absence of an obvious correlation with clinic-radiologic modifications [16].

Further research has suggested the possibility of identifying patients subgroups from the point of view of their answer to chondroprotective treatment, according to the level of the biological markers [17].

Conclusions

In conclusion, we can state that the chondroitine-glucosamine combination is an effective form of medication in the treatment of osteoarthritis, being already considered a drug that modifies the condition SMOAD-Structure Modifying Osteoarthritis Drug).

The C terminal telopeptide of the type I collagen cannot be a tracking marker for patients with osteoarthritis undergoing chondroprotective treatment.

Considering the short duration of the study and the relatively small groups of patients included it is necessary that further studies extend the monitoring period to a minimum of three years.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int 2010;107(9):152-62.
2. Loeser RF. Molecular mechanisms of cartilage destruction in osteoarthritis. J Musculoskelet Neuronal Interact 2008;8(4):303-6.
3. Samuels J, Krasnokutsky S, Abramson SB. Osteoarthritis: a tale of three tissues. Bull NYU Hosp Jt Dis 2008;66(3):244-50.
4. Gaál J, Varga J, Szekanecz Z, Kurkó J, Ficzere A, Bodolay E, Bender T. Balneotherapy in elderly patients: effect on pain from degenerative knee and spine conditions and on quality of life. Isr Med Assoc J 2008;10(5):365-9.
5. Verbruggen G. Chondroprotective drugs in degenerative joint diseases. Rheumatology 2006;45(2):129-38.
6. Cohen M, Wolfe R, Mai T, Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheumatol 2003;30(3):523-8.
7. Bruyere O, Honoreb A, Ethgen O, Rovatid LC, Giacovelli G, Henrotinc YE, et al. Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a 3 year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate. Osteoarthritis & Cartilage 2003;1:1-5.
8. Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, Singer NG, Bradley JD, Silver D, Jackson CG, Lane NE, Oddis CV, Wolfe F, Lisse J, Furst DE, Reda DJ, Moskowitz RW, Williams HJ, Clegg DO. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. Arthritis Rheum 2008;58(10):3183-91.
9. Popescu R, Trăistaru R, Badea P. Ghid de evaluare clinică şi funcţională în recuperarea medicală. Vol I, Ed. Medicală Universitară Craiova 2004;299-303.
10. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G. Glucosamine therapy for treating osteoarthritis. The Cochrane Database of Systematic Reviews 2005; 2: Art.No.: CD002946. DOI: 10.1002/14651858.CD002946.pub2.
11. Bruyere O, Pavelka K, Rovati LC. Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies. Menopause 2004;11(2):138-43.
12. Christgau S, Henrotin Y, Tanko LB. Osteoarthritic patients with high cartilage turnover show increased responsiveness to the cartilage protecting effects of glucosamine sulphate. Clin Exp Rheumatol 2004;22(1):36-42.
13. Towheed TE, Anastassiades TP. Glucosamine and chondroitin for treating symptoms of osteoarthritis. Evidence is widely touted but incomplete. JAMA 2000;283:1483-4.
14. Pavelka K, Bruyere O, Rovati LC. Relief in mild-to-moderate pain is not a confounder in joint space narrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. Osteoarthritis Cartilage 2003;11(10):730-7.
15. Reginster JY, Deroisy R, Rovati LC. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet. 2001;357(9252):251-6.
16. Cibere J, Thorne A, Kopec JA. Glucosamine sulfate and cartilage type II collagen degradation in patients with knee osteoarthritis: randomized discontinuation trial results employing biomarkers. J Rheumatol 2005;32(5):896-902.
17. Christgau S, Henrotin Y, Tanko LB. Osteoarthritic patients with high cartilage turnover show increased responsiveness to the cartilage protecting effects of glucosamine sulphate. Clin Exp Rheumatol 2004;22(1):36-42.