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GLUCOSAMINE ADMINISTRATION IN ATHLETES: EFFECTS ON RECOVERY OF ACUTE KNEE INJURY

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The main aim of this study was to examine the effects of 4 weeks of glucosamine administration on the functional ability and the degree of pain intensity in competitive male athletes after acute knee injury. This study was a randomized, double-blind parallel trial of glucosamine (1500 mg per day) or a placebo for 28 days, utilising 106 patients with an acute knee injury. Pain and functional ability were evaluated at the beginning of the study and at 7, 14, 21, and 28 days after starting treatment. Pain intensity at rest and while walking was assessed using a visual analog scale. Passive knee flexibility (flexion and extension) of the injured limb was measured using a modified goniometer, and the degree of knee swelling was measured and compared with the noninjured limb. No significant difference was found between the glucosamine, and placebo group in mean pain intensity scores for resting and walking, and degree of knee swelling at the 7-day, 14-day, 21-day, and 28-day assessment. There was no significant difference between passive knee flexibility at the 7-day, 14-day, and 21-day assessment. After 28 days of treatment the patients from the glucosamine group demonstrated significant improvement in knee flexion and extension as compared with the placebo group.

Keywords: sports injury, osteoarthritis, flexibility

INTRODUCTION

The management of joint repair in people with different articular conditions is often facilitated by glucosamine, an aminomonosaccharide that is found in human cartilage, as a way to relieve pain and increase range of motion (Braham, Dawson, and Goodman 2003). Glucosamine is thought to prevent the breakdown of cartilage and stimulate the production of cartilage, although the exact biochemical mechanism is not known (Bassler, Reginster, and Franchimont 1993; Cibere, Thorne, Kopec, et al. 2005). Several clinical studies have shown that glucosamine is better than a placebo and is equal to but not better than nonsteroidal anti-inflammatory drugs to reduce pain and increase range of motion in osteoarthritis patients (Crolle and D'Este 1980; Drovanti, Bignamini, and Ravanti 1980; Muller-Fassbender, Bach, Haase, et al. 1994; Noack, Fischer, Forster, et al. 1994; Houpt, McMillan, Wein, et al. 1999; Reginster, Deroisy, Rovati et al. 2001; Braham, Dawson, and Goodman 2003). Others also have reported that the majority of improvements are present after 4 or more weeks of treatment (Houpt, McMillan, Wein, et al. 1999; Delafuente 2000; Poolsup, Suthisisang, Channark, et al. 2005). The usual doses of 1500 mg glucosamine daily are thought to be safe in the short term (up to 12 weeks), while long-term safety is not known. The methods used in these studies have been

highly criticized, however, and the results may be overstated due to insufficient subject numbers, low dosage and duration of administration, and the lack of inclusion of functional tests (McAlindon, LaValley, Gulin et al. 2000).

Several studies (Buckwalter 2003; Hespel, Maughan, and Greenhaff 2006; Maroon, Bost, Borden, et al. 2006) have shown that use of glucosamine is common practice among athletes at all ages and levels of participation. There is little if any evidence currently available, however, to support claims about anti-inflammatory, analgesic, or protective effects of glucosamine in the athletic environment (Gorsline and Kaeding 2005). Therefore, the main aim of the present study was to examine the effects of 4 weeks of glucosamine administration (1500 mg per day) on the functional ability and the degree of pain intensity in competitive male athletes who experienced acute sports injury of the knee.

MATERIALS AND METHODS

Subjects

Patients were eligible to participate in the study if they had a recent history of acute sports injury of the knee and had clinical findings consistent with trauma. Acute sports injury was defined as direct or indirect trauma an athlete incurred in any sport-related activity that caused absence from training or from match. During the 2005 season (from March to November) subjects (professional athletes) were recruited and examined by certified sports medicine specialists in the out-patient clinics of the medical center, in the first 24 hours after injury was sustained. Clinical findings were graded according to modified Outerbridge classification (Fu, Harner, and Vince 1994). Female athletes, patients who had been treated earlier with glucosamine, who were not ambulatory, or who had clinical findings classed as more severe than grade II, were excluded from the study. All subjects gave their informed consent and volunteered to participate in the study that had the approval of the academy's Ethical Advisory Commission. At the first assessment session, participants were fully informed verbally and in writing about the nature and demands of the study as well as the known health risks. They completed a health history questionnaire and were informed that they could withdraw from the study at any time, even after giving their written consent. All subjects were in good health (free from diabetes, heart disease, musculoskeletal dysfunction, cancer, and smoking), participating in consistent training (average of 12 hours per week) for the past 7 years, and not currently taking a drug or dietary supplement that contained glucosamine (or any similar preparation).

Experimental Procedures

According to standard procedure established by the National Antidoping Agency of Serbia, before the drug or supplement administration in athletic environment, evidence of quality assurance and accordance with good manufacturing practice (GMP) should be obtained from the relevant institution. After analysis, the National Institute of Health certified (No412C-145) the purity, composition and quality of the glucosamine preparation used in the current study along with verification of absence of contaminants that might have stimulant properties. The subjects were allocated to a double-blind design to two randomly assigned trials. Subjects in the glucosamine group ingested tablets that contained glucosamine at a dose of 1500 milligrams per day (in three divided doses of 500 mg each) for a period of 28 days while subjects in the placebo group ingested an equal number of identical-looking tablets that contained cellulose. Both groups ingested tablets under the supervision of a certified professional sports nutritionist, and during the administration period all subjects refrained from training. No other interventions were made.

Participants were evaluated at the beginning of the study and at 7, 14, 21, and 28 days after starting treatment. Baseline testing was performed prior to administration, and subjects were instructed not to change their current dietary habits. Pain intensity was assessed using a visual analog scale (Flandry, Hunt, Terry et al. 1991; Flaherty 1996). Participants completed two visual analog assessments at each visit, one representing pain intensity while at rest, and the other representing pain while walking. Passive knee flexibility (flexion and extension) of the injured limb was measured using a modified goniometer with spirit level (Creative Health Inc., Plymouth). The range of motion was assessed according to Bull and Amis (1998), with full knee extension defined at 180 degrees in this case. The degree of knee swelling was measured and compared with the noninjured limb according to Mendelsohn and Paiement (1996). In order to assess potential side effects to the supplementation regimen, all subjects were instructed to report any adverse effects of supplementation (e.g., nausea, vomiting, gastrointestinal upset, cramps, headache, bloating, dry mouth, tenderness in knee).

Statistical Analyses

The data are expressed as means ± standard deviation. A one-way ANOVA with repeated measures was used to analyze the data. Where appropriate, post hoc tests (paired *t* test with Bonferroni corrections) were

used to determine the location of any significant differences. A significance level of $p < 0.05$ was considered to be statistically significant. The data were analyzed using the statistical package SPSS for Windows version 8.0 (SPSS Inc., USA).

RESULTS

Although 121 participants were enrolled in the study, 13 patients (6 patients in the glucosamine group and 7 patients in the placebo group) were lost to followup and were not included in the analysis. Data were analyzed on 108 patients, 56 in the glucosamine group and 52 in the placebo group. Demographic and preadministration characteristics were shown in Table 1. There were no differences in demographic data, baseline functional and clinical tests between the glucosamine and placebo group ($p > 0.05$). No statistically significant difference was found between the glucosamine group and the placebo group in mean pain intensity scores for resting and walking at day 7, 14, 21, and 28 (Table 2; $p > 0.05$). There was also no significant difference between passive knee flexibility (both flexion and extension) at the 7-, 14-, and 21-day assessment (Table 3, $p > 0.05$). We found a significant difference, however, between the glucosamine and placebo group after 28 days of treatment, with a significantly improved knee flexion and extension in the glucosamine group ($p < 0.05$). When we analyzed the degree of knee

Table 1. Demographic and Preadministration Characteristics of Patients

	Treatment	
	Glucosamine	**Placebo**
Number of men	56	52
Age (years)	25.1 ± 3.6	24.8 ± 4.1
Professional experience (years)	7.2 ± 2.3	7.1 ± 2.2
Height (cm)	180.2 ± 6.3	179.5 ± 7.1
Weight (kg)	74.8 ± 5.6	75.3 ± 6.2
Pain intensity scores		
Resting	3.2 ± 1.8	3.3 ± 1.9
Walking	5.2 ± 2.0	5.1 ± 2.2
Knee flexibility (degrees)		
Flexion	119.1 ± 22.5	115.8 ± 21.8
Extension	143.8 ± 28.1	141.2 ± 25.6
Degree of swelling (%)	10.2 ± 2.5	9.8 ± 2.9

Note. Values are shown as mean ±SD.

Table 2. Scores of Pain Intensity as Measured with a Visual Analog Scale

	Treatment	
	Glucosamine (n=56)	Placebo (n=52)
Week 1		
Resting	3.0 ± 2.0	3.0 ± 2.2
Walking	4.9 ± 2.1	4.9 ± 2.3
Week 2		
Resting	2.9 ± 1.9	2.7 ± 1.8
Walking	4.4 ± 2.2	4.6 ± 1.9
Week 3		
Resting	2.5 ± 1.8	2.6 ± 2.0
Walking	4.0 ± 1.9	4.3 ± 2.1
Week 4		
Resting	2.1 ± 1.7	2.1 ± 1.9
Walking	3.8 ± 2.1	4.1 ± 1.8

Note. Values are shown as mean ± SD. A score of 0 indicated "no discomfort," while a score of 10 indicated "severe discomfort."

Table 3. Range of Motion (Degrees) of the Injured Knee During the Study

	Treatment	
	Glucosamine (n=56)	Placebo (n=52)
Week 1		
Knee flexion	125.6 ± 20.4	120.1 ± 24.3
Knee extension	150.2 ± 23.8	144.9 ± 26.1
Week 2		
Knee flexion	128.8 ± 19.5	123.9 ± 21.9
Knee extension	158.5 ± 24.9	152.5 ± 22.2
Week 3		
Knee flexion	134.7 ± 20.8	128.7 ± 18.1
Knee extension	162.8 ± 21.8	156.9 ± 23.8
Week 4		
Knee flexion	142.8 ± 18.9†	131.1 ± 21.5
Knee extension	173.1 ± 24.8†	161.5 ± 27.2

Note. Values are shown as mean ± SD. †Indicates significant difference between groups at $p < 0.05$.

swelling we found no differences between the two groups during the study ($p > 0.05$; Figure 1). No subject reported any untoward side effects from the glucosamine or placebo administration.

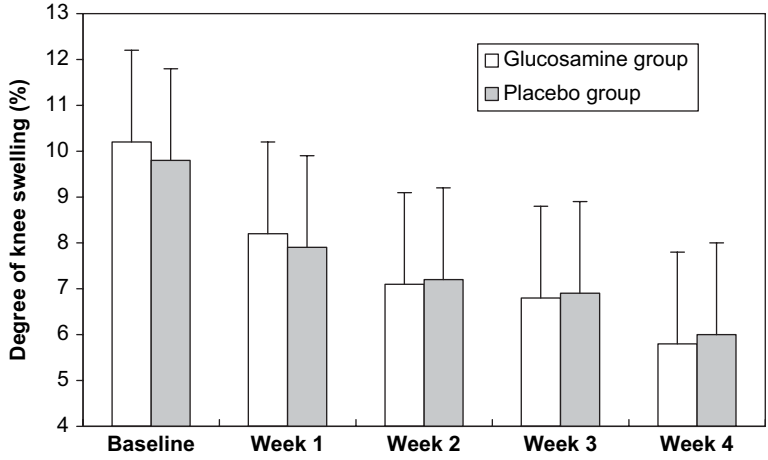

Figure 1. Degree of knee swelling (%) between groups during the study.

DISCUSSION

In comparison with other investigations, we believe the current study provides the well-controlled, direct analysis of effects of glucosamine administration on functional ability and pain scores after sports injury in athletes. The results of this study indicate that glucosamine administration for 4 weeks in male competitive athletes had little effects on recovery of acute knee injury.

In the context of knee pathology management, glucosamine (sole or coadministered with other agents) has been promoted as an analgesic, anti-inflammatory, and regenerative agent (Crolle and D'Este 1980; Barclay, Tsourounis, and McCart 1998; Braham et al. 2003; McAlindon and Biggee 2005). The mechanism of action of glucosamine, a sulphated aminomonosacharide, is unknown, but it is hypothesized that it may inhibit lysosomal enzymes and may stimulate proteoglycan synthesis (Bassler et al. 1993; Setnikar et al. 1993; Deal and Moskowitz 1999). Recent studies have indicated that glucosamine can provide relief from arthritic pain related symptoms (Houpt et al. 1999; Pavelka et al. 2002; McAlindon et al. 2004). Since the condition of arthropathy is manifested by degeneration of the joints in the body, glucosamine as a constituent of glucosaminoglycans could regenerate and reconstruct damaged cartilage (Noack et al. 1994). Pavelka et al. (2002) claimed that long-term treatment with glucosamine sulfate (1500 mg once a day) retarded the progression of knee osteoarthritis, possibly determining disease modification.

Braham, Dawson, and Goodman (2003) suggested that glucosamine supplementation (2000 mg per day for 12 weeks) may result in decreased pain ratings and self-reported improvements in functional ability of subjects suffering from chronic knee pain. However, McAlindon et al. (2000) concluded that glucosamine is only moderately effective for improving outcomes in knee osteoarthritis, but the magnitude of effect is unclear because of inconsistencies in study methods and dependence on industry support for study execution. Small sample size, short trial duration, lack of randomization of subjects, absence of double blinding, and use of hospitalized patients rather than free-living subjects have raised questions about the reliability and validity of the results (Poolsup et al. 2005). The results of our study are not in accordance with findings of other investigators who have suggested that glucosamine provides some degree of pain relief and decrease inflammation to subjects who experienced cartilage damage (Houpt et al. 1999; Reginster et al. 2001). We found no improvement in degree of pain intensity or degree of swelling of injured limb between the placebo and glucosamine group both at rest and while walking. Disagreement between the results of our study and results of previous investigators could be due to several factors. In this study, subjects tended to be younger with acute minor sports injury of knee, suggesting that our patients had less pronounced arthropathy, inflammation, cartilage damage, or all of these. Older patients with osteoarthritis may have more damage to their cartilage, and their cartilage could be more responsive to the effects of glucosamine (Drovanti et al. 1980; Noack et al. 1994; McAlindon 1999; Christgau et al. 2004). The majority of acute knee injuries presenting to the sports physician result from a direct blow to the joint or from indirect trauma leading to damage of osseous, muscular, tendinous, ligamentous, or cartilaginous tissue (Ostojic 2004). Since the positive effects of glucosamine mainly are related to joint cartilage damage, it could be postulated that glucosamine could be effective only if major sport injuries are present with severe harm of cartilage. Minor knee injuries (less that grade II according to Outerbridge classification) analyzed in the current study seem to be less responsive to glucosamine administration. Furthermore, our results could be due to the time period of treatment, which was insufficient to effect pain ratings in our patients. Other investigators have found improvement in pain ratings after 4–8 weeks of treatment with significant improvement at 4 weeks but not in the preceding weeks (Muller-Fassbender et al. 1994; Reginster et al. 2001; Poolsup et al. 2005). Additional studies are necessary to examine the analgesic and anti-inflammatory effects of glucosamine treatment in elite and recreational athletes of any age with longer duration of treatment and different types and severity of sports injuries.

Glucosamine is often cited as stiffness-reducing agent that could improve articular flexibility in patients with degenerative joint conditions (Barclay et al., 1998; da Camara and Dowless 1998; Pavelka et al. 2002). No published reports support its effectiveness at improving the range of motion with patients suffering from acute articular injury. According to results of our study, there were no marked changes in passive knee flexibility (flexion and extension) of the injured limb after 7, 14, and 21 days of treatment with administration of glucosamine as compared with placebo. After 28 days, however, the knee flexion and extension are significantly improved in the glucosamine group. Improved flexibility after 4 weeks of glucosamine treatment following acute knee injury could be of particular interest in an athletic environment. Regaining adequate range of movement (or absence of stiffness) after traumatic injury is an important factor for physical performance along with prevention of reinjury. Since glucosamine is incorporated into proteoglycans, which could attract water into the joint space, enhanced articular flexibility after administration of glucosamine could be due to increase of lubrication of the cartilage during movement (McCarty 1998).

The most obvious limitation of this study was the subjective and nondiscriminatory injury scoring system, which is not overly sensitive. Low reliability reported for the measures of range of motion and knee swelling (Wood et al. 2006) along with a large standard deviation of presented results could account for some of the nonsignificant findings. Therefore, future research should use advanced evaluation procedures (e.g., CT, MRI) to investigate and quantify the effects of glucosamine consumption on acute or overuse sports injuries. In addition, the current study did not analyze the nature, etiology, and severity of knee injury, factors that could affect the efficacy of this preparation (Gorsline and Kaeding 2005). Treatment with glucosamine or placebo only, without other interventions (e.g., cryomassage, physical therapy), could account for another possible limitation of the current study. It seems that glucosamine administration coupled with a standard treatment protocol and rehabilitative training program may be necessary to determine if glucosamine has a considerable regenerative effect in active persons. Moreover, further investigation will be improved greatly if some biochemical markers of glucosamine metabolism, collagen degradation, or proteoglycan synthesis have to be measured in this particular population.

Subjects in our study reported no acute side effects, yet caution should be used before widely recommending glucosamine to athletes. Both animal and human studies reported different occasional mild side effects (e.g., gastrointestinal discomfort, hyperglycemia, headache, knee sensitivity) of glucosamine administration (mostly 1500 mg per day) with fewer adverse effects than common pain-relieving medications (e.g.,

nonsteroidal anti-inflammatory drugs; Muller-Fassbender et al. 1994; Deal and Moskowitz 1999; Delafuente 2000). Several authors (Crolle and D'Este 1980; McAlindon 1999; Reginster et al. 2001) concluded that glucosamine was well tolerated throughout the administration, and it could be treated as a safe and nontoxic agent, which is in accordance with results of our study. Moreover, it is unclear whether the addition of other agents (e.g., chondroitin, sulfur, methylsulfonilmethane, hydrolyzed collagen) to glucosamine would have influenced the outcome of this study. In addition to glucosamine, the synthesis of glycosaminoglycans requires a substantial amount of sulfate, and it is known that sulfate depletion leads to a decrease in glycosaminoglycan synthesis so the sulfate found in glucosamine sulfate may be an important element in the efficacy of this preparation (van der Kraan et al. 1988). It is not clear if there is any positive effect of combination treatment in athletes after acute sports injury.

CONCLUSION

The main advantages of the current study includes the use of experienced competitive athletes, controlled and comparable conditions for all subjects during the study, and a double-blind, placebo-controlled design. Nevertheless, it is apparent that glucosamine ingestion had a minimal benefit for the relatively small sample of individuals in our study. The findings of the current study indicate that administration with glucosamine does not significantly alter pain score or degree of swelling after acute sports injury of the knee. Yet, glucosamine supplementation appears to be suitable as a flexibility improvement strategy in athletes after 4 weeks of treatment. In prescribed doses (1500 mg per day) glucosamine does not induce any acute adverse effects.

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