Joint Health of Athletes and the Chondroprotective Action of Glucosamine

ISAO NAGAOKA*

*Department of Host Defense and Biochemical Research, Juntendo University Graduate School of Medicine, Tokyo, Japan

In endurance athletes with intense joint loading, cartilage metabolism (degradation of type II collagen) is enhanced compared with non-athletes and non-endurance athletes. Recently, we have revealed that glucosamine, a functional food, exerts a protective action on cartilage metabolism in not only osteoarthritis patients but also endurance athletes (such as soccer players and rugby players) by suppressing the degradation of type II collagen. In this review, to demonstrate these findings, the following topics will be explained: 1. Biomarkers for cartilage metabolism; 2. Evaluation of osteoarthritis and endurance sports by using biomarkers of cartilage metabolism; 3. Chondroprotective action of glucosamine on osteoarthritis patients and endurance sports athletes; 4. Glucosamine as a “Food with Function Claim”.

Key words: athlete, joint health, glucosamine, type II collagen, biomarker

Introduction

The frequency and severity of joint loading are critical factors for the development of joint destruction, characterized by the damage of articular cartilage. In fact, excessive loading on the joint with motion and exposure causes the damage of articular cartilage1-4). Thus, sports with repetitive impact and torsional loading on the joints increase the risk of articular cartilage degeneration, and results in the clinical symptoms of osteoarthritis4).

The disease process of osteoarthritis is related to the degradation and functional loss of articular cartilage. Importantly, the early changes in the metabolic and biochemical properties of cartilage matrix can be detected before the appearance of morphological changes of cartilage2). Thus, various biomarkers have been developed as indicators of cartilage and bone metabolism in subjects with joint and bone disorders5). In this context, it is interest-
chondroprotective action of glucosamine on osteoarthritis patients and athletes, by analyzing type II collagen degradation and synthesis markers.

Biomarkers for cartilage and bone metabolism

Type II collagen is one of the major components of cartilage\textsuperscript{15}, and the fragments of type II collagen are utilized as biomarkers for cartilage metabolism (Figure-1). A C-terminal telopeptide (CTX-II) is cleaved during degradation of type II collagen\textsuperscript{16}, whereas a neo-epitope (C2C) is cleaved at the C terminus of the 3/4 piece of degraded type II collagen\textsuperscript{17}. Thus, both CTX-II and C2C are used as markers for type II collagen degradation. In contrast, a C-terminal type II procollagen peptide (CPII) is present in newly formed type II procollagen and cleaved during processing of synthesized type II procollagen; thus, CPII can be used as a marker for type II collagen synthesis\textsuperscript{18}. In addition, deoxypyridinoline (Dpyr), a crosslink product of type I collagen and cross–linked N-terminal telopeptides of type I collagen (NTx) are used as markers for type I collagen degradation in bone (bone resorption)\textsuperscript{5}.

Evaluation of osteoarthritis by using biomarkers

First, to evaluate the cartilage and bone metabolism in osteoarthritis, we measured the levels of biomarkers in knee osteoarthritis patients (16 subjects; 74.3±7.8 years old, mean±SD), and compared with those in healthy control (17 subjects; 70.5±5.2 year old)\textsuperscript{19}. In contrast to healthy control, osteoarthritis patient have pain at rest, and radiological findings of Kellgren and Lawrence grades\textsuperscript{20} of II–IV (minimal–severe). The patients were performing muscle training, and treated with NSAIDs (non-steroidal anti-inflammatory drugs) and intra-articular injection of hyaluronic acid.

Figures-2A, B and C show the levels of CTX-II, NTx and hyaluronic acid in healthy control and knee osteoarthritis patients, respectively. In
osteoarthritis patients, the levels of type II collagen degradation marker CTX-II, type I collagen degradation marker NTx and synovitis marker hyaluronic acid were significantly increased compared with healthy control. These results indicate that type II collagen degradation and type I collagen degradation are increased in osteoarthritis, accompanied with synovitis. Furthermore, we examined the levels of type II collagen synthesis marker CPII in healthy control and knee osteoarthritis patients (Figure-2D). Interestingly, CPII level was significantly decreased in osteoarthritis. These observations suggest that type II collagen degradation is increased, whereas type II collagen synthesis is decreased; thus, the imbalance between degradation and synthesis of type II collagen may be involved the cartilage damage in osteoarthritis. Actually, the imbalance between the degradation and synthesis of type II collagen is reported to be important for the progression of cartilage damage in osteoarthritis.

Next, we evaluated the chondroprotective action of glucosamine on osteoarthritis.

Chondroprotective action of glucosamine on osteoarthritis

Glucosamine is an amino monosaccharide with an amino group, and functions as a component of glycosaminoglycans (such as hyaluronic acid and chondroitin sulfate) (Figure-3). Figure-4 shows the synthetic pathway of glycosaminoglycans in our body; glucose is converted into glucosamine with the addition of amino group from glutamine, and further converted into N-acetyl-glucosamine and N-acetyl-galactosamine. Then, these glycosamine-derivatives are coupled with uronic acid to form glycosaminoglycans (such as hyaluronic acid, keratin sulfate and
Figure-3 Structures of glucosamine and glycosaminoglycans
Show are the basic structures of glucosamine and glycosaminoglycans such as hyaluronic acid and chondroitin sulfate, which are composed of uronic acid (such as glucuronic acid) and glucosamine-derived monosaccharides (such as N-acetyl-glucosamine and N-acetyl-galactosamine). Glucosamine is converted from glucose by the addition of amino group from glutamine.
(Nagaoka I: Juntendo Medical Journal, 2014; 60: 580-587 36))

Figure-4 Synthesis of glycosaminoglycans from glucosamine–derives and uronic acid
(Nagaoka I: Juntendo Medical Journal, 2014; 60: 580–587 36)
chondroitin sulfate) present in the articular cartilage, skin and other tissues. Importantly, glucosamine supplement is efficiently absorbed from the intestine, distributed to various tissues and used as a constituent of glycosaminoglycans. Thus, glucosamine is widely utilized as a functional food with a chondroprotective action to treat human diseases such as osteoarthritis as a precursor of glycosaminoglycans\(^9\)-\(^11\).

Furthermore, we demonstrated that glucosamine suppresses the activation of neutrophils\(^25\), synovial cells\(^26\) and intestinal epithelial cells\(^27\), endothelial cells\(^28\), and inhibits adjuvant arthritis\(^29\), colitis\(^30\) and atherosclerosis\(^31\) in animal models. Thus, glucosamine expectantly exhibits anti-inflammatory actions.

As a functional food, glucosamine is mostly manufactured from chitin, a polymer of N-acetyl-glucosamine present in the shells of shrimps and crabs (Figure-5). Chitosan, a polymer of glucosamine is produced from the chitin by deacetylation under alkaline condition. In contrast, glucosamine, a chitosan monomer is produced as glucosamine hydrochloride by hydrolysis and deacetylation of chitin under acidic condition.

To evaluate the chondroprotective action of

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**Figure-5**  Manufacturing processes of chitosan (a glucosamine polymer) and glucosamine from chitin (an N-acetyl-glucosamine polymer)

(Nagaoka I: Juntendo Medical Journal, 2014; 60: 580-587\(^{36}\))

**Figure-6**  Effects of glucosamine administration on serum levels of CTX-II and CPII in a rat osteoarthitis model

Serum levels of CTX-II (A) and CPII (B) are expressed as a percentage of baseline levels before anterior cruciate ligament transection (ACLT) (0 day). Data represent the mean±SD of six animals in each group (Sham, ACLT, and ACLP+ glucosamine 1,000 mg/kg/day). Values are compared between ACLT and Sham or ACLT+ glucosamine. **p<0.01, ***p<0.001.

glucosamine, we utilized the anterior cruciate ligament transection model as an osteoarthritis model \(^{32}\). A knee joint is stabilized by several ligaments such as collateral, posterior cruciate and anterior cruciate ligaments. By anterior cruciate ligament transection, osteoarthritis is developed due to instability of the knee joint, accompanied with the degeneration of cartilage \(^{33}\).

Actually, anterior cruciate ligament transection clearly induced the erosion in the cartilage; interestingly, however, glucosamine administration markedly suppressed the erosive change of the cartilage \(^{32}\). Furthermore, anterior cruciate ligament transection apparently induced the surface depletion and reduced toluidine blue staining of proteoglycans in the cartilage \(^{32}\). Notably, glucosamine administration suppressed the surface depletion and proteoglycan degeneration in the cartilage.

Moreover, the effects of glucosamine on the type II collagen-degradation and type II collagen-synthesis markers were evaluated (Figure-6). The level of CTX-II, a type II collagen-degradation marker, was significantly elevated by anterior cruciate ligament transection. Of importance, glucosamine administration suppressed the increase of CTX-II. In addition, the level of CPII, a type II collagen-synthesis marker, was substantially increased by glucosamine administration. Thus, the results suggest that glucosamine exerts a chondroprotective action by inhibiting type II collagen degradation but enhancing type II collagen synthesis in the articular cartilage in this osteoarthritis model.

Next, to evaluate the chondroprotective action of glucosamine on knee osteoarthritis patients, we performed a randomized double-blind placebo-controlled study \(^{12}\). In this study, patients with knee joint pain and Kellgren and Lawrence grades \(^{20}\) of 0–III were recruited, and glucosamine-containing diet (16 subjects; 54.5 ± 9.1 years old) or placebo diet (16 subjects; 56.4 ± 7.7 years old) was administered for 16 weeks. Glucosamine diet mainly contained glucosamine (1,200 mg) but also chondroitin sulfate (80 mg) and other functional substances. Importantly, the administration of glucosamine-containing diet significantly improved the symptoms of osteoarthritis, based on JKOM (Japanese Osteoarthritis Measure) total score \(^{34}\) (Figure-7A). Similarly, the administration of glucosamine-containing diet significantly reduced the level of type II collagen degradation marker C2C (Figure-7B), indicating the suppression of type II collagen degradation. Moreover, the administration of glucosamine-containing diet significantly reduced the serum level of hyaluronic acid, a synovial inflammation marker (Figure-7C), indicating the suppression of synovial inflammation. These observations suggest that the administration of glucosamine-containing diet exhibits a chondroprotective action on knee osteoarthritis by inhibiting type II collagen degradation and synovial inflammation, and improves the symptoms.

**Chondroprotective action of glucosamine on endurance athletes**

Finally, we looked at the chondroprotective
action of glucosamine on athletes. It has been already reported that sports and exercise affect cartilage and bone metabolism. O’Kane et al. compared the urine levels of type II collagen degradation marker CTX-II and type I collagen degradation marker NTx among non-athlete control, cross-country runners, swimmers and crew members\(^3\). The results indicated that the levels of CTX-II and NTx are increased in the cross-country runners and crew members compared with non-athletes and swimmers, suggesting that cartilage and bone metabolism (type II collagen degradation and bone resorption) is increased by endurance exercise with intense joint loading, such as cross country and boat racing.

So, we evaluated the effect of glucosamine on cartilage metabolism using collegiate soccer players with intense joint loading\(^13\). In this study, 10 non-athletes (23.5±2.5 years old) and 21 soccer players (20.3±0.9 years old) were recruited. Non-athletes experienced no hard exercise in the past year. In contrast, soccer players performed the training 5 days per week, and played the official match almost every weekend, during the test period.

Figures-8A and B show the levels of CTX-II and NTx in non-athlete control and soccer players. In soccer players, the levels of CTX-II and NTx were significantly increased compared with non-athlete control, indicating that cartilage and bone metabolism (type II collagen degradation and bone resorption) is increased in soccer players, as reported in other endurance athletes\(^9\). Moreover, a type II collagen synthesis marker CPII was evaluated in soccer players. Interestingly, the level of CPII was substantially increased in soccer players compared with non-athlete control (Figure-8C), suggesting that cartilage metabolism as evaluated by type II collagen synthesis is also increased in soccer players.

In addition, we evaluated the type II collagen degradation and synthesis balance in the cartilage of soccer players by calculating CTX-II/CPII ratio. As shown in Figure-9A, CTX-II/CPII ratio was significantly higher in soccer players than non-athlete control, suggesting that type II collagen degradation is relatively increased compared with type II collagen synthesis in soccer players.

Next, we examined the effect of glucosamine administration on type II collagen degradation and synthesis markers. Importantly, CTX-II level was significantly decreased after the glucosamine administration for 3 months at both 1.5 g and 3 g/day (Figure-10A). Interestingly, however, the CTX-II level returned to almost the pre-administration level after withdrawal of glucosamine administration in 1.5 g/day-group for 3 months, although the CTX-II level was still reduced in 3 g/day-group. In contrast, CPII level was not essentially changed even after the glucosamine administration and withdrawal of glucosamine administration (Figure-10B), suggesting that the increased level of type II collagen synthesis in soccer players is maintained during the test period.

Furthermore, we evaluated the effect of glucosamine on type II collagen degradation and synthesis balance in soccer players by using CTX-II/CPII ratio. Importantly, the ratio was reduced by glucosamine administration especially at 3 g/day, and returned to the pre-administration level after
withdrawal of glucosamine (Figure-9B).

These observations suggest that glucosamine exhibits a chondroprotective action in soccer players by preventing type II collagen degradation but maintaining type II collagen synthesis; however, its effect on type II collagen degradation is transient and disappears after withdrawal of administration.

Further, we evaluated the effect of glucosamine on cartilage metabolism using professional rugby players with intense joint loading. In this study, 19 rugby players (29.4±3.7 years old) and 19 non-athletes (29.4±3.7 years old) were recruited. Rugby players were administered with a jelly-type diet containing 3 g glucosamine for 16 weeks.

Figures-11A and B show the levels of CTX-II and NTx in non-athletes and rugby players. In rugby players, the levels of CTX-II and NTx were significantly increased compared with non-athletes, indicating that cartilage and bone metabolism (type II collagen degradation and bone resorption) is increased in rugby players, as reported in soccer players and other endurance athletes. Next, we evaluated a type II collagen synthesis marker CPII.
in rugby players; however, CPII level in rugby players was almost the same as in non-athletes (Figure-11C). Based on these findings, CTX-II/CPII ratio was slightly higher in rugby players than non-athletes (Figure-11D), suggesting that type II collagen degradation is relatively increased compared with type II collagen synthesis in rugby players.

Next, we examined the effect of glucosamine administration on type II collagen degradation and synthesis markers. Importantly, CTX-II level was significantly decreased after the glucosamine administration.
administration (Figure–12A). Interestingly, however, the CTX–II level returned to almost the pre-administration level after withdrawal of glucosamine administration. In contrast, CPII level was not essentially changed even after the glucosamine administration and withdrawal of glucosamine administration (Figure–12B). Finally, we evaluated the effect of glucosamine on type II collagen degradation and synthesis balance in rugby players by using CTX–II/CPII ratio. Importantly, the ratio was significantly reduced by glucosamine administration, and returned to the pre-administration level after withdrawal of glucosamine (Figure–12C).

These observations suggest that glucosamine exhibits a chondroprotective action also in rugby players by preventing type II collagen degradation but maintaining type II collagen synthesis. However, the effect is transient and disappears after withdrawal of administration.

What are “Foods with Function Claims”?

The system of “Foods with Function Claims機能性表示食品制度” has been launched in April 2015.13 “Foods with Function Claims機能性表示食品” are foods submitted to the Secretary–General of the Consumer Affairs Agency as products whose labels bear function claims based on scientific evidence, under the responsibility of food business operators.

Based on our findings, glucosamine has been submitted to the Secretary–General of the Consumer Affairs Agency as a “Food with Function Claim” of chondroprotective action with a submission number A147. Glucosamine is expected to be helpful for maintaining joint health during exercise and walking, because it suppresses the degradation of articular cartilage components such as type II collagen in endurance athletes with intense joint loading.

Conclusions

Our recent studies revealed the following findings.

1. Glucosamine exhibits a chondroprotective action in a rat osteoarthritis model by inhibiting type II collagen degradation and increasing type II collagen synthesis.
2. Glucosamine improves the symptom of osteoarthritis patients by suppressing type II collagen degradation and synovial inflammation (synovitis).
3. Type II collagen degradation is relatively increased compared with type II collagen synthesis in endurance athletes (soccer and rugby players). Glucosamine exhibits a chondroprotective action in athletes by preventing type II collagen degradation but maintaining type II collagen synthesis. However, the effect is transient and disappears after withdrawal of administration. Thus, glucosamine should be continuously administered for expecting joint health.

Based on these findings, glucosamine has been submitted to the Secretary–General of the Consumer Affairs Agency as a “Food with Function Claim”, which is helpful for maintaining joint health.

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