Effect of N-acetylglucosamine administration on cartilage metabolism and safety in healthy subjects without symptoms of arthritis: A case report

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Abstract. N-acetylglucosamine (GlcNAc) is a widely accepted treatment for osteoarthritis (OA); however, its effect on healthy individuals is poorly understood. To evaluate the effect of GlcNAc administration on healthy subjects that do not exhibit symptoms of arthritis, the present randomized, double-blind, placebo-controlled study was performed. In the present study, 68 male and female Japanese participants, without symptomatic and radiographic evidence of OA, were enrolled and randomly allocated to receive placebo or GlcNAc (500 or 1,000 mg/day) for 16 weeks. Effects were evaluated using biomarkers for type II collagen degradation and synthesis, collagen type II cleavage (C2C), procollagen type II carboxy-terminal propeptide (PIICP) and their ratio (C2C/PIICP). Furthermore, safety assessments were performed via physical parameters, hematology, blood biochemistry and urinalysis. The results indicated that there was no significant change in the biomarkers for type II collagen degeneration and synthesis during and after the intervention with the placebo and two GlcNAc groups. However, subgroup analysis using subjects with impaired cartilage metabolism (who exhibited enhanced type II collagen degradation and reduced type II collagen synthesis) indicated that the C2C levels were significantly decreased at 8 ($P<0.05$) and 16 ($P<0.01$) weeks during the intervention in the two GlcNAc (500 mg and 1,000 mg/day) groups, compared with the placebo group. In contrast, PIICP levels were not notably different in the placebo and two GlcNAc groups. The C2C/PIICP ratio was markedly decreased at 12 and 16 weeks during the intervention in the two GlcNAc groups, compared with the placebo group. Moreover, no supplement-related adverse events were observed during and after the intervention. In conclusion, these observations indicate that oral administration of GlcNAc at doses of 500 and 1,000 mg/day improves cartilage metabolism in healthy subjects without apparent adverse effects.

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Introduction

Osteoarthritis (OA) is the most common joint disease and is the leading cause of physical disability in elderly people, which results from progressive destruction of articular cartilage (1). The most common symptoms are joint pain and severe impaired mobility of the knee. This is due to the knee being a weight-bearing joint. In Japan, a country harboring one of the fastest aging societies in the world, the incidence and prevalence of knee OA is increasing, with a rapid increase exhibited in the elderly population, as with many other developed countries (2). Therefore, the management of knee OA, which requires extensive utilization of healthcare resources, has become a major social and economic topic.

Clinical management of knee OA usually includes analgesic agents (such as nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors) and intra-articular injection of hyaluronan or corticosteroids (3). However, accumulating data suggests that any of these pharmaceutical agents frequently produce insufficient benefit with an associated risk of adverse reactions (4-6). Therefore, it is necessary that OA patients have access to accepted complementary and alternative approaches to pain management of OA.

Glucosamine and N-acetyl-D-glucosamine (GlcNAc) are amino sugars, in which the hydroxyl group of glucose at position 2 is substituted by an amino group and acetoamide group (7,8), respectively. They are the key components of glycosaminoglycan polymers (such as chondroitin sulfate and hyaluronan) contained in articular cartilage (9). Since they are believed to have a crucial role in the formation of glycosaminoglycans in cartilage (10,11), they have been widely used as alternative medicines or dietary supplements for the treatment of OA. Previous clinical studies and meta-analyses

investigating the effect on OA have demonstrated the potential benefit of glucosamine sulfate or hydrochloride in relieving OA pain (12-14). In addition, oral administration of GlcNAc has been shown to be effective in relieving symptoms of OA, without generating any adverse reactions in human clinical studies. Hatano *et al* (15) conducted a randomized double-blind comparative study to evaluate the effects of GlcNAc on OA in 67 untreated patients, who presented with mild pain and discomfort in the knee. Subjects were divided into the two groups and given 200 ml of normal soy milk or soy milk containing 1,250 mg of GlcNAc once-daily for 12 weeks. Assessments of subjective symptoms and range of motion of the knee were performed. The results indicated a significant improvement in knee joint pain and the range of motion of the knee, beginning at 8 weeks after the administration of GlcNAc compared with placebo. Furthermore, blood chemistry and physical examination did not show any adverse reactions of clinical importance.

However, to our knowledge, almost all previous studies were performed using OA patients and no randomized clinical trials have been conducted in healthy subjects. However, it is difficult to assess the effect of dietary supplements on healthy subjects that are without symptoms of OA using the conventional methods, such as radiographs, the Western Ontario and McMaster Universities Arthritis Index, Lequesne Index, or visual analog scale. In a previous study, experimental OA models have revealed that the early changes in the cartilage matrix are detectable by biomarkers, which reflect the biochemical and metabolic changes in the cartilage, before emerging the radiographic abnormality energies (16). Magnetic resonance imaging (MRI) studies have also revealed the correlation between cartilage degeneration and biomarkers (17). Thus, in the present study, the effect of GlcNAc administration on the cartilage biomarkers was investigated, using healthy subjects without symptoms of OA. Doses of 500 and 1,000 mg per day were administered due to findings from previous studies, which demonstrated that GlcNAc at these doses can relieve the symptoms of OA (15). Furthermore, safety assessments of physical parameters, hematology, blood biochemistry and urinalysis were conducted. In particular, the effect of GlcNAc on the ratio of markers for type II collagen degradation (type II collagen cleavage neoepitope, C2C) and synthesis (carboxy-terminal propeptide of type II procollagen, PIICP) was the predominant focus, due to previous findings which demonstrated that analysis with the combination of markers for type II collagen degradation and synthesis has a significant association with the MRI-based changes of OA (18).

Materials and methods

Study design. A randomized, placebo-controlled, parallel-group comparative study was designed to assess the efficacy and safety of GlcNAc supplementation. The study was performed between October 2013 and August 2014, and involved four clinical service organization centers under the control of five medical investigators in Japan. The study protocol was approved by the local Ethics Committee (Tana Orthopedic Clinic, Kanagawa, Japan), and was conducted in accordance with the principles of the amended Declaration of Helsinki and 'Ethical Guidelines for Epidemiological Research' (recognized by the Japanese Government in 2008, accessible from: http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/0504sisin.html). Written informed consent was obtained from all participants prior to enrollment in the study. The overall design of the study consisted of a 16-week intervention period and 4-week post-intervention period. The subjects, who accomplished full clinical and laboratory examinations at the baseline, at weeks 4, 8, 12 and 16 during the intervention period, and at week 4 of post-intervention period, were analyzed.

Subjects. Healthy male and female Japanese subjects (male:female ratio, 33:43), aged 20-64 years, without symptoms of arthritis (such as pain) in the knee 0 and I in Kellgren-Lawrence grades (19) were included. Major exclusion criteria were: Hyperuricemia with risk of gouty attack; presence of rheumatoid arthritis that may cause joint pain; previous surgical treatment of knee joint(s) or necessity for during the test period; routine use of health foods for bone or cartilage health (containing hyaluronic acid, GlcNAc, collagen peptides, glucosamine and/or chondroitin sulfate) within 3 months of inclusion; administration of prescribed medicines or commercially available medicines more than three times a week; intra-articular hyaluronic acid or corticosteroids within 12 months of inclusion or during the test period; regular strenuous exercise that may affect articular cartilage; a history of osseous or articular diseases other than OA within the past 12 months; patients with a history of cancer, hypertension, heart disease, renal disease, thyroid dysfunction and hepatic disease; treatment with warfarin prior to or during the study period; daily alcohol intake of >60 g alcohol/day; potential for developing an allergy to the test supplement; person judged unsuitable by the lifestyle questionnaire; pregnant women; nursing mothers or women of childbearing potential; participation in another clinical study; and presence of any medical condition judged by the medical investigator to preclude the subjects' inclusion in the study.

Intervention and subject assignment. The test supplement contained green tea extract powder and 500 or 1,000 mg of GlcNAc in a daily dose. GlcNAc was a product of a commercial chitin hydrolysate, Marine Sweet 40 (Yaizu Suisankagaku Industry Co., Shizuoka, Japan), containing 40.8% of GlcNAc, 3.5% of N,N-diacetylchitobiose and dextrin as an excipient. The placebo supplement contained green tea extract powder without GlcNAc and was indistinguishable from the test supplement in taste, flavor, appearance and packaging. All subjects were sequentially assigned, based on random number tables, to the two GlcNAc supplement groups (500 or 1,000 mg/day) and a placebo supplement group. Following randomization, it was confirmed that the subjects were divided almost equally, in terms of age and gender (Table I). The allocation table was kept by an appointed person, who was not involved in the present study, and concealed until the completion of intervention, follow-up and data analysis from the subjects and the investigators, who recruited and assessed the participants. All subjects were instructed to take the supplements (dissolved in a cup of water) once a day, and self-record in the study diary. Adherence rate to the intervention was calculated based on the consumption record

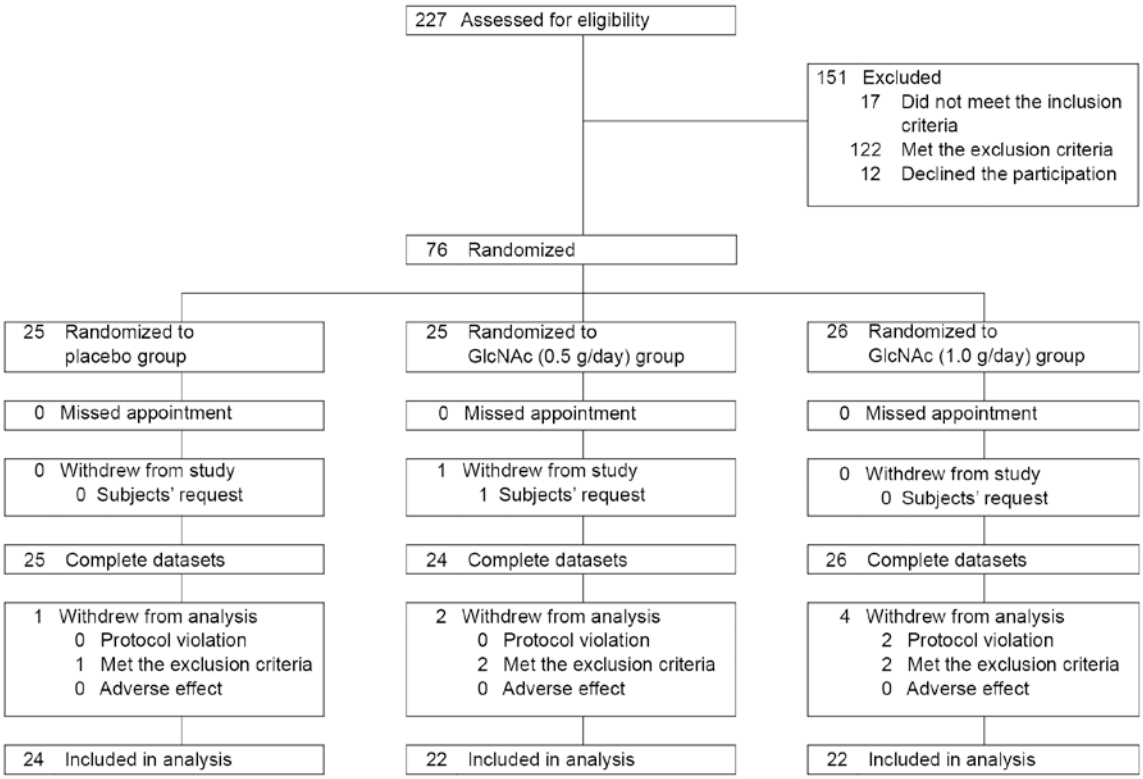

Figure 1. Flow diagram of the subjects that participated in the study.

in the diary and <80% adherence was considered a protocol violation.

Efficacy and safety assessment. Blood and urine samples were collected from fasting subjects at the visit of four clinical service organization centers by the standard methods, and analyzed by the same examination laboratory. Sera for biomarker analysis were stored frozen and analyzed at the same time after the follow-up period. The biomarkers analyzed were C2C and PIICP. C2C was measured in sera using a competitive inhibition enzyme-linked immunosorbent assay (Collagen Type II Cleavage ELISA; IBEX Technologies, Inc., Mont-Royal, QC, Canada). Serum PIICP was measured using an ELISA kit for Procollagen II C-terminal Propeptide (USCN Life Sciences, Inc., Wuhan, China).

Tolerability and safety were assessed throughout the study on the basis of the incidence and severity of intervention-related adverse events and changes in physical parameters, hematology, blood biochemistry and urinalysis. Subjective pain assessment by visual analog scale (VAS) and objective assessment of knee joints by the Japan Orthopaedic Association (JOA) criteria were also performed.

Statistical analysis. Values are expressed as mean ± standard error. Baseline data of subjects were compared with a placebo group and two GlcNAc groups, using one-way analysis of variance for continuous variables. The distributions of males and females, and Kellgren and Lawrence grades were analyzed by the Pearson's χ^2 test. Biomarker and safety data were compared between the placebo and GlcNAc groups using the unpaired Student's *t*-test with the Holm adjustment along with changes from baseline (20). The Holm step-down adjustment was used to correct for the multiple pairwise comparisons. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of subjects. A total of 227 subjects were assessed for eligibility, of which 76 subjects fulfilled the eligibility criteria and were randomly assigned into groups (Fig. 1). During the intervention, one female in the GlcNAc group (500 mg/day) discontinued the study due to her own request. The remaining 75 subjects completed the study, and the adherence rate to the assigned dietary supplement was 94.1-100.0%. Two subjects in the GlcNAc group (1,000 mg/day) were judged to have violated the protocol due to a substantial increase in body weight resulting from changes in dietary pattern and were excluded from the analysis. Five subjects were also excluded for meeting the exclusion criteria, including one subject in the placebo group due to the onset of hyperuricemia; two subjects in the GlcNAc (500 mg/day) group due to the onset of hyperuricemia and a marked increase of aspartate transaminase, alanine transaminase, gamma-guanosine-5'-triphosphate; and two subjects in the GlcNAc (1,000 mg/day) group due to a marked increase in body weight and acute ankle sprain. The remaining 68 subjects were analyzed for efficacy and safety. Table I presents the baseline characteristics of subjects who completed the study, including demographic characteristics (age, and distribution of male and female subjects), physiological characteristics (body height, body weight, body mass index, systolic blood pressure, diastolic blood pressure and pulse rate) and distribution of Kellgren and Lawrence grades. Within the groups of placebo and test supplement (500 mg and 1,000 mg of GlcNAc/day),

Table I. Baseline characteristics of subjects who completed the study.

Variables	Placebo (n=24)	GlcNAc 0.5 g/day (n=22)	GlcNAc 1.0 g/day (n=22)	P-value
Age (years)	49.7±2.4	50.5±2.3	50.0±2.4	0.972
Male/female (number)	10/14	10/12	10/12	0.956
Body weight (kg)	55.18±2.00	57.36±2.86	56.60±2.50	0.813
Body mass index (kg/m^2)	20.84±0.57	21.29±0.61	20.98±0.62	0.862
Systolic blood pressure (mmHg)	119.8±2.1	118.1±2.5	115.7±2.1	0.447
Diastolic blood pressure (mmHg)	72.5±1.7	72.9±1.7	72.6±1.6	0.984
Pulse rate (beats min^{-1})	69.5±1.5	66.4±1.8	72.7±2.2	0.058
Kellgren-Lawrence grades (0/I/II-IV)				
Right knee (number)	21/3/0	17/5/0	20/2/0	0.412
Left knee (number	20/4/0	19/3/0	20/2/0	0.749
C2C (ng/ml)	260.02±13.26	241.59±9.80	244.00±13.43	0.512
PIICP (ng/ml)	52.09±2.46	45.20±2.27	43.74±1.91	0.022
C2C/PIICP ratio	5.26±0.34	5.67±0.40	5.95±0.51	0.503

Values are expressed as mean ± standard error, with the exception of the distributions of males, females and Kellgren-Lawrence grades as indicated. GlcNAc, N-acetylglucosamine; C2C, collagen type II cleavage; PIICP, procollagen type II carboxy-terminal propeptide.

these parameters were not significantly different. Levels of biomarkers for type II collagen metabolism (C2C, PIICP and C2C/PIICP ratio) exhibited no significant differences at the baseline in C2C, PIICP and C2C/PIICP ratio between the placebo and GlcNAc groups, with the exception that PIICP levels in the placebo group were significantly higher than that of the GlcNAc (1,000 mg/day) group (P<0.05).

Effect on biomarkers. Fluctuations in the levels of C2C, PIICP and C2C/PIICP at 8, 12 and 16 weeks during the intervention and 4-week post-intervention are demonstrated in Fig. 2. Minor changes in the C2C levels of the placebo and the two GlcNAc (500 mg and 1,000 mg/day) groups (Fig. 2A) were observed. In contrast, the PIICP levels in the placebo group were substantially decreased, although the changes were not statistically significant, at 12 and 16 weeks during the intervention, compared with the two GlcNAc groups and returned to the same level as that of the two GlcNAc groups at four weeks after the intervention (Fig. 2B). Moreover, the C2C/PIICP ratio was marginally decreased at 16 weeks during the intervention in the GlcNAc (500 mg/day) group when compared with the placebo and GlcNAc (1,000 mg/day) groups (Fig. 2C).

To further clarify the effect of GlcNAc administration, subgroup analysis was performed using the subjects with enhanced levels of type II collagen degradation and reduced levels of type collagen synthesis in the articular cartilage. Subjects with reduced levels of type II collagen degradation (C2C<210 ng/ml) and enhanced levels of type collagen synthesis (PIICP≥55 ng/ml) were excluded. Subgroup analysis was performed using 39 subjects (baseline, C2C≥210 ng/ml and PIICP<55 ng/ml). Their baseline characteristics are shown in Table II. Within the placebo and the two GlcNAc groups, no significant differences in demographic characteristics, physiological characteristics and distribution of Kellgren and Lawrence grades were demonstrated. Levels of biomarkers for type II collagen metabolism revealed no significant differences in C2C, PIICP and C2C/PIICP ratio at the baseline between the placebo and GlcNAc groups. Fig. 3A demonstrates that the C2C level was decreased at 8 and 16 weeks during the intervention in the two GlcNAc (500 mg and 1,000 mg/day) groups compared to the placebo group. C2C levels in the GlcNAc (500 mg/day) group was significantly decreased compared with the placebo group at 8 (P<0.05) and 16 (P<0.01) weeks during the intervention and 4 weeks after the intervention. In contrast, PIICP levels within the placebo and two GlcNAc groups were not notably different (Fig. 3B). As a result, the C2C/PIICP ratio was markedly decreased, although the changes were not statistically significant, at 12 and 16 weeks during the intervention in the two GlcNAc groups compared with the placebo group (Fig. 3C). These observations suggest that the oral administration of GlcNAc likely improves cartilage metabolism, predominantly by suppressing the degradation of type II collagen in healthy subjects without symptoms of arthritis.

Safety assessment. A total of 66 adverse events occurred in 12, 10 and 9 subjects receiving placebo, 500 mg/day GlcNAc and 1,000 mg/day GlcNAc, respectively, and there was no significant difference in the frequency among the three groups. Relatively frequent adverse events reported included cold symptoms, gastric distress and pain (head, low back pain, muscle, or knee); however, these events were generally mild. There were no serious adverse events or deaths. No adverse events were judged by the investigator to be related to the intervention.

Routine physical and cardiovascular characteristics, hematology and blood chemistry did not show any significant abnormalities during the intervention and follow-up periods in all the three groups (data not shown). Changes in subjective

Table II. Baseline characteristics of subjects with ≥210 ng/ml of C2C and <55 ng/ml of PIICP.

Variables	Placebo (n=13)	GlcNAc		P-value
		0.5 g/day (n=12)	1.0 g/day (n=14)	
Age (years)	46.9±3.1	49.6±3.0	49.8±2.7	0.183
Male/female (number)	6/7	5/7	8/6	0.715
Body weight (kg)	54.87±2.93	57.29±3.80	58.26±3.52	0.769
Body mass index (kg/m^2)	20.08±0.81	21.50±0.84	21.07±0.90	0.502
Systolic blood pressure (mmHg)	121.5±2.4	116.3±3.1	114.7±2.1	0.149
Diastolic blood pressure (mmHg)	74.4±2.6	73.5±2.3	72.0±2.1	0.754
Pulse rate (beats min^{-1})	69.0±1.8	65.6±2.5	72.5±2.8	0.144
Kellgren-Lawrence grades (0/I/II-IV)				
Right knee (number)	12/1/0	10/2/0	12/2/0	0.782
Left knee (number)	12/2/0	11/1/0	12/2/0	0.852
C2C (ng/ml)	248.64±8.72	269.68±9.46	277.80±14.30	0.183
PIICP (ng/ml)	44.06±2.64	41.38±2.17	42.04±1.98	0.693
C2C/PIICP ratio	5.90±0.40	6.77±0.49	6.91±0.62	0.339

Values are expressed as mean ± standard error, with the exception of the distributions of males, females and Kellgren-Lawrence grades as indicated. C2C, collagen type II cleavage; PIICP, procollagen type II carboxy-ter minal propeptide; GlcNAc, N-acetylglucosamine.

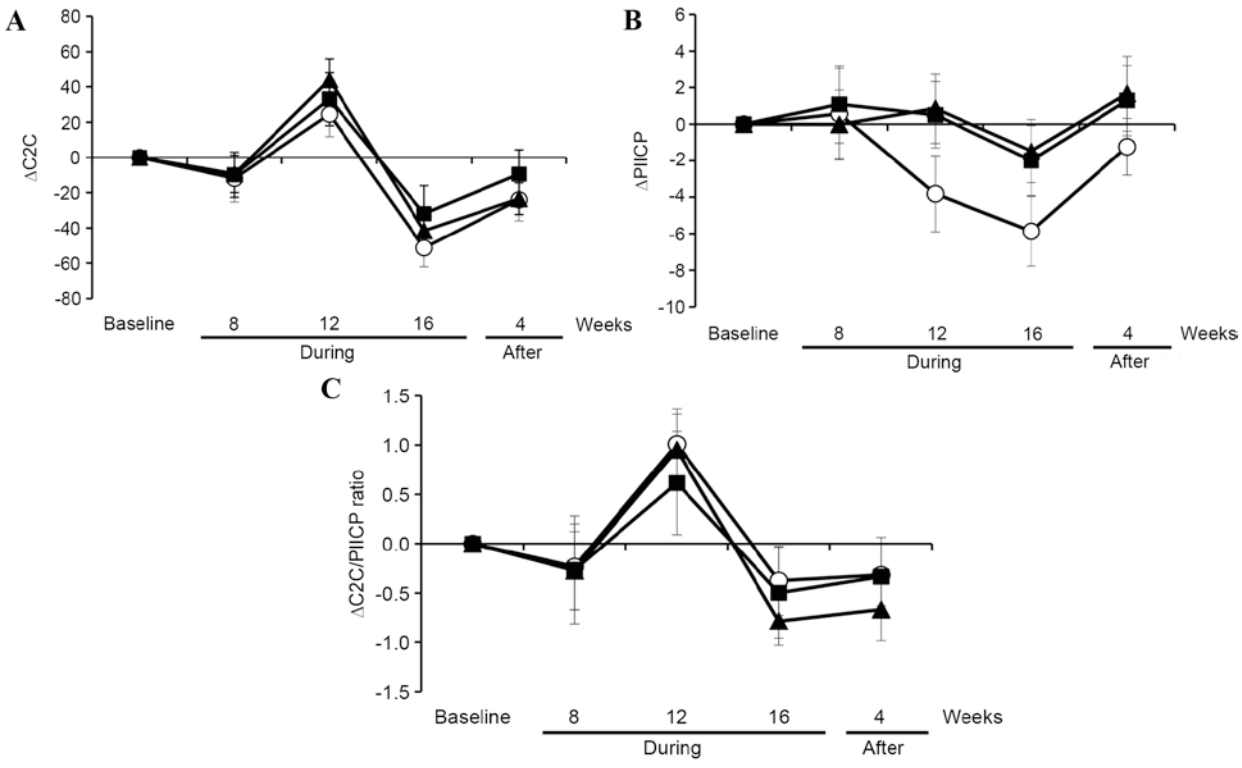

Figure 2. Changes of C2C, PIICP and the ratio of C2C and PIICP in subjects in the placebo and GlcNAc groups during and after the intervention. (A) C2C and (B) PIICP were analyzed, and (C) the ratio of C2C and PIICP was calculated using serum samples collected from subjects in the placebo (n=24; open circles), 500 mg/day GlcNAc (n=22; closed triangles) and 1,000 mg/day GlcNAc (n=22; closed squares) groups at baseline, weeks 8, 12 and 16 during the intervention period, and during week 4 of the post-intervention period. Data are expressed as the mean ± standard error. The unpaired *t*-test was used to evaluate between-group differences. There were no significant differences between groups. C2C, collagen type II cleavage; GlcNAc, N-acetylglucosamine; PIICP, procollagen type II carboxy-terminal propeptide; During, during the intervention; After, After the intervention; Open circles, placebo; closed triangles, 500 mg/day GlcNAc; closed squares, 1,000 mg/day GlcNAc.

pain assessment values by VAS and objective assessment of knee joints by JOA criteria were not significantly different among the three groups during the intervention and follow-up periods.

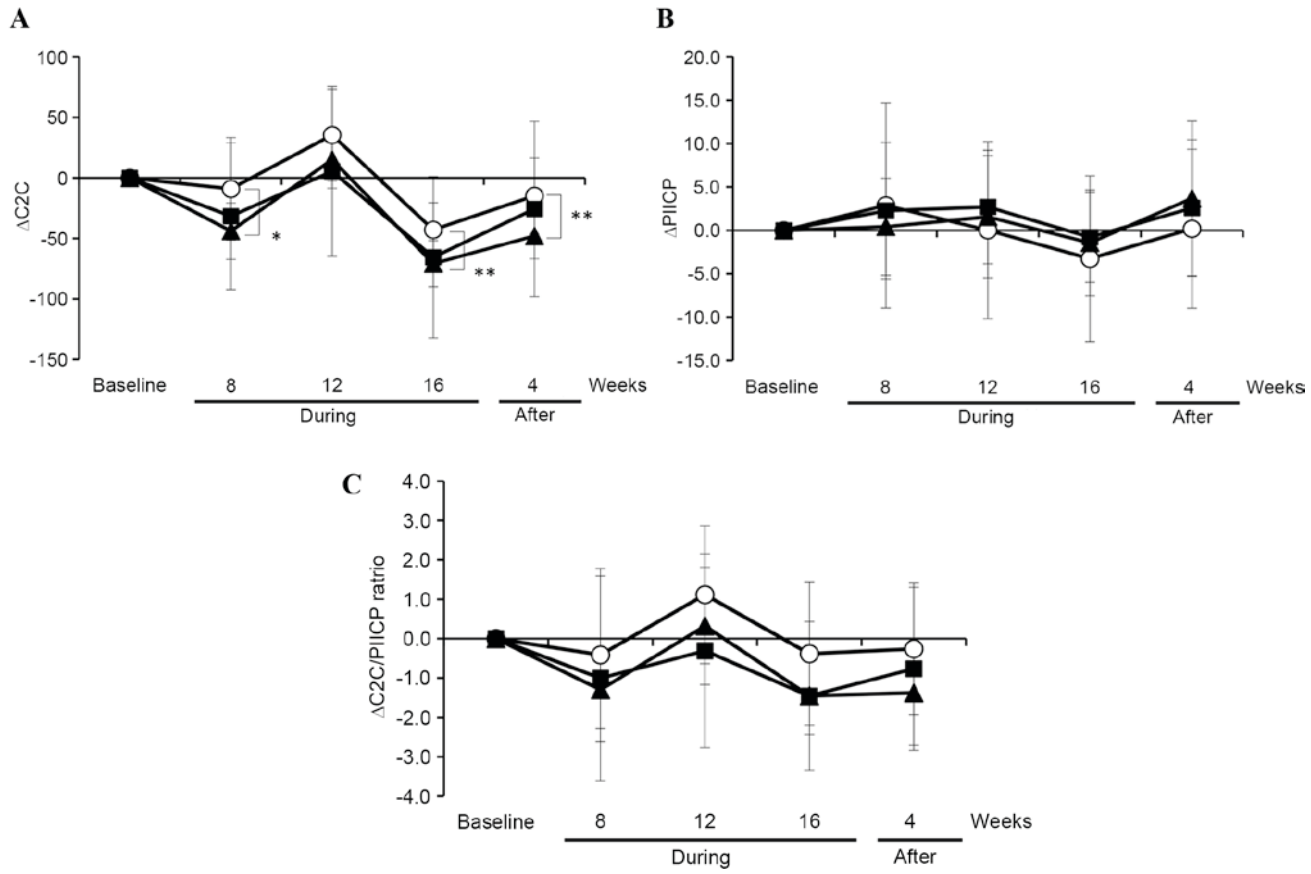

Figure 3. Changes of C2C, PIICP and the ratio of C2C and PIICP in subjects in the placebo and GlcNAc groups with enhanced type II collagen degradation and lowed type collagen synthesis in the articular cartilage during and after the intervention. (A) C2C and (B) PIICP were analyzed, and (C) the ratio of C2C and PIICP was calculated using serum samples collected from 39 subjects (at the baseline, C2C≥210 ng/ml and PIICP<55 ng/ml) in the placebo (n=13; open circles), 500 mg/day GlcNAc (n=12; closed triangles) and 1,000 mg/day GlcNAc (n=14; closed squares) groups during and after the intervention. Data are expressed as the mean ± standard error. The unpaired *t*-test was used to evaluate between-group differences. Holm step-down adjustment was used to correct for the multiple pairwise comparisons. *P<0.05; **P<0.01. C2C, collagen type II cleavage; GlcNAc, N-acetylglucosamine; PIICP, procollagen type II carboxy-terminal propeptide; During, during the intervention; After, After the intervention; Open circles, placebo; closed triangles, 500 mg/day GlcNAc; closed squares, 1,000 mg/day GlcNAc.

Discussion

In the present randomized, double-blinded, placebo-controlled study, the effect of GlcNAc on serum biomarkers of type II collagen metabolism using healthy subjects without symptoms of arthritis (0 and I of K/L grades) was evaluated. Previous studies have indicated the efficacy of GlcNAc for pain relief and improvement of motion in knee OA subjects (15,21). In addition, GlcNAc administration not only reduced subjective symptoms but also improved the metabolism of type II collagen by relatively increasing the synthesis of type II collagen compared to degradation in knee OA subjects (22,23). However, it remains to be elucidated how GlcNAc administration exhibits this beneficial action on healthy individuals without symptoms of OA. In the present study, there was no significant change in the biomarkers for type II collagen degeneration and synthesis during and post-intervention among the placebo and two GlcNAc groups, using all subjects who completed the study. However, the subgroup analysis, using subjects with enhanced type II collagen degradation and lowed type II collagen synthesis (C2C ≥210 ng/ml and PIICP <55 ng/ml), indicated that the C2C/PIICP ratio was markedly decreased at 12 and 16 weeks during the intervention in the two GlcNAc groups compared with the placebo group. In addition, significant suppression of type II collagen degradation in the GlcNAc (500 mg/day) group was demonstrated when compared with the placebo group, as evidenced by the changes of serum C2C levels. However, GlcNAc administration did not significantly increase the synthesis of type II collagen (serum PIICP), although GlcNAc significantly increased the synthesis of type II collagen in the subjects with arthritis (22,23). Together these observations suggest that GlcNAc administration at doses of 500 and 1,000 mg/day similarly suppresses type II collagen degradation in the articular cartilage of healthy individuals without symptoms of arthritis. Conventionally, pharmacotherapy of OA is limited to the administration of anti-inflammatory agents for pain relief and the intra-articular injection of hyaluronan for supplementation of synovial fluid; there has been no effective agent that regenerates articular cartilage. Thus, the present results suggest that GlcNAc has the potential to improve the metabolism of cartilage by suppressing the degradation of type II collagen in the joints.

In regard to the action of orally administered GlcNAc on OA, GlcNAc is reported to be incorporated into glycosaminoglycans, proteoglycans and synovial fluid. A prior study on the oral administration of radiolabeled GlcNAc into animals indicated that radioactivity in the blood peaked at 4 h following administration and then rapidly decreased; however, the

residual activity (24.7%) remained in the body even at 168 h post-administration (24). Moreover, autoradiograms revealed that the residual radioactivity was distributed in the various glycosaminoglycan-containing tissues, such as the skin, cartilage and eyes, suggesting that the administered GlcNAc is utilized for the biosynthesis of glycosaminoglycans. Notably, a previous study revealed that oral administration of GlcNAc to the experimental cartilage injury model demonstrated that injuries were significantly repaired by GlcNAc administration, accompanied with the synthesis of glycosaminoglycans and proteoglycans (25).

In addition, GlcNAc was also reported to stimulate hyaluronan synthesis via the upregulation of hyaluronan synthase-2 in human articular chondrocytes (26). Hyaluronan is reported to inhibit interleukin (IL-) 1β-induced matrix metalloproteinase-13 expression and IL-1α-induced expression of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-4 through CD44 signaling in arthritic chondrocytes (27,28). Moreover, GlcNAc inhibits the IL-1β-induced gene expression and production of nitric oxide, cyclooxygenase-2 and IL-6 in human articular chondrocytes (29). Based on these observations and the present study, we hypothesize that GlcNAc exerts chondroprotective and anti-inflammatory effects, possibly by suppressing the degradation of type II collagen in the joints of healthy individuals due to the inhibition of cartilage degrading enzymes (such as the matrix metalloproteinases and ADAMTS) via the upregulation of hyaluronan synthesis.

GlcNAc has been used safely in multiple clinical trials; no adverse effects have been observed at >2,000 mg/kg/day of GlcNAc, based on previous chronic toxicity and carcinogenicity studies (30). In the present study, no serious adverse events after oral administration of GlcNAc were exhibited. In contrast, administration of glucosamine hydrochloride or sulfate may induce insulin resistance and progression of diabetes, since glucosamine has the potential to inhibit glucokinase in glucose metabolism. GlcNAc has a lower affinity for glucokinase when compared with glucosamine and therefore does not notably affect glucose metabolism (31). Furthermore, a previous study has demonstrated that 12-week administration of GlcNAc (1,250 mg/day) does not affect the levels of blood glucose, glycoalbumin and haemoglobin A1c (15). In the present study, blood glucose levels were not significantly changed in the GlcNAc groups (500 and 1,000 mg/day). Thus, this suggests that GlcNAc may be safe to administer as a supplement.

Glucosamine and GlcNAc are reported to clinically alleviate knee OA; however, GlcNAc likely exhibits a potential effect on the cartilage metabolism at a lower dose (500-1,000 mg/day) compared with glucosamine (1,500 mg/day), based on the present and previous results (32). In addition, the taste of GlcNAc is sweet and more appealing than glucosamine, which is salty and bitter. To conclude, the present study revealed that GlcNAc can be safely administered as an appealing dietary supplement, and oral administration of GlcNAc may improve the type II collagen metabolism of articular cartilage in healthy subjects without symptoms of arthritis.

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