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The Effects of Chondroitin and/or Glucosamine on Patients with Kashin-Beck Disease

Xiaofang Wu, MD; Jing Han, PhD; Jianhua Yi, MD; Zuyong Wang, PhD; Chengjuan Qu, PhD; Danyang Li, MD; Fangfang Yu, PhD; Xiong Guo, MD

SUMMARY
Kashin-Beck disease (KBD), an endemic disease, is a special type of osteoarthritis (OA). Nowadays, due to prevention and treatment methods including selenium supplements, changing grains and water source as well as health education, the morbidity of KBD is reduced significantly as compared to that in the 1950s. However, many elderly adult KBD patients are still suffering from the degenerative changes of cartilage, pain, stiffness and deformation of joints, which are quite similar or even more serious than OA. Chondroitin sulfate and glucosamine have been widely used as symptomatic slow-acting drugs for the treatment of OA. Although their therapeutic effects, biochemical data, pharmacokinetics, preclinical studies, safety and economic evaluation have been well investigated in OA, they are not clearly studied in KBD. In this review, we will evaluate the clinical evidence (randomized controlled trials and non-randomized controlled trials), safety and cost-effectiveness of chondroitin sulfate and glucosamine for the treatment of KBD. Moreover, the therapeutic mechanisms of chondroitin sulfate and glucosamine are also discussed in details.

KEYWORDS
Kashin-Beck disease; Chondroitin sulfate; Glucosamine; Safety; Cost-effectiveness; Therapeutic mechanisms


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Kashin-Beck disease (KBD) is a chronic endemic disease (1). The morbidity and prevalence of KBD are higher in certain regions, from northeast to southwest of China, from south-eastern Siberia to North Korea (2). The degenerative changes of cartilage, similar to osteoarthritis (OA), are the main pathological features of KBD (3). Most of the patients suffering from KBD are started from their childhood. With the progress of the disease, pain in joints, enlarged and deformed joints become more and more serious, which leads to the damage of cartilage and joints. Even worse, some patients have become disabled or semi-disabled (4).

There are three factors proposed as the etiology of KBD, including deficiency of selenium, mycotoxin contamination of cereal grains, and poisoning of organic compounds in drinking water (5-7). For the prevention and treatment of KBD, selenium supplements, changing grains and water source as well as health education are carried out (8). Meanwhile, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to alleviate the joint pain in the treatment of KBD (9-11). Hyaluronic, chondroitin sulfate and glucosamine also have been used in the treatment of KBD for protecting and repairing the cartilage (12-14).

Chondroitin sulfate, a kind of glycosaminoglycans (GAGs), is widely distributed in the extracellular matrix (ECM) of animal connective tissues. The carbohydrate chains of chondroitin sulfate compose of repeated units of sugar residues, including glucuronic acid and N-acetyl galactosamine. The alternations of carbohydrate chains in chondroitin sulfate are demonstrated to be related with the damages of cartilage in OA (15). Glucosamine is also known as an amino sugar in which one hydroxyl group has been replaced by an amine group. Glucosamine is an important nutrient in stimulating the formation and growth of chondrocytes. Glucosamine could relieve pain, stiffness and swelling caused by OA. With aging process, the content of glucosamine is reduced in the joints, and the degeneration of articular cartilage is increased in OA and KBD patients (16-17).

The application of chondroitin sulfate or glucosamine has been carried out for the treatment of OA for decades. The therapeutic effects, the biochemical data, pharmacokinetics, preclinical studies, safety and economic evaluation of chondroitin sulfate and glucosamine in OA are well established (18-20). In recent years, chondroitin sulfate and/or glucosamine have also been applied in the treatment of KBD (21-22). However, the recognition of their therapeutic effectiveness and mechanism as well as safety and cost effectiveness in the treatment of KBD patients still remains unclear. In this review, we systematically summarize the clinical evidence, safety and cost-effectiveness of chondroitin sulfate and/or glucosamine for the treatment of KBD, and discuss their potential therapeutic mechanism in KBD treatment.

**Review**

**Clinical Evidence**

**Randomized Controlled Trials (RCTs) of Chondroitin Sulfate in the Treatment of KBD**

The treatment effects of chondroitin sulfate on KBD were reported in two randomized controlled trials (RCTs). Study by Yue et al (14) was related to the comparison of chondroitin sulfate with placebo. From Table 1, there was no statistical difference in the changes of Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain and physical function scores in the chondroitin sulfate group when compared with placebo group; however, the WOMAC stiffness score decreased significantly in the chondroitin sulfate group (P<0.05). In another trial performed by Li et al (23) described the effects of chondroitin sulfate on the treatment of KBD by the comparison with several nonsteroidal anti-inflammatory drugs (NSAIDs). The results indicated that chondroitin sulfate effectively improved the joint stiffness and physical function; meanwhile, celecoxib and meloxicam obviously reduced the joint pain rather than the joint stiffness (Table 2).

**RCTs of Glucosamine in the Treatment of KBD**

Three RCTs evaluated the effectiveness of glucosamine on the patients of KBD. Two trials compared the effects of glucosamine with placebo, which were conducted in KBD endemic areas including Sichuan and Shaanxi Province in China, respectively (Table 1). However, the dosage strategies of glucosamine were extremely different, the trial by Yue et al (14) administrated 1 440 mg glucosamine hydrochloride daily for 6 months, and the trial by Xia et al (13) prescribed 1 500 mg glucosamine sulfate daily for 3 months (Table 1). It is reported that there was no significant difference in the changing of WOMAC pain, stiffness and physical function scores between glucosamine hydrochloride and placebo.
Table 1. RCTs of Chondroitin and/or Glucosamine Compared with Placebo

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment/Comparison (daily)</th>
<th>Follow Up (wk)</th>
<th>Number of Participants (Begin-End)</th>
<th>Mean Changes of WOMAC Score (P Value)</th>
<th>Mean Changes of Joint Space Narrowing (P Value)</th>
<th>Adverse Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yue et al. 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Chondroitin (1 200 mg)/Placebo</td>
<td>1-24</td>
<td>64-54/62-51</td>
<td>0.055</td>
<td>0.023</td>
<td>0.057</td>
</tr>
<tr>
<td>Xia et al. 2014&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Glucosamine (1 500 mg)/Placebo</td>
<td>1-20</td>
<td>50-45/50-46</td>
<td>0.040&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.113</td>
<td>0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yue et al. 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Glucosamine (1 440 mg)/Placebo</td>
<td>1-24</td>
<td>62-51/62-51</td>
<td>0.488</td>
<td>0.646</td>
<td>0.924</td>
</tr>
<tr>
<td>Yue et al. 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Chondroitin (1 200 mg) and Glucosamine (1 440 mg)/Placebo</td>
<td>1-24</td>
<td>63-52/62-51</td>
<td>0.032&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.043&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.055</td>
</tr>
<tr>
<td>Zhang et al. 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Chondroitin (1 600 mg) and Glucosamine (1 600 mg)/Placebo</td>
<td>1-32</td>
<td>40-31/40-35</td>
<td>&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td>16.1/18</td>
</tr>
</tbody>
</table>

Chondroitin means chondroitin sulfate; Glucosamine means glucosamine hydrochloride.  
<sup>*</sup>: P<0.05, All P values are for the comparison with the placebo group.

(P>0.05) by Yue et al. However, the research by Xia et al showed that WOMAC pain and physical function scores were found to be obviously reduced (P<0.05) in the glucosamine sulfate group rather than in placebo group (Table 1). Obviously, glucosamine sulfate was much better than glucosamine hydrochloride in decreasing the WOMAC pain, stiffness and physical function scores of KBD patients, which might due to the difference in the acid radical of the two types of glucosamine. The metabolic disorders of sulfur in the cartilage of KBD were found earlier, from the article by Luo et al (24), it was reported that the sulfation of GAGs could affect many physiological processes. It has also been suggested that the reason for the effectiveness of glucosamine sulfate could be the increased level of sulfate in plasma and synovial fluid after oral administration of glucosamine sulfate (25).

In addition, there was another trial by Liu et al (4) which included two kinds of NSAIDs (Diclofenac sodium and Naproxen) as positive controls for investigating the therapeutic effect of glucosamine on KBD (Table 2). Total of 183 patients were recruited in this study with taking the three drugs for 6 weeks. It was found that the WOMAC pain and physical function scores decreased after treatments when compared with baseline values in different drug groups (P<0.05). The WOMAC stiffness scores showed little change, but no statistically significant difference, before and after treatments. Additionally, no statistically significant difference was found between the treatments of glucosamine and NSAIDs with respect to change in the WOMAC scores (P>0.05).

RCTs of the Combination of Chondroitin Sulfate and Glucosamine in the Treatment of KBD

Yue et al (14) compared the changes of WOMAC pain, stiffness and physical function scores between the combination of chondroitin sulfate and glucosamine hydrochloride v.s. chondroitin sulfate or glucosamine hydrochloride or placebo groups. After treatment, the WOMAC pain and stiffness scores statistically significantly decreased (P<0.05) in the combination group compared with placebo group (Table 1). However, no significant differences could be visible on the WOMAC pain and stiffness scores when KBD patients were administered with chondroitin sulfate or glucosamine hydrochloride alone as compared to the placebo group, although the rate of response in chondroitin sulfate or glucosamine hydrochloride group were higher than that in the placebo group. The results suggested that the combination group had better treatment effects for KBD than them used alone (Table 1). Zhang et al (26) and Liu et al (27) investigated the change of joint space narrowing as the main outcome. It was found that the mean
Table 2. RCTs of Chondroitin or Glucosamine Compared with NSAIDs

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment (dose)</th>
<th>Follow Up (wk)</th>
<th>Number of Participants (Begin/End)</th>
<th>WOMAC Pain Score</th>
<th>WOMAC Stiffness Score</th>
<th>WOMAC Function Score</th>
<th>Adverse Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRT</td>
<td>POT</td>
<td>PRT</td>
<td>POT</td>
</tr>
<tr>
<td>Li et al. 2009</td>
<td>Chondroitin (900 mg)</td>
<td>1-24</td>
<td>100/100</td>
<td>18.20±0.76</td>
<td>18.09±0.79</td>
<td>7.52±0.35</td>
<td>6.17±0.37</td>
</tr>
<tr>
<td></td>
<td>Celecoxib (200 mg)</td>
<td></td>
<td>100/100</td>
<td>19.18±0.56</td>
<td>13.75±0.79</td>
<td>6.73±0.45</td>
<td>6.92±0.51</td>
</tr>
<tr>
<td></td>
<td>Meloxicam (7.5 mg)</td>
<td></td>
<td>40/40</td>
<td>19.07±0.64</td>
<td>14.35±0.75</td>
<td>7.17±0.41</td>
<td>7.63±0.45</td>
</tr>
<tr>
<td>Liu et al. 2012</td>
<td>Glucosamine (1 500 mg)</td>
<td>1-6</td>
<td>70/68</td>
<td>10.71±2.95</td>
<td>9.60±2.53</td>
<td>2.40±2.17</td>
<td>2.43±2.05</td>
</tr>
<tr>
<td></td>
<td>Diclofenac (100 mg)</td>
<td></td>
<td>55/50</td>
<td>10.82±3.43</td>
<td>9.02±3.11</td>
<td>2.18±1.79</td>
<td>1.84±1.53</td>
</tr>
<tr>
<td></td>
<td>Naproxen (600 mg)</td>
<td></td>
<td>70/65</td>
<td>11.53±2.82</td>
<td>9.96±2.95</td>
<td>2.06±1.77</td>
<td>1.79±1.54</td>
</tr>
</tbody>
</table>

Chondroitin means chondroitin sulfate; Glucosamine means glucosamine hydrochloride.


Values are presented as mean ± SD.

The significance of P value in the study of Liu et al. were extracted from the original article and representing the comparison of post-treatment with pretreatment, ***P<0.001, **P<0.01, *P<0.05.

Table 3. Cost-effectiveness Analysis of Chondroitin or Glucosamine in the Treatment of KBD Patients

<table>
<thead>
<tr>
<th>Studies</th>
<th>Treatment/Comparison</th>
<th>Follow Up (wk)</th>
<th>Number of Participants</th>
<th>Calculations of Effect Indicators</th>
<th>Cost (CNY per Person)</th>
<th>Effect Indicators</th>
<th>Cost-effectiveness Rations (C/E)</th>
<th>Incremental Cost-effectiveness Rations (ΔC)/(ΔE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. 2009</td>
<td>Chondroitin sulfate</td>
<td>20</td>
<td>100/100</td>
<td>Changes of WOMAC score</td>
<td>215.93/954.32</td>
<td>2.48/6.17</td>
<td>87.07/154.67</td>
<td>200.11</td>
</tr>
<tr>
<td></td>
<td>/Celecoxib</td>
<td></td>
<td></td>
<td>Effective rate: WOMAC index score</td>
<td>7%/31%</td>
<td></td>
<td>3 085/3 078</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>improvement ≥ 20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu et al. 2014</td>
<td>Glucosamine sulfate</td>
<td>24</td>
<td>50/50</td>
<td>Effective rate: Joint dysfunction</td>
<td>1 468/860</td>
<td>62.6%/80%</td>
<td>2 345/1 075</td>
<td>-3 494</td>
</tr>
<tr>
<td></td>
<td>/Hyaluronic</td>
<td></td>
<td></td>
<td>index score improvement ≥ 30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C: Cost; E: Effectiveness; ΔC: the difference between the cost of chondroitin sulfate and glucosamine; ΔE: the difference between the effectiveness of chondroitin sulfate and glucosamine on KBD treatment.
change of joint space narrowing were evidently smaller in the combination group than that in the placebo group (P<0.05), which confirmed that the application of chondroitin sulfate plus glucosamine medications could protect the articular cartilage of KBD patients from further damage.

**Non-RCTs of Chondroitin Sulfate or Glucosamine in the Treatment of KBD**

Study by Liu et al (28) enrolled 44 KBD patients with receiving intravenous Yunke injection (technetium-99 methylenediphosphonate) and oral chondroitin sulfate medication in the intervention group, and other 35 KBD patients with only receiving intravenous Yunke injection in the control group from Hulun Buir (KBD endemic area of China). Three months later, the WOMAC index change, grip strength, 15-minute walking time and blood calcium were found to be significantly improved after the treatment in the two groups separately. However, there was no statistical significance between the therapeutic effects of the two groups. With more participants, longer treatment period and placebo as comparator, the treatment effects of chondroitin sulfate for KBD patients would be verified.

To observe the effects of chondroitin sulfate, meloxicam and vitamins in the treatment of KBD, Xing et al (29) selected 405 KBD patients, and divided them into four treatment groups (chondroitin sulfate and vitamin E, meloxicam and vitamin E, chondroitin sulfate and vitamin C, and chondroitin sulfate alone, respectively). The results from this study showed that the comprehensive evaluation index of joint dysfunction in the experiment group were 29.73%, 34.68%, 34.97% and 42.95%, respectively. All the drugs had a certain therapeutic effect. Additionally, chondroitin sulfate alone had the best therapeutic effect for KBD patients among the four groups, but this conclusion still needed to be confirmed by standard RCTs.

**Safety and Cost-effectiveness Analyses**

**Safety Analysis**

All the RCTs mentioned the adverse events. Study by Yue et al (14) showed that no significant difference in the incidence of adverse events between the chondroitin sulfate and placebo groups (P>0.05) (Table 1). Li et al (23) suggested taking NSAIDs after meal, so that no adverse events were reported in chondroitin sulfate group and NSAIDs group (Table 2). The adverse events for glucosamine mainly were gastrointestinal symptoms including dyspepsia, abdominal pain, diarrhea and nausea. Both studies by Xia et al (13) and Yue et al (14) reported that there was no difference in the incidence of adverse events between glucosamine group and placebo group (P>0.05) (Table 1). Liu et al (4) performed a 6-week trial, there was also no difference in the incidence of adverse events between glucosamine group and NSAIDs group (P>0.05) (Table 1). In addition, studies performed by Yue et al (14) and Zhang et al (26) found no significant difference in the incidence of adverse events between the combinations of chondroitin sulfate/glucosamine sulfate or glucosamine hydrochloride and placebo (P>0.05) (Table 1).

**Cost-effectiveness Analysis**

Liu et al (30) had analyzed the cost-effectiveness of chondroitin sulfate in the RCTs study of KBD patients performed by Li et al (23). Meanwhile, Yu et al (31) analyzed the cost-effectiveness of glucosamine in the RCTs study carried out by Xia et al (13). The results of cost-effectiveness analysis of chondroitin sulfate or glucosamine were presented in Table 3, which illustrates the calculations of WOMAC index change, effective rate (ER), cost-effectiveness (C/E) ration and the incremental cost-effectiveness (ΔC/ΔE) ratio. Liu et al (30) and Yu et al (32) calculated ER by WOMAC index score change ≥ 20% or joint dysfunction index change ≥ 30% as effective indicators, respectively. In the study of Liu et al (30), if using WOMAC index change as effect indicator, the C/E ratios of chondroitin sulfate group and celecoxib group were 87.07 CNY v.s. 154.67 CNY, respectively, the ΔC/ΔE of celecoxib group was 200.11 CNY compared with chondroitin sulfate group; however, when the effective rate was used as effect indicator, the C/E ratios were 3 085 CNY v.s. 3 078 CNY, respectively, the ΔC/ΔE was 3 077 CNY. From the results, chondroitin sulfate can be considered better than celecoxib for KBD treatment. But this is not absolute, if there were sufficient funds, the celecoxib should be still recommended. The study performed by Yu et al (31) showed that the ratio of glucosamine sulfate and hyaluronic acid were 2 345 CNY and 1 075 CNY, respectively, after 6-month treatment to KBD patients. Hyaluronic acid was better than glucosamine sulfate because of its good curative effect and low cost (the ΔC/ΔE of glucosamine sulfate was -3 494).
Therapeutic Mechanisms of Chondroitin Sulfate and Glucosamine

Compensating for the Loss of Matrix

Chondroitin sulfate was one of the main GAGs in the forming of proteoglycans (PG), which composed the ECM together with collagen fibers in articular cartilage. ECM, serving as the “living environment” of chondrocytes, affected the functions and metabolisms of chondrocytes in turn. Recently, lots of evidences suggested that the maintenance and performance of PG functions were affected by the sugar chains of chondroitin sulfate in a great degree (24). Moreover, loss of PGs in the ECM and death of focal chondrocyte in articular cartilage were observed in KBD patients, or animal models (32, 33).

In the early stage of KBD patients, chondroitin sulfate had already been found to have a significant decrease in contrast to normal healthy controls (34). Zhang et al (35) qualitatively observed the difference of articular cartilage PG component in normal children and KBD children using alcian blue staining method; it was found that keratin sulfate and chondroitin sulfate in the articular cartilage of KBD children were reduced. In addition to the decreased content of chondroitin sulfate in the KBD patients (34), the sulfation extent of mucopolysaccharides of KBD patients was also lower than that in the normal cartilage (36). Chang et al (37, 38) also verified the above observation by breeding the rhesus monkey with the water and food taken from KBD endemic area, it was reported that keratin sulfate and chondroitin sulfate in the articular cartilage of KBD children were reduced. In addition to the decreased content of chondroitin sulfate in the KBD patients (34), the sulfation extent of mucopolysaccharides of KBD patients was also lower than that in the normal cartilage (36). Chang et al (37, 38) also verified the above observation by breeding the rhesus monkey with the water and food taken from KBD endemic area, it was reported that keratin sulfate and chondroitin sulfate in the articular cartilage of KBD children were reduced.

According to a previous study (43), selenium deficiency could make the cartilage premature aging, such as the reduction of sulfated polysaccharide in cartilage and the ratio of chondroitin sulfate and collagen. Tan et al (44, 45) had investigated the water quality in KBD endemic areas. As a result, chondroitin sulfate enzyme was found to be produced by the anaerobic bacteria detected in the water, which could destroy the structure of chondroitin sulfate and damage the ECM of cartilage. Meanwhile, T-2 toxin, a commonly detectable mycotoxin in most of the KBD areas, was highly considered as one of etiologies for KBD occurrence and development. Thus nano-selenium-chondroitin sulfate nanoparticles produced by Han et al (46) were combined the pharmacological effects of chondroitin sulfate and nano-selenium, and observed effectively in inhibiting the apoptosis of cultured chondrocyte induced by T-2 toxin.

Glucosamine was an amino saccharide, which could be used as synthetic raw materials for the synthesis of many glycans, including chondroitin sulfate as well. It is demonstrated that oral administration of glucosamine could control the degradation of cartilage effectively by increasing the level of hyaluronic acid and chondroitin sulfate in an OA rabbits’ model (47). Additionally, it was also reported that glucosamine increased the synthesis of PGs by increasing the expression of protein kinase C (PKC) levels in the OA chondrocyte cultures (17).

Dong (48) had conducted an epidemiological observation on the mechanism of chondroitin sulfate and glucosamine in the treatment of KBD patients. In this epidemiological test, four biochemical markers including unsaturated disaccharides (ΔDi-0S and ΔDi-4S), pyridine (PYD) and hydroxyproline (HYP), have been measured. ΔDi-0S and ΔDi-4S reflected the changes of mucopolysaccharide metabolism in cartilage, yet PYD and HYP incarnated the changes of collagen metabolism. At the end of the experiment, all the four biochemical markers had been significantly decreased in the experimental group, but significantly increased in the placebo group, which indicated that the degeneration and de-
struction of cartilage matrix was controlled and alleviated in the experimental group of KBD patients due to the medication, but continued in the control group of KBD patients.

**Anti-oxidative and Anti-inflammatory Effects**

Many studies reported the effect of chondroitin sulfate in several arthritis animal models (49, 50); chondroitin sulfate proved to be effective in reducing synovitis, hind paw edema and destruction of cartilage by resisting oxidative stress and inflammation. Furthermore, chondroitin sulfate was demonstrated to play an important role in enhancing efficiency of Cathepsin K (CatK) collagenase activity, which was produced by osteoclasts and played an important role in the resorption of bone (51, 52).

In addition, it was found that glucosamine could alleviate the inflammation of cartilage in several arthritis rats’ models (53). Glucosamine was usually applied together with chondroitin sulfate for the treatment of OA and KBD. The combination of chondroitin sulfate and glucosamine was found to alleviate the joint pain and stiffness of KBD patients (14) and significantly relieve moderate to severe pain in knees of OA patients. Moreover, the combination might improve knee stiffness and function limitation in OA better than celecoxib as well (54, 55). In in vitro animal studies, it was reported that glucosamine and chondroitin sulfate could reduce the inflammation by inhibiting NF-κB, a main inflammatory pathway (56, 57). A randomized, placebo-controlled, double-blind cross-over study also demonstrated that glucosamine and chondroitin could significantly reduce the systemic inflammation by decreasing serum C-reactive protein concentration in the healthy overweight adults (58).

**Conclusion**

This review has clearly shown the effectiveness of chondroitin sulfate and/or glucosamine in the treatment of KBD. The combination of chondroitin sulfate and glucosamine is highly recommended for the KBD treatment rather than chondroitin sulfate or glucosamine used alone. Meanwhile, glucosamine sulfate might be better than glucosamine hydrochloride for the KBD treatment due to its physiological functions of sulfate groups in vivo. In the treatment of KBD, the main therapeutic mechanism of chondroitin sulfate and glucosamine involves compensation for the matrix loss of cartilage, anti-oxidative and anti-inflammatory effects. However, more long-term high-quality trials are still necessary for evaluating the effects of chondroitin sulfate, glucosamine and their combination on KBD treatment. Moreover, preclinical studies are still needed to illustrate their therapeutic mechanism in the treatment of KBD. Safety and cost-effectiveness analyses of chondroitin sulfate and/or glucosamine are also needed by selecting other appropriate drugs for KBD treatments.

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**Critical revision of the manuscript for important intellectual content:** Yi J, Qu C. 

**Statistical analysis:** Li D. 

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**Study supervision:** Guo X. 

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