Clinical Rheumatology (2019) 38:3595–3607
https://doi.org/10.1007/s10067-019-04704-0

ORIGINAL ARTICLE

The effectiveness of treatments for Kashin–Beck disease: a systematic review and network meta-analysis

Kun Zou[1] · Jinliang Hu[2] · Qiao Zhou[3] · Jiang Su[3] · Birong Dong[4] · Weiya Zhang[5]

Received: 20 June 2019 / Revised: 8 July 2019 / Accepted: 17 July 2019 / Published online: 2 August 2019

Abstract

Objectives This study aims to evaluate the efficacy of treatments for Kashin–Beck disease (KBD).

Method We searched PubMed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, SinoMed, Chinese National Knowledge Infrastructure, reference lists and published systematic reviews and registries of ongoing trials through May 2015 for randomised controlled trials (RCTs) of treatments for KBD. Outcomes of interest were pain, function, stiffness, overall clinical improvement, radiographic improvement (X-ray) and adverse events. Frequentist network meta-analyses were conducted using random-effects consistency model to assess the efficacy of treatments for KBD.

Results Forty-four RCTs with 9815 participants were included in the review. In children or adolescents, selenium (risk ratio 1.88, 95% confidence interval (CI) 1.51–2.33), vitamin C (2.03, 1.40–2.95) and aspirin (2.14, 1.12–4.08) were effective for radiographic structure improvement. In adults, chondroitin plus glucosamine was the best for pain (standardised mean difference 1.46, 95% CI 1.07–1.85), followed by intra-articular injection of hyaluronic acid (IAH) (1.09, 0.70–1.48), chondroitin (0.84, 0.47–1.21), diclofenac (0.63, 1.18–1.08), naproxen (0.55, 0.12–0.98), meloxicam (0.52, 0.03–1.01) and glucosamine (0.40, 0.13–0.67) compared to placebo, with similar results for other clinical outcomes in adults. However, the strength of most evidence was limited by the small number of trials with low to moderate quality.

Conclusions Selenium supplement has demonstrated some benefits for structural improvement of the disease in children. Chondroitin, glucosamine, IAH and nonsteroid anti-inflammatory drugs are effective for symptom improvements of KBD in adults. Evidence of surgical and complementary treatments for symptoms and aspirin and vitamin C for structure has yet to be established.

Key Points

- *There were 23 nutraceuticals, pharmaceuticals and surgical and complementary treatments assessed for Kashin–Beck disease (KBD) in randomised trials.*
- *Among the 23 treatments, chondroitin, glucosamine, IAH and non-steroid anti-inflammatory drugs are more effective than placebo to relieve symptoms for adults with KBD.*
- *Selenium supplement is more effective than placebo for radiographic improvement in children or adolescents.*
- *The efficacy of surgeries, aspirin, vitamin C and complementary treatments for KBD has not been established yet.*

Kun Zou and Jinliang Hu contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10067-019-04704-0) contains supplementary material, which is available to authorized users.

✉ Weiya Zhang
weiya.zhang@nottingham.ac.uk

[1] West China Research Centre of Rural Health Development, Department of Health Policy and Management, West China School of Public Health, West China Forth Hospital, Sichuan University, Chengdu, China

[2] Institution of Health Policy and Hospital Management, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Affiliated Hospital of the University of Electronic Science and Technology, Chengdu, China

[3] Department of Rheumatology and Immunology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Affiliated Hospital of the University of Electronic Science and Technology, Chengdu, China

[4] Centre of Gerontology and Geriatrics, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, China

[5] Academic Rheumatology, Division of Rheumatology, Orthopedics and Dermatology, School of Medicine, Nottingham City Hospital, University of Nottingham, Room A18, Hucknall Road, Nottingham NG5 1PB, UK

Keywords Beck disease · Efficacy · Kashin · Network meta-analysis · Randomised controlled trials · Systematic review · Treatments

Introduction

Kashin–Beck disease (KBD) is an endemic osteoarthropathy with unclear aetiology [1]. Nutrient (selenium or iodine) deficiency, toxicity (humic acid) in water and mycotoxins in grains have been suggested as causes of the disease, but none was conclusive [2–8]. To date, it is believed that multifaceted aetiologies are involved in the disease [9]. KBD usually starts from childhood or adolescence, causing joint deformation (big joint), decreased limb length and short stature, persistent pain and function limitations. The most affected joints are ankles, knees, waists and elbows [10, 11]. In China, KBD is geographically distributed like a ribbon spanning from northeast to southwest across 15 provinces including Heilongjiang, Shaanxi, Sichuan and Tibet. Approximately three million people are affected, with a prevalence of 8.0 to 43.4% [12, 13]. Although the prevalence is declining recently, new cases are still occurring [14].

From the 1970s, the Chinese authority and scientific community have launched several waves of national endeavours to tackle the endemic KBD [1, 15]. These endeavours include exploring the aetiology and epidemiology of KBD and, more recently, prevention and treatments of the disease. Similar to osteoarthritis, treatments of KBD primarily or mainly aim to relieve pain and improve function, since the impairment of cartilage, bone and joint is hard to reverse. A number of randomised controlled trials (RCTs) have been conducted. Two systematic reviews suggested selenium and intra-articular injection of hyaluronic acid (IAH) were more effective than placebo, no treatment or other treatments [16, 17]. However, the effectiveness of other treatments, for example, non-steroid anti-inflammatory drugs (NSA), surgeries and complementary treatments, has not been systematically reviewed. This is because many of them have never been compared with placebo in RCTs. In addition, the comparative efficacy of these treatments compared with each other is unclear as head-to-head comparisons of these treatments (direct evidence) in RCTs are substantially lacking.

We therefore undertook this comprehensive systematic review attempting to gather all RCT evidence in KBD, including placebo-controlled, no treatment-controlled and active treatment-controlled trials. We used a network meta-analysis (NWM) method to link different treatments together through a common comparator (node). This would allow us to estimate both the efficacy of a treatment versus placebo/no treatment and the relative efficacy between treatments, with all direct and indirect evidence [18].

Methods

Eligible criteria

We included all RCTs comparing a treatment with placebo, no treatment or active comparators for KBD, reporting at least one of the following clinical outcomes: radiographic structure improvement (X-ray manifestation) [19, 20], pain score, function score, stiffness score, clinical improvement score (e.g. Western Ontario and McMaster Universities Arthritis Index (WOMAC) total score), clinical improvement rate (e.g. according to national criteria [20] or a specific cut-off of pain or function scale defined by the researcher) and adverse events. Studies evaluating only laboratory outcomes were excluded. We searched English and Chinese databases (below) with no language restriction on the selection of eligible studies.

Search strategy

We searched databases of PubMed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, SinoMed (CMB) and Chinese National Knowledge Infrastructure (CNKI) from the inception to May 2015. Mesh and free texts related to "Kashin–Beck disease" were used. RCTs were searched using Cochrane Highly Sensitive Search Strategy for identifying randomised trials in PubMed and Embase [16] and adopted for Chinese literature database (online supplementary search strategy). We also searched Chinese Clinical Trial Registry (ChiCTR) and ClinicalTrials.gov for ongoing trials, reference lists of included studies and published systematic reviews.

Study selection, data extraction and quality appraisal

Two reviewers independently selected studies according to the inclusion criteria (KZ and JLH). One reviewer extracted the data and assessed the quality of all trials using a standard form (KZ), which was checked by another (JLH). Disagreements were resolved by discussion until a consensus was reached. Data extracted were first author, year, study location, age and gender of participants, treatments, duration and outcomes of interests. The quality of the study was assessed using Cochrane Risk of Bias tool in terms of generation of random sequence, allocation concealment, blinding of participants, blinding of assessor, incomplete data of outcome, selective reporting and other bias [16]. The quality of evidence for each outcome by comparison was assessed using the Grading of

Recommendations Assessment, Development, and Evaluation (GRADE) system as high, moderate, low and very low [18]. With the GRADE system, the quality of evidence may be downgraded/upgraded according to risk of bias, inconsistency (heterogeneity), indirectness and imprecision of the evidence [21, 22].

Statistical analysis

For meta-analysis, relative ratio (RR) was estimated for binary outcomes. Standardised mean difference (SMD) was estimated for continuous outcomes to standardise different outcome measures (e.g. VAS scale and WOMAC pain score for pain) across trials. Their 95% confidence intervals (CIs) were also estimated. The primary outcomes were radiographic improvement and pain. Secondary outcomes were function, stiffness, WOMAC total score and overall clinical improvement score/rate. For the primary outcome radiographic improvement, the endpoint closest to 12 months was chosen, considering the nature of radiographic changes. For other outcomes, the endpoint right after the last treatment was used in meta-analyses, most of which were of short to medium duration (≤ 6 months).

Frequentist NWM was conducted using the random-effects consistency model [23, 24]. A simplest example of network analysis is that a trial compares treatment A with B, and another compares treatment B with C, then the indirect comparison between A and C can be made through the shared comparator B, and the comparative effect of the three treatments can be estimated. In our study, the comparative efficacy of each treatment versus placebo and each other was estimated for all clinical outcomes. The rank (possibility of being the best treatment) of treatments was estimated and presented as surface under the cumulative ranking curves (SUCRA) [23]. The value of SUCRA ranges from 1 (the max probability to be the best treatment) to 0 (no chance of being the best). One important assumption of NWM is the consistency (inconsistency) of evidence, which refers to the similarity between direct evidence and indirect evidence of a comparison. In our study, the consistency was assessed using the node-split method and loop-specific heterogeneity estimates—the inconsistency factor (IF) [25, 26]. Publication or small study bias was examined using comparison-adjusted funnel plot for primary outcomes [23].

Additional analyses were conducted to estimate the overall effect size of NSA and traditional complimentary medicines (TCM) for pain, function, stiffness, WOMAC total score and clinical stiffness compared to placebo using NWM. In trials with two or more NSAIDs arms, the pooled effect of NSAIDs was estimated using Hedges' method [27], which was then used in the sensitivity NWM. We planned to do subgroup or sensitivity analysis to examine the impact of methodological quality on the estimates of effect size for the primary outcomes. However, it was not applicable for the limited number of available RCTs. Conventional meta-analysis was also conducted using random-effects model. The heterogeneity was examined using Q test and I^2, where $Q < 0.05$ or $I^2 \geq 50\%$ indicates significant heterogeneity. All analyses were conducted using STATA 13.0.

Results

Characteristics of included studies

We identified 698 citations through systematic literature search. After screening the title and abstract and full text reading, 44 trials were eligible for this study (Fig. 1). The characteristics of included studies are presented in Table 1. Of these, 24 trials were for children with KBD and 20 were for adults. Twenty-three treatments were assessed, including nutraceuticals (selenium (SE), iodine (IO), vitamin C (VC), yeast (YE), glucosamine (GLU) and/or chondroitin (CHO)), pharmacological (paracetamol (PAR), NSA including aspirin (ASP), celecoxib (CEL), diclofenac (DIC), ibuprofen (IBU), meloxicam (MEL), naproxen (NAP)), intra-articular injection of hyaluronic acid (IAH), surgical (arthroscopic debridement (AD), arthroscopic drilling decompression (DD)) and TCMs (KBD1 capsule, KBD2 capsule, KBD3 patch, KBD4 capsule, Xiao Huo Luo capsule (XHL), Kang Gu Zeng Sheng tablet (KGZ), trimming skin therapy (TST) and nerve electrical stimulation (NST)). The duration of the study ranged from 1 week to 48 months. A RCT comparing DIC, GLU and their combination with placebo is ongoing (ChiCTRTRC08000038). The quality of included studies is presented in Online Supplementary Fig. 1.

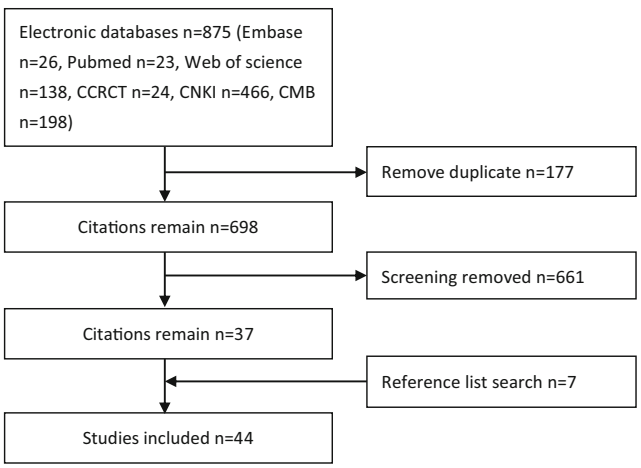

Fig. 1 Flowchart of the study selection

Table 1 Characteristics of included randomised controlled trials

Study	Location	Participants	Mean age (range), years	Male/ female	Treatments (number of participants)	Follow-up, months	Outcomes
1979 Chen	Heilongjiang	Children	6–17	UC	AS (17) vs. NT (17)	4	Radiographic improvement*, clinical improvement, adverse events
1980 Wang	Henan	Children	5–12	UC	SE + VE (41) vs. PLA (36)	11	Radiographic improvement
1981 Niu	Heilongjiang	Children	6–13	UC	SE (27) vs. PLA (29)	9	Radiographic improvement
1982 YSSG	Shaanxi	Children	3–13	UC	SE (182) vs. PLA (174)	12	Radiographic improvement
1984 Cui	Henan	Children	5–15	UC	VC injection (19) vs. SE (17) vs. PLA (19)	12	Radiographic improvement
1984 Niu	Heilongjiang	Children	6–13	UC	SE (UC) vs. PLA (UC)	24	Radiographic improvement
1985 Guo	Hebei	Children	≤ 14	UC	SE (50) vs. SE + YE (50) vs. PLA (50)	12	Radiographic improvement
1985 Niu	Heilongjiang	Children	6–13	UC	SE (1256) vs. PLA (1209)	12	Radiographic improvement
1986 Cui	Jilin	Children	4–13	UC	SE (45) vs. VC (45)	12	Radiographic improvement
1986 Guo	Hebei	Children	5–14	UC	SE + YE (60) vs. SE (60) vs. YE (60)	13	Radiographic improvement
1986 Niu	Heilongjiang	Children	6–13	UC	SE (285) vs. PLA (277)	24	Radiographic improvement
1986 Wu	Heilongjiang	Children	5–16	UC	SE (171) vs. PLA (177)	12	Radiographic improvement
1986 Zhong	Heilongjiang	Children	5–13	UC	SE (UC) vs. PLA (UC)	36	Radiographic improvement
1988 Deng	Sichuan	Children	2–13	UC	SE (84) vs. UC (94)	36	Radiographic improvement
1988 He	Henan	Children	3–13	UC	SE (UC) vs. NT (UC)	48	Prevalence (defined by X-ray criteria)
1988 Zhou	Gansu	Children	3–13	UC	SE (UC) vs. SDA 1/year (UC) vs. SDA 2/year (UC)	12	Radiographic improvement (abstract not included in the meta-analysis)
1990 Niu	Heilongjiang	Children	6–13	UC	SE (210) vs. PLA (228)	12	Radiographic improvement, adverse events
1991 Zhou	Heilongjiang, Shaanxi, Gansu	Children	4–12	63/56	SEs + SE (30) vs. SE vs. IO salt + VC (35) vs. IO salt (29)	12	Radiographic improvement
1992 Liang	Heilongjiang	Children	6–13	UC	SE (46) vs. VC (29)	12	Radiographic improvement
1999 Zhou	Inner Mongolia	Children	≤ 12	UC	AS (68) vs. PLA (60)	6	Radiographic improvement
2003 Chen	Shaanxi	Children	6–11	UC	SE (50) vs. VC (50) vs. SE + VC (50)	12	Radiographic improvement
2004 Li	Qinghai	Children	6–12	UC	SE (10) vs. SEs + VE (10) vs. SEs (10)	12	Radiographic improvement
2005 Cai	Gansu	Children	7–13	40/40	SE (40) vs. PLA (40)	18	Radiographic improvement
2003 Moreno-Reyes	Tibet	Children	≥ 10	150/102	SE (113) vs. PLA (95) vs. NT (44)	12	Joint pain, function, stiffness, clinical improvement, weight, height, skeletal delay, adverse events
2004 Cao	Shaanxi	Adults	≥ 18	65/52	XHL (41) vs. KGZ (33) vs. IBU (43)	2	Clinical improvement, adverse events
2004 Xu	Shaanxi	Adults	30–62	UC	IAH (50) vs. VC (40)	6	Function score (Lequesne score), clinical improvement, adverse events
2009 Liu	Sichuan	Adults	56	77/123	CHO (100) vs. CEL (100)	5	WOMAC total score, clinical improvement (WOMAC score improvement > 20%)
2009 Tu	Shaanxi	Adults	53 (48–69)	47/39	AD + DD (40) vs. AD (30) vs. DD (30)	18	Function score (Tegner scale)
2010 Li	Shaanxi	Adults	UC	30/22	TST (26) vs. NES (26)	1/3	Clinical improvement (decrease of VAS pain score ≥ 4)
2010 Liu	Heilongjiang	Adults	≥ 40	53/27	CLU (70 knees) vs. PLA (62 knees)	8	Knee joint space

Table 1 (continued)

Study	Location	Participants	Mean age (range), years	Male/ female	Treatments (number of participants)	Follow-up, months	Outcomes
2011 Liu	Tibet	Adults	50 (35–68)	97/90	K1 (70) vs. IBU (67) vs. VC (50)	6	Clinical improvement, adverse events
2011 Yu	Shaanxi	Adults	53 (28–84)	462/292	AD + IAH (566) vs. AD (188)	18	Function score (Lequesne score), adverse events
2011 Zhang and Luo	Sichuan	Adults	≥18	73/137	K1 (105) vs. IBU (105)	15	Clinical improvement, adverse events
2011 Zhang and Yang	Sichuan	Adults	43 (18–65)	61/101	K2 (61) vs. IBU (50) vs. KGZ (51)	9	Clinical improvement, adverse events
2012 Ji	Sichuan	Adults	54	33/65	K4 (48) vs. IBU (50)	8	Clinical improvement, adverse events
2012 Li	Sichuan	Adults	55	33/72	K1 (55) vs. IBU (55)	3	Pain score (McGill SF-MPQ), Clinical improvement (according to SF-MPQ pain score), adverse events
2012 Xu	Sichuan	Adults	18–75	35/37	K3 (36) vs. DIC (36)	2	Clinical improvement (VAS pain score reduction≥ 25%), adverse events
2010 Zhang	Heilongjiang	Adults	51 (≥ 40)	54/26	CHO + GLU (40) vs. PLA (40)	8	Mean joint space, adverse events
2011 Luo	Sichuan	Adults	54	49/119	CEL (52) vs. MEL (72) vs. PAR (44)	1.5	VAS pain, Patients global assessment of disease activity scale, physician's global assessment of disease activity scale, Adverse events
2012 Liu	Sichuan	Adults	51	56/127	DIC (50) vs. NAP (65) vs. GLU (68)	1.5	VAS pain, WOMAC overall score, WOMAC pain score, WOMAC function score, WOMAC stiffness score, daily self-care activities
2012 Tang	Sichuan	Adults	63	66/96	MEL (82) vs. IAH (80)	3	VAS pain, WOMAC pain score, WOMAC stiffness score, WOMAC function score, patient's global assessment of disease response, physician's global assessment of disease response, adverse events
2012 Yue	Sichuan	Adults	51	114/137	CHO (64) vs. GLU (62) vs. GLU + CHO (63) vs. PLA (62)	6	Clinical improvement (WOMAC pain scale reduction ≥ 20%), WOMAC pain score, WOMAC stiffness score, WOMAC function score, WOMAC total score, SF-12 score, adverse events
2014 Xia	Shaanxi	Adults	55	59/91	GLU (50) vs. IAH (50) vs. PLA (50)	5	WOMAC pain score, WOMAC function score, WOMAC stiffness score, WOMAC total score, Lequesne score, adverse events
2014 Yu	Shaanxi	Adults	57	36/63	IAH (50) vs. PLA (49)	24	Joint dysfunction index scale, patient's global assessment

AS, aspirin; *CEL*, celecoxib; *DIC*, diclofenac; *IAH*, intra-articular injection of hyaluronic acid; *IBU*, ibuprofen; *MEL*, meloxicam; *NAP*, naproxen; *CHO*, chondroitin; *GLU + CHO*, glucosamine + chondroitin; *GLU*, glucosamine; *IO*, iodine; *SE*, selenium; *SEs*, selenium-rich salt; *VC*, vitamin C; *YE*, yeast; *AD*, arthroscopic debridement; *DD*, arthroscopic drilling decompression; *K1*, KBD1 capsule; *K2*, KBD2 capsule; *K3*, KBD3 patch; *K4*, KBD4 capsule; *KGZ*, Kang Gu Zeng Sheng tablet; *NES*, nerve electrical stimulation; *TST*, trimming skin therapy; *XHL*, Xiao Huo Luo capsule; *NT*, no treatment; *PLA*, placebo; *SDA*, seleno-diacetic acid injection; *VAS*, visual analogue scale; *WOMAC*, Western Ontario & McMaster Universities Osteoarthritis Index

*There were four major guidelines of criteria of radiographic improvement of KBD chronologically: in 1973, the first criteria of radiographic improvement of KBD were published (trial); in 1982, a new criteria (trial) was published; in 1996, the Ministry of Health published The National Health Standard document 'The judging of treatment effect on Kashin–Beck disease' (WS/T 79-1996); in 2011, the Ministry of Health of China published 'Assessment for therapeutic efficacy on Kashin–Beck disease' (WS/T 79-2011) in replacement of WS/T 79-1996 (online supplementary criteria of radiographic improvement of Kashin–Beck disease)

Outcomes for adults

Pain

Six trials accessed nine treatments for reduction of pain score in adults with KBD, including two nutraceuticals: GLU and/or CHO and six pharmaceutical treatments: PAR and NSA including CEL, DIC, MEL and NAP, and IAH (Fig. 2).

In the NWM, the most effective treatment was GLU + CHO (SMD 1.46, 95% CI: 1.07 to 1.85), followed by IAH (1.09, 0.70 to 1.48), CHO (0.84, 0.47 to 1.21), DIC (0.63, 1.18 to 1.08), NAP (0.55, 0.12 to 0.98), MEL (0.52, 0.03 to 1.01) and GLU (0.40, 0.13 to 0.67) compared to placebo, respectively. However, PAR and CEL were not significantly more effective than placebo (Fig. 3, Table 2). The relative efficacies of treatments are reported in Online Supplementary Table 2. No evidence of inconsistency in the network loops was found (Online Supplementary Table 10). The comparison-adjusted funnel plot was symmetry (Online Supplementary Fig. 3).

Function

In the NWM, six trials with eight nutraceuticals or pharmaceutical treatments versus placebo or each other were included (Fig. 2). Comparing with placebo, GLU + CHO was the most effective treatment (SMD 3.22, 95% CI: 2.75 to 3.69), followed by CHO (3.17, 2.72 to 3.62), IAH (1.08, 0.77 to 1.39), DIC (0.78, 0.33 to 1.23), NAP (0.72, 0.29 to 1.15) and GLU (0.69, 0.42 to 0.96). However, MEL was not more effective than placebo (0.02, − 0.43 to 0.47), while VC was worse than placebo (− 1.03, − 1.64 to − 0.42) (Fig. 3). The head-to-head comparisons between treatments are shown in Online Supplementary Table 6. No inconsistency was found in the network (Online Supplementary Table 10).

Surgeries of AD, DD, AD + DD and AD + IAH were not connected in the network as there were no shared comparators. The conventional meta-analysis found that AD + IAH was significantly better than AD alone, while no difference was found between AD, DD and their combination (Online Supplementary Table 12).

Stiffness

Four trials with eight nutraceuticals or pharmaceutical treatments including GLU and/or CHO, NSA (DIC, NAP, MEL) and IAH were included in the NWM for stiffness in adults (Fig. 2). Comparing with placebo, CHO was the most effective treatment (SMD 3.51, 95% CI: 2.78 to 4.24), followed by G+C (3.23, 2.50 to 3.96), DIC (1.29, 0.41 to 2.17), NAP (1.26, 0.38 to 2.14) and GLU (1.09, 0.58 to 1.60). However, MEL (0.65, − 0.32 to 1.63) and IAH (0.46, − 0.23 to 1.14) were not better than placebo (Fig. 3). The head-to-head comparison of treatments can be found in Online Supplementary Table 7. All loops of the network were consistent (Online Supplementary Table 10).

WOMAC total score

Four trials assessing seven nutraceuticals or pharmaceutical treatments including GLU and/or CHO, NSAIDs (CEL, DIC, NAP) and IAH were included in the NWM for WOMAC total score in adults (Fig. 2). Comparing with placebo, CEL was the most effective treatment (SMD 3.43, 95% CI: 2.84 to 4.02), followed by GLU + CHO (3.36, 2.85 to 3.87), CHO (3.29, 2.78 to 3.80), IAH (1.31, 0.90 to 1.72), DIC (0.97, 0.46 to 1.48), NAP (0.90, 0.41 to 1.39) and GLU (0.84, 0.53 to 1.15) (Fig. 3). The head-to-head comparisons of treatments can be found in Online Supplementary Table 8. No inconsistency was found in the network (Online Supplementary Table 10).

Clinical improvement

Eleven trials with 13 treatments including nutraceuticals: VC, GLU and/or CHO; pharmaceuticals: NSA of CEL, DIC and IBU; and TCM treatments including KGZ, KBD1 capsule, KBD2 capsule, KBD3 patch, KBD4 capsule and XHL capsule were included in the NWM for clinical improvement rate in adults (Fig. 2). IBU, DIC and CEL were combined as NSA to enable the construction of the network. Comparing with placebo, NSA was the most effective treatment (RR 7.58, 95% CI: 2.98 to 19.32), followed by IAH (7.47, 2.20 to 25.41), KBD4 (7.38, 2.86 to 19.03), KBD1 (7.24, 2.83 to 18.54), KBD3 (7.19, 2.68 to 19.26), KGZ (6.90, 2.69 to 17.68), XHL (6.43, 2.48 to 16.67), KBD2 (5.69, 2.20 to 14.73) and GLU + CHO (1.96, 1.17 to 3.28). However, GLU alone (1.32, 0.75 to 2.34) and VC (1.80, 0.61 to 5.30) were not more effective than placebo (Fig. 3). The comparative effectiveness of treatments with each other is presented in Online Supplementary Table 9. No inconsistency was found in the loops of the network (Online Supplementary Table 10).

Other clinical outcomes

According to conventional meta-analysis, three studies that reported patient global assessment showed no difference between IAH and MEL and between IAH and placebo, or among CEL, MEL and PAR. Two studies reported physician global assessment and no difference was found among IAH, MEL and placebo, or among MEL, CEL and PAR. One study assessed SF-12, in which GLU plus CHO and CHO alone were significantly more effective than GLU alone or placebo, but no difference was found between GLU plus CHO and CHO alone. Two RCTs accessed joint space for adults, in which no difference was found between GLU plus CHO and placebo (Online Supplementary Table 12).

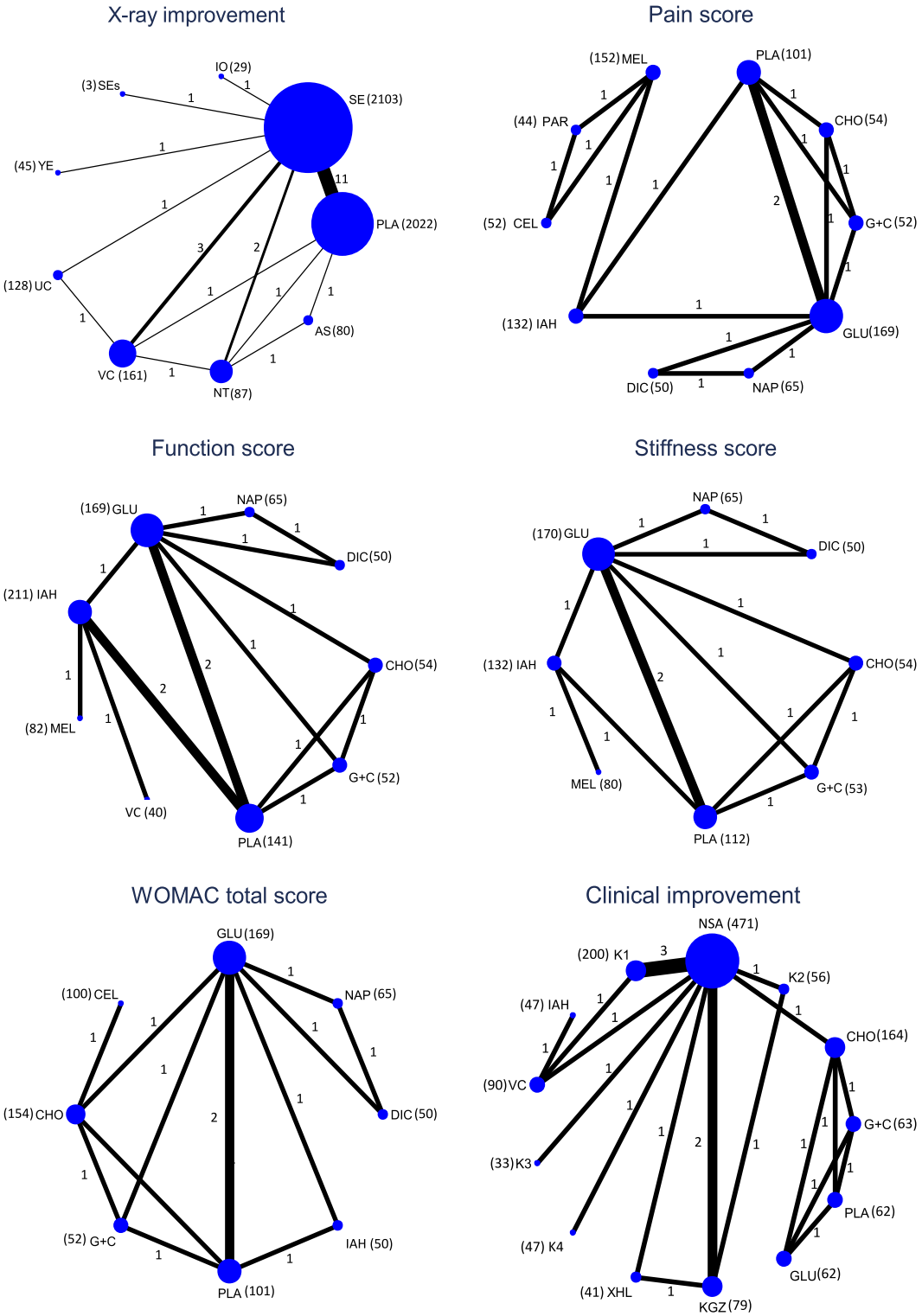

Fig. 2 Network maps for efficacy outcomes. AS, aspirin; CEL, celecoxib; DIC, diclofenac; IAH, intra-articular injection of hyaluronic acid; IBU, ibuprofen; MEL, meloxicam; NAP, naproxen; CHO, chondroitin; G+C, glucosamine + chondroitin; GLU, glucosamine; IOD, iodine; SE, selenium; VC, vitamin C; YEA, yeast; AD, arthroscopic debridement; DD, arthroscopic drilling decompression; K1, KBD1 capsule; K2, KBD2 capsule; K3, KBD3 patch; K4, KBD4 capsule; KGZ, Kang Gu Zeng Sheng tablet; NES, nerve electrical stimulation; TST, trimming skin therapy; XHL, Xiao Huo Luo capsule; NT, no treatment; PLA, placebo. (The width of the line is proportional to the number of trials directly comparing the treatments, with the number of trials directly comparing the treatments besides the lines; the size of the bubble is proportional to the number of participants randomly allocated to the treatment with the number of participants in the arm in the brackets)

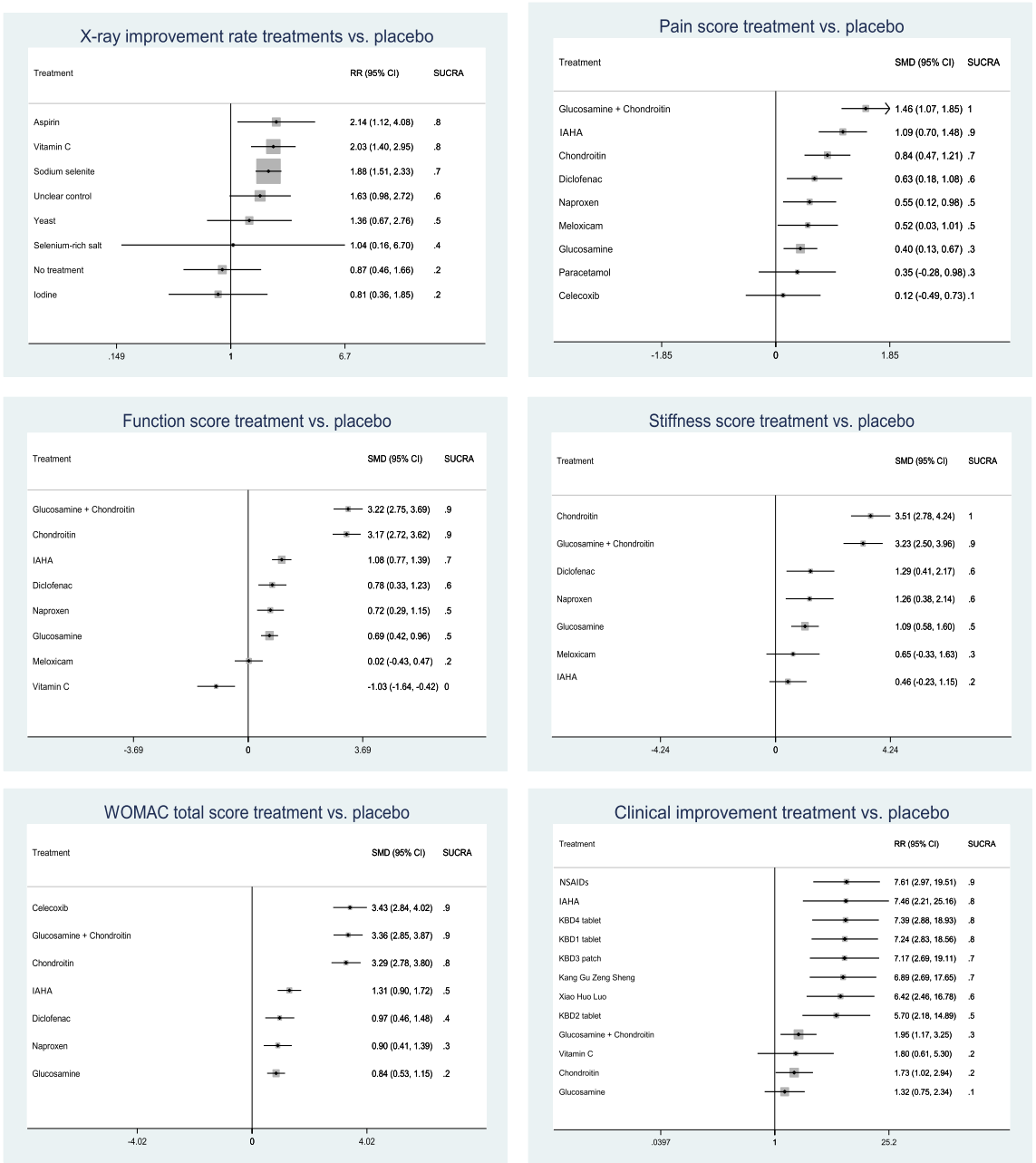

Fig. 3 Network meta-analysis of efficacy outcomes compared with placebo. RR, rate ratio; SMD, standardised mean difference; CI, confidence interval; SUCRA, surface under the cumulative ranking curves; IAH, intra-articular injection of hyaluronic acid; NSA, non-steroid anti-inflammatory drugs; KGZ, Kang Gu Zeng Sheng tablet; XHL, Xiao Huo Luo capsule

Adverse events

Fifteen RCTs reported AEs in adults. For NSA, the AEs ranged from 0% for AS to 27.8% for MEL, which were mainly gastrointestinal events and skin itch, palpitation, headache, dizziness and elevated alanine transaminase (ALT) were also documented. For TCM, the rate of AEs ranged from 0.0 to 3.0%, which mainly were also gastrointestinal events, which was similar to PAR. The AEs of IAH were mainly swelling and pain at the joint of injection (10.0 to 29.8%). CHO and GLU had similar rates of AEs as placebo which include dyspepsia, abdominal pain, constipation, diarrhea, nausea, cough and headache. No sever adverse events were reported (Online Supplementary Table 14).

Outcomes for children or adolescents

Radiographic structure

In total, 22 trials assessed the efficacy of treatments on radiographic improvement (X-ray) in children or adolescents aged

Table 2 Summary table of network meta-analysis of treatments versus placebo and GRADE quality assessment

Outcome/treatment vs. placebo	Direct				Indirect				Network			
Radiographic improvement in children or adolescents	RR	[95% CI]		Quality	RR	[95% CI]		Quality	RR	[95% CI]		Quality
Aspirin	1.96	1.29	2.98	Low*‡	3.07	0.73	12.81	Low**	2.15	1.13	4.09	Low
Vitamin C	2.14	1.14	4.04	Low*‡	2.23	1.38	3.61	Low**	2.04	1.40	2.97	Low
Sodium selenite	1.77	1.55	2.01	Low*†	1.33	0.43	4.17	Low**	1.87	1.50	2.34	Low
Unclear control	/			/	1.63	0.97	2.73	Low**	1.63	0.97	2.73	Low
Yeast	/			/	1.36	0.67	2.78	Low**	1.36	0.67	2.78	Low
Selenium-rich salt	/			/	1.04	0.16	6.69	Low**	1.04	0.16	6.69	Low
No treatment	0.47	0.01	24.41	Moderate*	1.18	0.62	2.26	Low**	0.87	0.46	1.64	Moderate
Iodine	/			/	0.81	0.35	1.84	Low**	0.81	0.35	1.84	Low
Chondroitin	1.74	1.03	2.97	Moderate‡	/			/	1.73	1.02	2.95	Moderate
Glucosamine	1.33	0.75	2.37	Moderate‡	/			/	1.33	0.75	2.36	Moderate
Pain score in adults	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality
Glucosamine + chondroitin	1.45	1.04	1.86	Moderate‡	1.54	0.47	2.61	Moderate¶[	1.46	1.08	1.85	Moderate
IAH	1.10	0.69	1.51	Low*‡	1.01	− 0.05	2.06	Low**	1.09	0.70	1.47	Low
Chondroitin	0.83	0.44	1.23	Moderate‡	0.92	− 0.23	2.08	Moderate¶[	0.84	0.48	1.21	Moderate
Diclofenac	/				0.63	0.17	1.09	Low**	0.63	0.17	1.09	Low
Naproxen	/				0.55	0.11	0.99	Low**	0.55	0.11	0.99	Low
Meloxicam	/				0.52	0.02	1.01	Low**	0.52	0.02	1.01	Low
Glucosamine	0.40	0.12	0.67	Moderate‡	0.42	− 157.96	157.11	Moderate¶[	0.40	0.12	0.67	Moderate
Paracetamol	/				0.35	− 0.28	0.97	Low**	0.35	− 0.28	0.97	Low
Celecoxib	/				0.12	− 0.50	0.73	Low**	0.12	− 0.50	0.73	Low
Function score in adults	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality
Glucosamine + chondroitin	3.22	2.72	3.71	Moderate‡	3.22	2.19	4.25	Moderate¶[	3.22	2.75	3.68	Moderate
Chondroitin	3.17	2.68	3.66	Moderate‡	3.17	2.14	4.20	Moderate¶[	3.17	2.71	3.63	Moderate
IAH	1.08	0.75	1.40	Moderate*	1.08	0.04	2.12	Low**	1.08	0.77	1.39	Moderate
Diclofenac	/				0.78	0.33	1.24	Low**	0.78	0.33	1.24	Low
Naproxen	/				0.72	0.28	1.16	Low**	0.72	0.28	1.16	Low
Glucosamine	0.71	0.43	1.00	Moderate‡	0.31	− 0.96	1.58	Moderate¶[	0.69	0.42	0.97	Moderate
Meloxicam	/				0.02	0.44	0.47	Moderate¶[	0.02	− 0.43	0.47	Moderate
Vitamin C	/				− 1.03	− 1.65	− 0.42	Moderate¶[	− 1.03	− 1.65	− 0.42	Moderate

Table 2 (continued)

Stiffness score in adults	SMD	[95%	CI]	Quality	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality
Chondroitin	3.65	3.18	4.13	Moderate‡	2.60	1.58	3.61	Moderate¶	3.51	2.78	4.24	Moderate
Glucosamine + chondroitin	3.37	2.91	3.83	Moderate‡	2.31	1.30	3.32	Moderate¶	3.23	2.50	3.95	Moderate
Diclofenac	/				1.29	0.41	2.18	Very low**	1.29	0.41	2.18	Very low
Naproxen	/				1.26	0.38	2.13	Very low**	1.26	0.38	2.13	Very low
Glucosamine	1.09	0.58	1.61	Moderate†‡	− 0.09	− 55.50	55.32	Moderate¶	1.09	0.58	1.61	Moderate
Meloxicam	/				0.65	− 0.32	1.63	Low**	0.65	− 0.32	1.63	Low
IAH	0.32	− 0.07	0.71	Low*‡	1.38	0.36	2.40	Low**	0.46	− 0.23	1.14	Low
WOMAC total score in adults	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality	SMD	[95% CI]		Quality
Celecoxib	/				3.43	2.83	4.03	Low**	3.43	2.83	4.03	Low
Glucosamine + chondroitin	3.47	2.95	3.98	Moderate‡	2.84	1.78	3.89	Moderate¶	3.36	2.86	3.87	Moderate
Chondroitin	3.39	2.89	3.90	Moderate‡	2.76	1.71	3.82	Moderate¶	3.29	2.79	3.79	Moderate
IAH	1.22	0.81	1.64	Low*†‡	1.85	0.80	2.90	Low**	1.31	0.89	1.73	Low
Diclofenac	/				0.97	0.47	1.48	Very low**	0.97	0.47	1.48	Very low
Naproxen	/				0.90	0.41	1.39	Very low**	0.90	0.41	1.39	Very low
Glucosamine	0.84	0.53	1.15	Moderate‡	1.22	− 56.60	54.15	Moderate¶	0.84	0.53	1.15	Moderate
Clinical improvement in adults	RR	[95% CI]		Quality	RR	[95% CI]		Quality	RR	[95% CI]		Quality
NSA	/			/	7.58	2.98	19.32	Low**	7.58	2.98	19.32	Low
IAH	/			/	7.47	2.20	25.41	Low**	7.47	2.20	25.41	Low
KBD4 tablet	/			/	7.38	2.86	19.03	Low**	7.38	2.86	19.03	Low
KBD1 tablet	/			/	7.24	2.83	18.54	Low**	7.24	2.83	18.54	Low
KBD3 patch	/			/	7.19	2.68	19.26	Low**	7.19	2.68	19.26	Low
Kang Gu Zeng Sheng	/			/	6.90	2.69	17.68	Low**	6.90	2.69	17.68	Low
Xiao Huo Luo	/			/	6.43	2.48	16.67	Low**	6.43	2.48	16.67	Low
KBD2 tablet	/			/	5.69	2.20	14.73	Low*	5.69	2.20	14.73	Low
Glucosamine + chondroitin	1.97	1.17	3.30	Moderate‡	/			/	1.96	1.17	3.28	Moderate
Vitamin C	/			/	1.80	0.61	5.27	Low**	1.80	0.61	5.27	Low
Chondroitin	1.74	1.03	2.95	Moderate‡	/				1.74	1.02	2.94	Moderate
Glucosamine	1.33	0.75	2.36	Moderate‡	/				1.32	0.74	2.35	Moderate

IHA, intra-articular injection of hyaluronic acid; *NSA*, non-steroid anti-inflammatory drugs; *RR*, relative ratio; *CI*, confidence interval; *SMD*, standardised mean difference

*Limitations (risk of bias), †Inconsistency, ‡Imprecision, §Severe imprecision, ¶Contributing direct evidence of moderate quality, **Contributing direct evidence of low or very low quality

from 2 to 16 years. Treatments included nutraceuticals (SE, IO, VC, VE or their combinations) and pharmaceuticals (AS) compared with no treatment, placebo or each other. To simplify the interpretation of the results, only 20 trials with monoregimen were included in the network meta-analysis (Fig. 2).

In the NWM, AS, VC and SE were significantly more effective than placebo, and the RRs (95% CIs) were 2.14 (1.12 to 4.08), 2.03 (1.40 to 2.95) and 1.88 (1.51 to 2.33), respectively, while no significant difference was found for YE (1.36, 0.67–2.76) and SEs (1.04, 0.16–6.70) (Fig. 3). The head-to-head comparisons are presented in Online Supplementary Table 4. There was significant inconsistency for the loop of SE–unclear control–VC (Online Supplementary Table 10).

Pain, function and stiffness

Only one RCT assessed pain, function and stiffness for children, in which no difference was found among IO plus SE, IO plus PLA and no treatment for these outcomes at 12-month follow-up through conventional meta-analysis (Online Supplementary Table 11).

Clinical improvement

Two RCTs appraised clinical improvement in children. Through conventional meta-analysis, one RCT showed AS was significantly more effective than no treatment (RR 27.00, 95% CI 1.73 to 420.68), and another found no difference among IO plus SE, IO plus placebo and no treatment (Online Supplementary Table 11).

Other clinical outcomes

One RCT accessed height, weight and skeletal delay in children, in which no difference was found among IO plus SE, IO plus placebo and no treatment (Online Supplementary Table 11).

Adverse events

Three studies reported AEs of treatments for children. Chen 1979 reported no AEs were observed for AS during 4 months of treatment. [48] Niu 1990 reported few children who received SE tablets had mild nausea and vomiting but no detail was given. [49] Moreno-Reyes 2003 described 4 among 208 children (1.9%) who had transient biochemical hyperthyroidism related to IO injection. [50]

Additional analysis

In additional analysis, the overall effect size of NSA and TCMs was estimated using NWM for outcomes of pain, function, stiffness, WOMAC total score and clinical improvement where data were available. The results were similar to the main analysis (Online Supplementary Fig. 4). However, we were unable to conduct sensitivity or subgroup analysis by methodological quality or sample size of the studies, due to the limited number of included trials.

Discussion

To the best of our knowledge, this is the first network meta-analysis assembling evidence from all RCTs for treatments in KBD. In total, 44 trials with 23 nutraceuticals, pharmacological and surgical treatments and TCMs were examined. The main findings of this study are as follows: (1) in adults, CHO, GLU, IAH and NSA are effective for pain and function; (2) in children or adolescent, selenium supplement was effective for structure improvement; and (3) the efficacy of surgeries, aspirin, vitamin C and TCMs has yet to be established.

The analgesic effect of NSA was well established in other chronic pain conditions such as osteoarthritis [28, 29], mainly by blocking enzyme cyclooxygenase (COX) [30]. Chondroitin, glucosamine and hyaluronic acid are important components of the extracellular matrix and articular cartilage and vital in maintaining and repairing of cartilage [31, 32]. The use of chondroitin, glucosamine and hyaluronic acid in KBD is based on the evidence from osteoarthritis—a condition characterised by imbalance of cartilage loss and impairment, though their effectiveness is still controversial [33–37]. The reduction of pain and improvement of function may be achieved through their role in maintaining and repairing of cartilage, which may be similar for KBD. Yu and colleagues conducted a systematic review (SR) including seven trials comparing IAH with vitamin C, drugs or other treatments and found that IAH was significantly better in achieving overall effectiveness (OR 10.44, 3.57–30.51) for KBD [17].

The efficacy of selenium supplement for structure improvement in children or adolescents has been well documented. In a SR, Yue and colleagues included 10 trials comparing sodium selenite with placebo or no treatment and showed that sodium selenite was more effective than controls in repairing metaphyseal lesions (OR 5.63, 95% CI 3.67–8.63) and distal end of phalanges (OR 2.98, 95% CI 1.32–6.70) based on radiographic assessment [15]. During our preparation of the manuscript, another NWM has been conducted for selenium supplement, concluding that it is more effective than placebo or no treatment in repairing metaphysis impairment, with the combination of sodium selenite and vitamin C being the best [38]. However, as shown in our study, the strength of the evidence was weakened due to the methodological limitations of the included trials. SRs of prevention and epidemiological studies also supported the efficacy of selenium supplementation in preventing KBD in children [39]. SRs found that environmental selenium concentration was significantly lower in endemic regions than non-endemic regions, and serum selenium concentration in people with KBD was significantly lower than healthy

persons [5, 40]. Recent studies show that KBD is characterised not only by articular cartilage damage and chondrocyte apoptosis but also involves inflammation and oxidative stress [41]. The role of selenium in KBD mainly involves maintenance of thyroid function and antioxidation [9]. However, meta-analyses found no relationship between iodine deficiency and KBD [5, 8].

There were studies showing that aspirin is associated with reduced cartilage loss [42, 43], but contradicting evidence also exists [44]. Little is known about the mechanisms of aspirin in relation to joint structure in KBD. The effect of vitamin C may relate to its antioxidation role. However, there is no convincing evidence that vitamin C is effective for any other type of arthritis [45, 46]. Thus, further investigation of the role of aspirin and vitamin C in KBD is needed.

This review has several limitations. First, due to the small number of trials/participants in most comparisons in current networks, a small study effect may not be ruled out [47], though the comparison-adjusted funnel plot did not show obvious asymmetry. Second, most comparisons in the NWM were of low to moderate quality. As most of the outcomes in KBD were subjective, the lacking of allocation concealment and blinding to the participants and assessors may distort the efficacy estimates. Unfortunately, due to the limited number of studies, we were unable to conduct sensitivity or subgroup analysis to investigate their impact on the efficacy estimates. Due to the reasons described above, the ranks of probability of being the best treatment estimated using SUCRA in this study may be interpreted with caution. The solo relying on estimated ranks may be misleading. A patient-tailored discussion considering both the efficacy and safety of treatments is needed. Finally, we did not hand-search journals and conference abstracts; thus, publication bias may exist, though both important English and Chinese literature databases, reference lists, published systematic reviews and trial registers have been searched.

In conclusion, CHO, GLU, IAH and NSA are more effective than placebo to relieve symptoms for adults with KBD. Selenium supplement is more effective than placebo for radiographic improvement in children or adolescents. However, the efficacy of surgeries, aspirin, vitamin C and TCMs for KBD has not been established yet.

Contributors KZ conceptualised and designed the study. KZ and JLH screened the literature and selected the study. KZ extracted data and accessed the quality of trials, conducted the analysis and wrote the draft of the manuscript. QZ wrote part of the discussion. WZ and BD advised on the analysis and the representation of the results. All authors contributed to the intellectual interpretation of the findings and approved the final manuscript.

Funding QZ was supported by the Innovation Research Grant from the University of Electronic Science and Technology, Chengdu, China.

Compliance with ethical standards

Disclosures None.

References

1. Allander E (1994) Kashin-Beck disease. An analysis of research and public health activities based on a bibliography 1849-1992. Scand J Rheumatol Suppl 99:1–36
2. Moreno-Reyes R, Suetens C, Mathieu F, Begaux F, Zhu D, Rivera MT, Boelaert M, Neve J, Perlmutter N, Vanderpas J (1998) Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. N Engl J Med 339(16):1112–1120. https://doi.org/10.1056/NEJM199810153391604
3. Utiger RD (1998) Kashin-Beck disease—expanding the spectrum of iodine-deficiency disorders. N Engl J Med 339(16):1156–1158. https://doi.org/10.1056/NEJM199810153391611
4. Li D, Han J, Guo X, Qu C, Yu F, Wu X (2016) The effects of T-2 toxin on the prevalence and development of Kashin-Beck disease in China: a meta-analysis and systematic review. Toxicol Res 5(3): 731–751. https://doi.org/10.1039/C5TX00377F
5. Yang L, Zhao GH, Yu FF, Zhang RQ, Guo X (2016) Selenium and iodine levels in subjects with Kashin-Beck disease: a meta-analysis. Biol Trace Elem Res 170(1):43–54. https://doi.org/10.1007/s12011-015-0463-8
6. Chasseur C, Suetens C, Nolard N, Begaux F, Haubruge E (1997) Fungal contamination in barley and Kashin-Beck disease in Tibet. Lancet 350(9084):1074. https://doi.org/10.1016/S0140-6736(05)70453-0
7. Suetens C, Moreno-Reyes R, Chasseur C, Mathieu F, Begaux F, Haubruge E, Durand MC, Neve J, Vanderpas J (2001) Epidemiological support for a multifactorial aetiology of Kashin-Beck disease in Tibet. Int Orthop 25(3):180–187
8. Li L, Wang Q, Tian JH, Yang KH, Tian HL, Shi CH, Jiang J, Wu TX, Liao YJ (2013) The relationship between the exposure and metabolism of iodine and Kaschin-Beck disease:a systematic review. Chinese Journal of Evidence-Based Pediatrics: 176–180 [In Chinese]. https://www.cjebp.net/CN/abstract/abstract9054.html
9. Yao Y, Pei F, Kang P (2011) Selenium, iodine, and the relation with Kashin-Beck disease. Nutrition 27(11-12):1095–1100. https://doi.org/10.1016/j.nut.2011.03.002
10. Wang Y, Yang Z, Gilula LA, Zhu C (1996) Kashin-Beck disease: radiographic appearance in the hands and wrists. Radiology 201(1): 265–270. https://doi.org/10.1148/radiology.201.1.8816556
11. Mathieu F, Begaux F, Lan ZY, Suetens C, Hinsenkamp M (1997) Clinical manifestations of Kashin-Beck disease in Nyemo Valley, Tibet. Int Orthop 21(3):151–156
12. Wang FQ, Wang ZW, Ping ZG, Guo X (2005) Epidemiological investigation of the declined prevalence of Kashin-Beck disease in Linyou County, Shaanxi Province, China. Chin J Endemiol 06: 637–638 [in Chinese]
13. Li FZ, Deng JY, Yang RM, Li DW, Ma GJ, Liao P, Hou CH, Zheng YT, Zhang L, Wu G (2006) Investigating report on prevalence rate of Kaschin-Beck disease in adults in Sichuan Province in 2005. Endemic Dis Bull 01:23–25 [in Chinese]
14. Sun L-Y, Yuan L-J, Fu Y, Deng J-Y, Wang L-H (2012) Prevalence of Kaschin-Beck disease among Tibetan children in Aba Tibetan and Qiang Autonomous Prefecture: a 3-year epidemiological survey. World J Pediatr 8(2):140–144. https://doi.org/10.1007/s12519-012-0351-7
15. Tomlinson R (1999) Beijing conference reviews Kashin-Beck disease. BMJ 318(7182):485
16. Jirong Y, Huiyun P, Zhongzhe Y, Birong D, Weimin L, Ming Y, Yi S (2012) Sodium selenite for treatment of Kashin-Beck disease in children: a systematic review of randomised controlled trials. Osteoarthr Cartil 20(7):605–613. https://doi.org/10.1016/j.joca.2012.02.012
17. Yu FF, Xia CT, Fang H, Han J, Younus MI, Guo X (2014) Evaluation of the therapeutic effect of treatment with intra-articular hyaluronic acid in knees for Kashin-Beck disease: a

meta-analysis. Osteoarthr Cartil 22(6):718–725. https://doi.org/10.1016/j.joca.2014.04.012
18. Mills EJ, Thorlund K, Ioannidis JP (2013) Demystifying trial networks and network meta-analysis. BMJ 346:f2914. https://doi.org/10.1136/bmj.f2914
19. General office of endemic disease control, People's Republic of China (1983) X-ray criteria of treatment effect on Kashin-beck disease (trial)
20. Ministry of Health, People's Republic of China (1996) The judging of treatment effect on Kashin-beck disease (WS/T 79-1996)
21. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64(4):383–394. https://doi.org/10.1016/j.jclinepi.2010.04.026
22. Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, Kessels AG, Guyatt GH, Group GW (2014) A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 349:g5630. https://doi.org/10.1136/bmj.g5630
23. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G (2013) Graphical tools for network meta-analysis in STATA. PLoS One 8(10):e76654. https://doi.org/10.1371/journal.pone.0076654
24. White IR (2015) Network meta-analysis. Stata J 15(4):951–985
25. Bucher HC, Guyatt GH, Griffith LE, Walter SD (1997) The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 50(6):683–691
26. Dias S, Welton NJ, Caldwell DM, Ades AE (2010) Checking consistency in mixed treatment comparison meta-analysis. Stat Med 29(7-8):932–944. https://doi.org/10.1002/sim.3767
27. Higgins JPT, Green S (editors) (2011) Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from http://www.cochrane-handbook.org/.
28. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Juni P, Trelle S (2016) Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 387(10033):2093–2105. https://doi.org/10.1016/S0140-6736(16)30002-2
29. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P (2010) OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthr Cartil 18(4):476–499. https://doi.org/10.1016/j.joca.2010.01.013
30. Vane JR, Botting RM (1998) Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med 104(3A):2S–8S discussion 21S-22S
31. Monfort J, Pelletier JP, Garcia-Giralt N, Martel-Pelletier J (2008) Biochemical basis of the effect of chondroitin sulphate on osteoarthritis articular tissues. Ann Rheum Dis 67(6):735–740. https://doi.org/10.1136/ard.2006.068882
32. Henrotin Y, Mobasheri A, Marty M (2012) Is there any scientific evidence for the use of glucosamine in the management of human osteoarthritis? Arthritis Res Ther 14(1):201. https://doi.org/10.1186/ar3657
33. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ (2015) Chondroitin for osteoarthritis. Cochrane Database Syst Rev 1:CD005614. https://doi.org/10.1002/14651858.CD005614.pub2
34. Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G (2005) Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev (2):CD002946. https://doi.org/10.1002/14651858.CD002946.pub2
35. Zou K, Wong J, Abdullah N, Chen X, Smith T, Doherty M, Zhang W (2016) Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 75(11):1964–1970. https://doi.org/10.1136/annrheumdis-2015-208387
36. Trigkilidas D, Anand A (2013) The effectiveness of hyaluronic acid intra-articular injections in managing osteoarthritic knee pain. Ann R Coll Surg Engl 95(8):545–551. https://doi.org/10.1308/003588413X1362996004943210.1308/rcsann.2013.95.8.545
37. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G (2006) Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev (2):CD005321. https://doi.org/10.1002/14651858.CD005321.pub2
38. Xie DM, Wang RH, Liao YL, Xu L, Yue JR, Deng CY (2016) Selenium supplement for Kashin-Beck disease: a network meta-analysis. Chin J Evid Based Med 16(11):1284–1290 [in Chinese]. https://doi.org/10.7507/1672-2531.20160195
39. Zou K, Liu G, Wu T, Du L (2009) Selenium for preventing Kashin-Beck osteoarthropathy in children: a meta-analysis. Osteoarthr Cartil 17(2):144–151. https://doi.org/10.1016/j.joca.2008.06.011
40. Quan W, Xiu-xia L, Lun L, Jin-hui T, Ke-hu Y, Tai-xiang W, Yong-jian L (2013) Correlation between selenium and Kaschin-Beck disease. Chin J Evid Based Med 13(12):1421–1430
41. Han J, Wang W, Qu C, Liu R, Li W, Gao Z, Guo X (2015) Role of inflammation in the process of clinical Kashin-Beck disease: latest findings and interpretations. Inflamm Res 64(11):853–860. https://doi.org/10.1007/s00011-015-0861-6
42. Roach JE, Tomblin W, Eyring EJ (1975) Comparison of the effects of steroid, aspirin and sodium salicylate on articular cartilage. Clin Orthop Relat Res 106:350–356
43. Wluka AE, Ding C, Wang Y, Jones G, Urquhart DM, Cicuttini FM (2015) Aspirin is associated with reduced cartilage loss in knee osteoarthritis: data from a cohort study. Maturitas 81(3):394–397. https://doi.org/10.1016/j.maturitas.2015.04.015
44. Manicourt DH, Druetz-Van Egeren A, Haazen L, Nagant de Deuxchaisnes C (1994) Effects of tenoxicam and aspirin on the metabolism of proteoglycans and hyaluronan in normal and osteoarthritic human articular cartilage. Br J Pharmacol 113(4):1113–1120
45. Canter PH, Wider B, Ernst E (2007) The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. Rheumatology 46(8):1223–1233. https://doi.org/10.1093/rheumatology/kem116
46. Rosenbaum CC, O'Mathuna DP, Chavez M, Shields K (2010) Antioxidants and antiinflammatory dietary supplements for osteoarthritis and rheumatoid arthritis. Altern Ther Health Med 16(2):32–40
47. Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, Egger M, Juni P (2010) Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ 341:c3515. https://doi.org/10.1136/bmj.c3515
48. Chen ZL, Ma JM (1979) "Aspirin for Kashin-Beck disease: A preliminary observation on the efficacy." Medical Journal of Chinese People's Liberation Army(02):128. [in Chinese]
49. Niu GH, Zhang BZ, Hou SF (1990) The effect of half dose of selenium supplementation on prevention and treatment of Kaschin Beck disease Chinese Journal of Endemic Diseases 9(2):99–100 [in Chinese]
50. Moreno-Reyes R, Mathieu F, Boelaert M, Begaux F, Suetens C, Rivera MT, Nève J, Perlmutter N, Vanderpas J (2003) Selenium and iodine supplementation of rural Tibetan children affected by Kashin-Beck osteoarthropathy. Am J Clin Nutr 78(1):137–144