Am J Transl Res 2023;15(1):548-555
www.ajtr.org /ISSN:1943-8141/AJTR0147708

Original Article

Diacerein plus glucosamine hydrochloride improves the safety and efficacy and inhibit inflammatory factors in the treatment of knee osteoarthritis

Zhiyu Wang[1*], Jianing Wang[2*], Li Zhang[3], Xiangning Meng[4], Guangming Dai[5], Quan Wang[6]

[1]South China Hospital of Shenzhen University, Shenzhen 518000, Guangdong, P. R. China; [2]Gastrointestinal Surgery, Beidahuang Group General Hospital, Harbin 150088, Heilongjiang, P. R. China; [3]Department of Orthopedics, Rehabilitation Hospital, National Research Center for Rehabilitation Technical Aids, Beijing 102676, P. R. China; [4]Peking University First Hospital, Beijing 100034, P. R. China; [5]Department of Orthopedic Medicine, Third Affiliated Hospital of Inner Mongolia Medical, Inner Mongolia 010050, P. R. China; [6]Inner Mongolia Bailige Medical Science and Technology Co., Ltd., Inner Mongolia 010010, P. R. China. [*]Equal contributors and co-first authors.

Received November 12, 2022; Accepted December 22, 2022; Epub January 15, 2023; Published January 30, 2023

Abstract: Objectives: The aim of this study is to elucidate the safety and efficacy of diacerein (DIA) plus glucosamine hydrochloride (GlcN·HCl) in the treatment of knee osteoarthritis (KOA) and their effect on inflammatory factors (IFs). Methods: Retrospectively, 116 KOA patients admitted between August 2018 and August 2021 were selected. Among them, 55 cases received DIA monotherapy (control group, Con) and 61 cases received DIA + GlcN·HCl (observation group, Obs). The efficacy, safety, scores of Lequesne Index, and Visual Analogue Scale (VAS), as well as the levels of IFs of the two groups were observed and compared. Further, Cox regression was used to perform an in-depth analysis of factors influencing the occurrence of complications in patients with KOA. Results: The analyses revealed a higher overall response rate and a lower adverse event rate in the Obs group compared with the Con group, with statistical significance. Decreased scores of Lequesne Index and VAS and levels of IFs were determined in the Obs after treatment, which were all significantly lower compared with those of the Con. Cox regression analysis identified that TNF-α, IL-1β, hs-CRP, and treatment mode affected the occurrence of complications in KOA patients. Conclusions: DIA + GlcN·HCl can significantly inhibit the inflammation level in KOA, with definite curative effects and a favorable safety profile.

Keywords: Knee osteoarthritis, diacerein, glucosamine hydrochloride, therapeutic effect, inflammatory factors

Introduction

Knee osteoarthritis (KOA) is a degenerative cartilage disease involving joint function, that is accompanied by microscopic and macroscopic damage, synovial inflammation, and abnormal subchondral bone remodeling [1]. The disease, as indicated by KOA statistics, carries a lifetime risk of up to 44% and is the most common among the elderly and populations with obesity and severely injured knees, making it the 12th leading cause of disability worldwide [2, 3]. Age, diet, trauma, obesity, and genetics are risk factors for KOA [4]. KOA patients primarily present with knee joint pain, which leads to limited joint function and gradual loss of self-care ability [5]. Treatment for KOA mainly aims to relieve pain, reduce cartilage destruction, and improve patient quality of life [6]. Without a cure at present, KOA is mainly treated by surgery, medicine, and life interventions [7]. It is generally believed that surgical treatments such as arthroscopy or total knee arthroplasty are indicated for those with end-stage KOA, while life interventions such as weight loss and diet control are feasible for specific overweight people [8, 9]. Therefore, this study attempts to explore effective treatment for KOA from a pharmacologic perspective, which has important implications for optimizing the management of this disease.

Diacerein (DIA), an anthraquinone anti-KOA drug with chondroprotective action, can also be used as a first-line treatment for osteoporosis

and musculoskeletal diseases [10]. DIA has been confirmed to exert anti-KOA activity through effective inhibition of the over-expression of antioxidant enzymes and inflammatory factors (IFs) in mouse experimental models [11]. Martel-Pelletier et al. [12] pointed out that DIA had anti-catabolic function in KOA tissue, and mainly exerted related effects by modulating IL-1β and its signaling pathways. Glucosamine hydrochloride (GlcN·HCl) is demonstrated to exert a lasting effect on pain relief and functional improvement in KOA, playing a therapeutic role by exerting anti-inflammatory function, and inhibiting matrix metalloproteinase (MMP) activity, nitric oxide production, and glycosaminoglycan degradation [13]. In a rabbit KOA model experiment, GlcN·HCl lowered the apoptosis level of KOA chondrocytes by modulating TRPV5 expression [14].

Given the limited research on DIA + GlcN·HCl in KOA therapy, this study aims to fill in knowledge gaps. The innovation of this study is to confirm the efficacy and safety of DIA + GlcN·HCl in the treatment of KOA from the aspects of efficacy, safety, and prognostic factors, among which prognostic factors analysis can further validate the safety and reliability of this treatment regimen. Moreover, from the aspect of Lequesne Index, Visual Analogue Scale (VAS) and the levels of IFs, we analyzed if the combined scheme can curb disease progression of KOA, relieve pain, and inhibit inflammatory reactions. This study should provide a clinical basis and reference for the clinical application and selection of KOA treatment.

Data and methods

Baseline data

The research participants of this retrospective study were 116 KOA patients admitted between August 2018 and August 2021. The patients were assigned to a control group (the Con; n=55) and an observation group (the Obs; n=61) that were intervened by DIA monotherapy and DIA + GlcN·HCl intervention, respectively.

Patients in the Con group aged (53.44±11.08) years on average, with a disease course of (5.29±2.25) years, while the mean age and the course of disease of the Obs group were (54.59±13.23) years and (5.74±2.26) years, respectively. The two patient cohorts were clinically comparable with no difference in baseline data (P>0.05). Informed consent was obtained before patient enrollment, and the research protocol was approved by the Ethics Committee of South China Hospital of Shenzhen University.

Eligibility criteria

Patients were eligible if they were all confirmed to have KOA [15], were operated on by the same group of doctors, with complete clinical records, with normal communication and cognitive skills, and actively cooperated with the research.

Patients were excluded if they had allergic constitution or allergies to the study medication, had diabetes or coagulation dysfunction, had serious lesion of the knee joint, had other joint diseases, or had severe infections.

Treatment methods

The Con group was treated with 50 mg DIA (Shanghai Yuntai Information Technology Co., Ltd., YG11305) capsules, per os, twice a day.

On this basis, the Obs group was given oral GlcN·HCl (Shanghai Yuntai Information Technology Co., Ltd., YG11719), 480 mg/time, three times a day.

The treatment course was 24 weeks in each group, with other painkillers discontinued 2 weeks before and during the experiment.

Curative effect evaluation

The overall response rate (ORR) is the percentage of the sum of patients with marked response and any response in the total number of cases.

Marked response: Normal laboratory test results and basically disappearance of clinical symptoms such as joint pain, tenderness, joint swelling, and morning stiffness.

Response: Improved laboratory test results, with relieved clinical symptoms.

Non-response: No improvement or worsening of the clinical symptoms described above.

Outcome measures

The efficacy, safety, scores of Lequesne Index [16] and VAS [17], and levels of IFs were com-

Table 1. Baseline data of patients in both groups [n (%), mean ± SD]

Factor	n	Control group (n=55)	Observation group (n=61)	χ^2/t	P
Sex				0.146	0.703
Male	59	29 (52.73)	30 (49.18)		
Female	57	26 (47.27)	31 (50.82)		
Average age (years old)	116	53.44±11.08	54.59±13.23	0.505	0.615
Course of disease (years)	116	5.29±2.25	5.74±2.26	1.073	0.286
BMI (kg/m^2)	116	26.57±4.31	27.44±4.50	1.061	0.291
Bilateral knee osteoarthritis				0.022	0.881
Yes	73	35 (63.64)	38 (62.30)		
No	43	20 (36.36)	23 (37.70)		
Drinking history				0.707	0.401
No	67	34 (61.82)	33 (54.10)		
Yes	49	21 (38.18)	28 (45.90)		
Smoking history				0.798	0.372
No	54	28 (50.91)	26 (42.62)		
Yes	62	27 (49.09)	35 (57.38)		
Marital status				0.104	0.747
Single	29	13 (23.64)	16 (26.23)		
Married	87	42 (76.36)	45 (73.77)		

BMI, Body Mass Index.

pared and analyzed. The efficacy evaluation criteria are shown in the *Curative effect evaluation* section. The safety analysis was mainly to observe and record the incidence of adverse events (AEs) such as abdominal discomfort, hot flashes, dizziness, or nausea and vomiting, and the incidence rate was calculated. The Lequesne Index score ranges from 1 to 24 points, with higher scores indicating worse disease severity and functional status. The score range of VAS is 0-10 points, with the score being proportional to the degree of pain. ELISA quantified the concentrations of IFs such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and high-sensitivity C-reactive protein (hs-CRP) following the corresponding human ELISA kit (Guangzhou Ruite Biotechnology Co., Ltd., 639-13749, 111010, 001397) instructions. Efficacy, safety, VAS, and IFs were primary outcome measures while the Lequesne Index was the secondary outcome measure.

Statistics and analysis

The data of this study were analyzed using SPSS 16.0. The number of cases/percentage (n/%) and mean ± SEM were used to indicate counted data and measured data, respectively. The χ^2-test was used for comparison of counted data between groups, while independent sample t-test and paired t-test were adopted to identify inter-group and intra-group (before and after treatment) differences of the measured data, respectively. The Cox regression model was used to perform an in-depth analysis of factors influencing the occurrence of complications in KOA patients. P<0.05 indicated significance.

Results

Comparison of baseline data

We found no significant difference when comparing the baseline data between the two groups in terms of sex, average age, course of disease, body mass index, bilateral KOA, drinking history, smoking history, marital status, etc. (P>0.05), suggesting compatibility. See **Table 1** for details.

Efficacy of DIA + GlcN·HCl in KOA patients

As shown in **Table 2**, the inter-group comparison of curative efficacy revealed an ORR of 63.64% in the Con group, which was obviously lower than 83.61% in the Obs group (P<0.05).

Safety of DIA + GlcN·HCl in KOA patients

The incidence of abdominal discomfort, hot flashes, dizziness, and nausea and vomiting in both groups were observed, counted, and ana-

Table 2. Clinical efficacy in two groups of patients [n (%)]

Group	n	Marked response	Response	Non-response	Overall response rate
Control group	55	19 (34.55)	16 (29.09)	20 (36.36)	35 (63.64)
Observation group	61	28 (45.90)	23 (37.70)	10 (16.39)	51 (83.61)
χ^2 value	-	-	-	-	6.016
P value	-	-	-	-	0.014

Table 3. Incidence of adverse events in two groups of patients [n (%)]

Category	Control group (n=55)	Observation group (n=61)	χ^2 value	*P* value
Abdominal discomfort	2 (3.64)	1 (1.64)	-	-
Hot flashes	3 (5.45)	1 (1.64)	-	-
Dizziness	3 (5.45)	2 (3.28)	-	-
Nausea and vomiting	3 (5.45)	0 (0.00)	-	-
Overall incidence	11 (20.00)	4 (6.56)	4.642	0.031

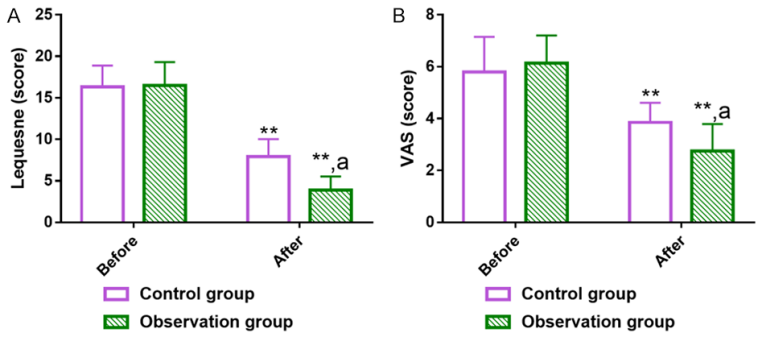

Figure 1. Impact of diacerein plus glucosamine hydrochloride on Lequesne Index score and VAS score of KOA patients. A. The observation group showed markedly lower Lequesne Index score after treatment, lower than that of the control group. B. The VAS score of the observation group decreased significantly after treatment and was lower than that of the control group. Note: VAS, Visual Analogue Scale; KOA, Knee Osteoarthritis.

lyzed, as shown in **Table 3**. It was found that the total AE rate in the Obs was 6.56%, which was significantly lower than 20.00% in the Con (P<0.05).

Impact of DIA + GlcN·HCl on Lequesne index and VAS scores of KOA patients

The Lequesne Index and VAS scores of both patient cohorts were analyzed to evaluate the impacts of the two drug regimens on KOA patients' condition, functional status, and pain (**Figure 1**). The analyses showed no significant difference in pre-treatment Lequesne Index score and VAS score between the two groups (P>0.05), while significant decreases in the two scores were observed in both cohorts after treatment, with markedly lower scores in the Obs group than those in the Con (P<0.05).

Impact of DIA + GlcN·HCl on IFs in KOA patients

Further, we tested patients' IFs to compare and analyze the effects of the two intervention methods on patients' inflammatory responses (**Figure 2**). The data determined no significant differences in hs-CRP, TNF-α and IL-1β between groups before treatment (P>0.05), but these three IFs decreased statistically in the Obs group after treatment and were lower compared with those in the Con group (P<0.05).

Analysis of prognostic factors affecting the occurrence of complications in KOA patients

The analysis of the prognostic factors influencing the occurrence of complications in KOA patients showed that rather than Lequesne and VAS scores (P>0.05), TNF-α (P=0.006), IL-1β (P=0.019), hs-CRP (P=0.033) and treatment mode (P=0.011) were prognostic factors affecting the occurrence of complications in KOA patients (**Table 4**).

Discussion

Knee osteoarthritis (KOA), a chronic degenerative joint disease, has caused varying degrees of negative impact on millions of people worldwide [18]. Hence, optimizing drug treatments for KOA patients carries huge implications for

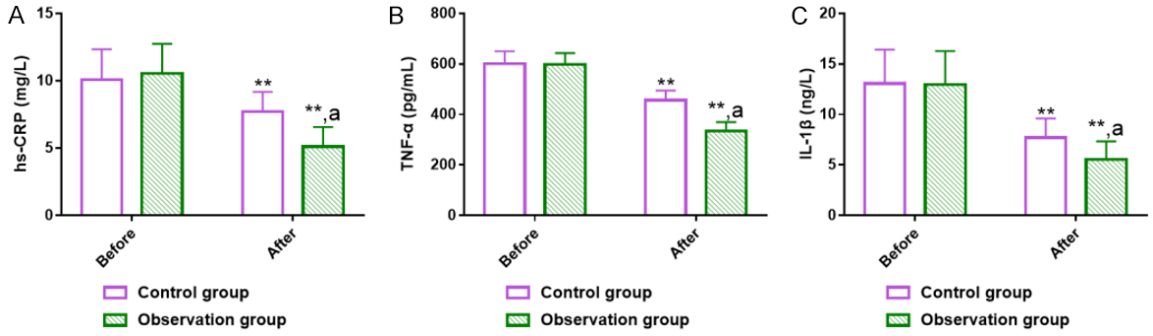

Figure 2. Impact of diacerein plus glucosamine hydrochloride on inflammatory factors in KOA patients. A. The observation group showed statistically decreased post-treatment hs-CRP level, which was lower than that in the control group. B. The observation group showed statistically decreased post-treatment TNF-α level, which was lower than that in the control group. C. The observation group showed statistically decreased post-treatment IL-1β level, which was lower than that in the control group. Note: KOA, Knee Osteoarthritis; hs-CRP, high-sensitivity C-Reactive Protein; TNF-α, Tumor Necrosis Factor α; IL-1β, Interleukin 1β.

Table 4. Cox multivariate analysis of prognostic factors influencing the occurrence of complications in KOA patients

Category	B	SE	Wald	P	OR (95% CI)
Lequesne	0.186	0.141	1.742	0.187	1.205 (0.914-1.589)
VAS	0.174	0.338	0.264	0.607	1.190 (0.614-2.307)
TNF-α	0.026	0.010	7.601	0.006	1.027 (1.008-1.046)
IL-1β	0.393	0.168	5.474	0.019	1.482 (1.066-2.060)
hs-CRP	0.376	0.176	4.563	0.033	1.457 (1.032-2.057)
Treatment mode	-3.451	1.357	6.467	0.011	0.032 (0.002-0.453)

Note: KOA, Knee Osteoarthritis; VAS, Visual Analogue Scale; TNF-α, Tumor Necrosis Factor α; IL-1β, Interleukin 1β; hs-CRP, high-sensitivity C-Reactive Protein.

alleviating joint pain and preventing disease progression in such patients.

In this study, we enrolled 55 patients treated with DIA monotherapy (Con group) and 61 patients treated with DIA + GlcN·HCl (Obs group). The inter-group comparison of curative efficacy determined a higher ORR in the Obs group versus the Con (83.61% vs. 63.64%), indicating better clinical efficacy of the combined intervention than single drug intervention in the treatment of KOA. DIA is known to protect cartilage in vivo and in vitro by blocking the release of IL-1 and inhibiting its activity, thus reducing joint pain to a certain extent and playing a therapeutic role [19]. GlcN·HCl, as mentioned above, can play a synergistic role in anti-KOA treatment through different action pathways with DIA, which may also be the reason why the combined treatment of the two is superior to DIA monotherapy. In our case series, patients mainly experienced AEs such as abdominal discomfort, hot flashes, and dizziness, as shown by the safety analysis. A statistically lower total AE rate was determined in the Obs group than in the Con group (6.56% vs. 20.00%), indicating a higher safety profile of DIA + GlcN·HCl. Shakya et al. [20] reported that DIA was superior to conventional NSAIDs in efficacy and safety in the treatment of KOA. In the study of Zhang et al. [21], the ORR of patients with osteoarthritis after GlcN·HCl intervention was 75.4%, with no serious AEs. The safety of DIA in KOA may be attributed to the fact that it does not cause gastrointestinal mucosal injury nor cardiovascular events in patients [22]. We also evaluated the Lequesne Index score and VAS score of both cohorts of patients. It was found that the condition of KOA patients with DIA + GlcN·HCl intervention was significantly milder, and their improvements of functional status and the alleviation of pain were more significant than those of patients with DIA intervention. In a report by Provenza et al. [23], GlcN·HCl plus chondroitin sulfate exerted a sustained analgesic effect in KOA, similar to our findings. As reported by Gang et al. [24], GlcN·HCl had an effect of alleviating symptoms and improving joint function in knee degenerative osteoarthritis. The analgesic mechanism of GlcN·HCl on KOA mainly lies in improving cartilage metabolism and joint lubrication by increasing the body's absorption of bone calcium, so as to reduce the pain caused by joint activity and improve the condition [25].

Inflammation is considered a risk factor for KOA progression [26]. Over-stimulation of IFs can lead to an imbalance in the intra-articular microenvironment, causing damage to cartilage, subchondral bone, and meniscus, thus accelerating disease progression [27]. hs-CRP is known to be not only closely related to the clinical symptoms of KOA patients such as tenderness, swelling, and patellar tenderness, but its elevated level is also strongly associated with the degree of KOA pain [28, 29]. TNF-α and IL-1β are vital mediators in the pathological disorder of KOA, closely associated with the degeneration of articular cartilage matrix [30]. The above three indicators are all pro-inflammatory factors [31]. Our data showed that compared with the Con group, the hs-CRP, TNF-α and IL-1β in the Obs groupwere notably lower after treatment, indicating that DIA + GlcN·HCl can better ameliorate the inflammatory microenvironment of KOA patients than DIA monotherapy. In the study of Zhang et al. [32], GlcN·HCl plus celecoxib exerted positive effects on functional recovery and inflammation inhibition of KOA patients, which is consistent with our findings. The anti-inflammatory mechanism of GlcN·HCl is related to its inhibition of MMP-3, MMP-13, and cyclooxygenase-2 [33]. Finally, Cox multivariate analysis identified that TNF-α, IL-1β, hs-CRP, and treatment mode were prognostic factors affecting occurrence of complications in KOA patients. That is to say, KOA patients with high TNF-α, IL-1β, and hs-CRP levels were at increased risk of complications, and a combination therapy regimen was a protective factor against complications in such patients, which once again demonstrates the safety of DIA + GlcN·HCl for the clinical treatment of KOA.

Although our research confirmed that DIA + GlcN·HCl was effective and safe in the treatment of KOA, it still has some limitations that need to be addressed. First, analysis of long-term efficacy should be supplemented, as we still do not understand the long-term efficacy of this combination therapy in KOA. Second, this is a single-center and small-sample study. If the sample size can be increased, and multi-center samples can be included, the accuracy of the research results will be improved. Further improvements will be made based on these two points in the future.

Conclusion

DIA plus GlcN·HCl are effective in the treatment of KOA, contributing to a lower incidence of AEs, improved functional status of patients, and better pain relief and inflammation inhibition. This suggests clinical usefulness.

Disclosure of conflict of interest

None.

Address correspondence to: Quan Wang, Inner Mongolia Bailige Medical Science and Technology Co., Ltd., Inner Mongolia 010010, P. R. China. Tel: +86-13552686107; E-mail: wangzy202208@163.com

References

[1] Henrotin Y, Bannuru R, Malaise M, Ea HK, Confavreux C, Bentin J, Urbin-Choffray D, Conrozier T, Brasseur JP, Thomas P, Hick AC, Marinello A, Giordan N and Richette P. Hyaluronan derivative HYMOVIS(R) increases cartilage volume and type II collagen turnover in osteoarhritic knee: data from MOKHA study. BMC Musculoskelet Disord 2019; 20: 293.

[2] Magnusson K, Turkiewicz A and Englund M. Nature vs nurture in knee osteoarthritis-the importance of age, sex and body mass index. Osteoarthritis Cartilage 2019; 27: 586-592.

[3] Deveza LA, Bierma-Zeinstra SMA, van Spil WE, Oo WM, Saragiotto BT, Neogi T, van Middelkoop M and Hunter DJ. Efficacy of bisphosphonates in specific knee osteoarthritis subpopulations: protocol for an OA Trial Bank systematic review and individual patient data meta-analysis. BMJ Open 2018; 8: e023889.

[4] Wang H and Ma B. Healthcare and scientific treatment of knee osteoarthritis. J Healthc Eng 2022; 2022: 5919686.

[5] Hawker GA. Osteoarthritis is a serious disease. Clin Exp Rheumatol 2019; 37 Suppl 120: 3-6.

[6] McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, Kwoh K, Lohmander S, Rannou F, Roos EM and Underwood M. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014; 22: 363-388.

[7] Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS and Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, part

II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008; 16: 137-162.
[8] Paredes-Carnero X, Escobar J, Galdo JM and Babe JG. Total knee arthroplasty for treatment of osteoarthritis associated with extra-articular deformity. J Clin Orthop Trauma 2018; 9: 125-132.
[9] Loeser RF, Beavers DP, Bay-Jensen AC, Karsdal MA, Nicklas BJ, Guermazi A, Hunter DJ and Messier SP. Effects of dietary weight loss with and without exercise on interstitial matrix turnover and tissue inflammation biomarkers in adults with knee osteoarthritis: the Intensive Diet and Exercise for Arthritis trial (IDEA). Osteoarthritis Cartilage 2017; 25: 1822-1828.
[10] Bruyere O, Cooper C, Pelletier JP, Branco J, Luisa Brandi M, Guillemin F, Hochberg MC, Kanis JA, Kvien TK, Martel-Pelletier J, Rizzoli R, Silverman S and Reginster JY. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum 2014; 44: 253-263.
[11] Chen X, Zhu X, Dong J, Chen F, Gao Q, Zhang L, Cai D, Dong H, Ruan B, Wang Y, Jiang Q and Cao W. Reversal of epigenetic peroxisome proliferator-activated receptor-gamma suppression by diacerein alleviates oxidative stress and osteoarthritis in mice. Antioxid Redox Signal 2022; 37: 40-53.
[12] Martel-Pelletier J and Pelletier JP. Effects of diacerein at the molecular level in the osteoarthritis disease process. Ther Adv Musculoskelet Dis 2010; 2: 95-104.
[13] Hochberg MC, Martel-Pelletier J, Monfort J, Moller I, Castillo JR, Arden N, Berenbaum F, Blanco FJ, Conaghan PG, Domenech G, Henrotin Y, Pap T, Richette P, Sawitzke A, du Souich P and Pelletier JP; MOVES Investigation Group. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. Ann Rheum Dis 2016; 75: 37-44.
[14] Chen B, Fang L, Lin L, Lv Y, Huang Z, Lin X and Wang X. Aerobic exercise combined with glucosamine hydrochloride capsules inhibited the apoptosis of chondrocytes in rabbit knee osteoarthritis by affecting TRPV5 expression. Gene 2022; 830: 146465.
[15] Sukerkar PA and Doyle Z. Imaging of osteoarthritis of the knee. Radiol Clin North Am 2022; 60: 605-616.
[16] Nadrian H, Moghimi N, Nadrian E, Moradzadeh R, Bahmanpour K, Iranpour A and Bellamy N. Validity and reliability of the persian versions of WOMAC osteoarthritis index and lequesne algofunctional index. Clin Rheumatol 2012; 31: 1097-1102.
[17] Shalhoub M, Anaya M, Deek S, Zaben AH, Abdalla MA, Jaber MM, Koni AA and Zyoud SH. The impact of pain on quality of life in patients with osteoarthritis: a cross-sectional study from palestine. BMC Musculoskelet Disord 2022; 23: 248.
[18] Nakagawa Y, Mukai S, Yamada S, Murata S, Yabumoto H, Maeda T and Akamatsu S. The efficacy and safety of highly-bioavailable curcumin for treating knee osteoarthritis: a 6-month open-labeled prospective study. Clin Med Insights Arthritis Musculoskelet Disord 2020; 13: 1179544120948471.
[19] Panova E and Jones G. Benefit-risk assessment of diacerein in the treatment of osteoarthritis. Drug Saf 2015; 38: 245-252.
[20] Shakya Shrestha S, Tamrakar S, Shrestha R, Shrestha R, Basi A, Malla M and Khadka SK. Comparative efficacy and safety of diacerein in patients with knee osteoarthritis: a pilot study. Kathmandu Univ Med J (KUMJ) 2021; 19: 260-264.
[21] Zhang WB, Zhuang CY, Li JM, Yang ZP and Chen XL. Efficacy and safety evaluation of glucosamine hydrochloride in the treatment of osteoarthritis. Zhonghua Wai Ke Za Zhi 2007; 45: 998-1001.
[22] Li G, Zhang Z, Ye Y, Li H, Luo H, Tang K and Lai Y. Efficacy, residual effectiveness and safety of diacerein in the treatment of knee osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Medicine (Baltimore) 2022; 101: e31700.
[23] Provenza JR, Shinjo SK, Silva JM, Peron CR and Rocha FA. Combined glucosamine and chondroitin sulfate, once or three times daily, provides clinically relevant analgesia in knee osteoarthritis. Clin Rheumatol 2015; 34: 1455-1462.
[24] Gang X and Gao L. Therapeutic results of glucosamine hydrochloride for knee degenerative osteoarthritis. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2008; 22: 29-31.
[25] Block JA, Oegema TR, Sandy JD and Plaas A. The effects of oral glucosamine on joint health: is a change in research approach needed? Osteoarthritis Cartilage 2010; 18: 5-11.
[26] He W, Wu Y, Liu Q, Cheng X, Wu J, Han X and Huang Z. Effect of Etoricoxib on miR-214 and inflammatory reaction in knee osteoarthritis patients. Am J Transl Res 2021; 13: 9586-9592.
[27] Zeng CY, Zhang ZR, Tang ZM and Hua FZ. Benefits and mechanisms of exercise training for knee osteoarthritis. Front Physiol 2021; 12: 794062.

[28] Hanada M, Takahashi M, Furuhashi H, Koyama H and Matsuyama Y. Elevated erythrocyte sedimentation rate and high-sensitivity C-reactive protein in osteoarthritis of the knee: relationship with clinical findings and radiographic severity. Ann Clin Biochem 2016; 53: 548-553.

[29] Shadyab AH, Terkeltaub R, Kooperberg C, Reiner A, Eaton CB, Jackson RD, Krok-Schoen JL, Salem RM and LaCroix AZ. Prospective associations of C-reactive protein (CRP) levels and CRP genetic risk scores with risk of total knee and hip replacement for osteoarthritis in a diverse cohort. Osteoarthritis Cartilage 2018; 26: 1038-1044.

[30] Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP and Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol 2011; 7: 33-42.

[31] Lin ZK, Ma SJ, Qian JL, Lin SH, Xia YR, Xie YF, Wang HY and Shu R. Association between periodontitis and mild cognitive impairment: a clinical pilot study. Zhonghua Kou Qiang Yi Xue Za Zhi 2022; 57: 576-584.

[32] Zhang J, Ge R and Yang Z. Effect of celecoxib combined with glucosamine hydrochloride in promoting the functional recovery and decreasing the inflammatory factor levels in patients with knee osteoarthritis. Pak J Pharm Sci 2021; 34: 1277-1282.

[33] Bascoul-Colombo C, Garaiova I, Plummer SF, Harwood JL, Caterson B and Hughes CE. Glucosamine hydrochloride but not chondroitin sulfate prevents cartilage degradation and inflammation induced by interleukin-1alpha in bovine cartilage explants. Cartilage 2016; 7: 70-81.