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Evaluation on the Effectiveness of Intraarticular Hyaluronic Acid Products as Dual Treatment in Chinese Population

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Authors' contributions

This work was carried out in collaboration among all authors. Authors LHYJ and CM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author CWKK managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Intraarticular hyaluronic acid injection is a common treatment option for osteoarthritis that has proven efficacy and safety. This study aims at investigating the effectiveness of a dual treatment on the physical and life condition of knee osteoarthritis patients in the Chinese population.
Methods: Patients with knee osteoarthritis received intraarticular injection of 2 hyaluronic acid products, namely RegenFlex Starter and RegenFlex Bio-Plus, with the latter injected one week subsequent to the first injection. The change in the range of movement, synovial fluid volume, pain score and Knee Injury and Osteoarthritis Outcome Score were compared and followed up to 6 months after injection.
Results: 84 patients with unilateral or bilateral knee osteoarthritis were involved in the study. 50 of them had synovial fluid detected prior to injections while 34 had not. The volume of synovial fluid was significantly reduced from 10 mL to 5 mL after hyaluronic acid injection. Significant

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improvements were also found in three Knee Injury and Osteoarthritis Outcome Score subcategories, namely Pain, Symptoms and Activities of Daily Living. A visual analogue scale for the pain scores of patients after injections showed significant decrement up to 6 months afterward.
Conclusion: A dual hyaluronic acid injection treatment of RegenFlex Starter and Bio-Plus is effective in reducing pain and improving daily functional capacities of patients in the Chinese population.

Keywords: Hyaluronic acid; osteoarthritis; intraarticular injection.

1. INTRODUCTION

As people age, they become prone to such degenerative diseases as osteoarthritis (OA) due to the characteristic deterioration of cells, tissues and organs over time. With age being the most prominent risk factor of OA [1], elderly subjects often experience pain in their joints especially in the knee. Amongst available treatments such as magnetic pulse therapy and stem cell therapy, most of them have been found to provide inconsistent and inconclusive evidence, prompting a new approach of treatment. RegenFlex Starter (2 mL) and RegenFlex Bio-Plus (3 mL), with hyaluronic acid (HA) as the main component of both products, have been shown to effectively reduce joint pain and simultaneously improve the quality of life [2].

1.1 The Impact of Aging on the Development of Knee Osteoarthritis

OA is a type of chronic disease that causes pain and reduction in mobility in the adult population [3], with a global prevalence of 22.9% in adults of 40 years or above [4]. Across different regions, the Asian population has the highest prevalence of 19.2% [4]. OA is generally believed to be caused by factors including change in bone modelling processes, destruction of cartilage, as well as the abnormal functioning of bone cells [5]. Two forms of OA, namely primary OA and secondary OA are commonly observed. While the latter occurs as a result of damage to the cartilage from diseases such as obesity or pre-existing injuries in the area, the former is well known for having age as its leading factor of disease development [6]. Typically seen in people above the age of 55, a central feature of OA is the imbalance in catabolic and anabolic signalling in cartilage, resulting in progressive matrix destruction. Such imbalance is caused by age-related oxidative stress, which leads to an inactivation of antioxidant systems and allows for rising levels of intracellular reactive oxygen species [7]. In other words, simple antioxidants fail to specifically target this disrupted physiologic signalling, promoting the degradation of cartilage within the joints and reducing the viscosity of the synovial fluid (SF). The pain experienced by a patient diagnosed with OA ranges from stiffness and minor joint pain to severe discomfort in carrying out daily activities, which can immensely impact the quality of life of affected individuals.

1.2 Function of RegenFlex Starter and RegenFlex Bio-Plus

Various conventional treatments for knee OA are available. Common options include the use of non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular steroids, hyaluronic acid, opioids and glucosamine [8]. Given that the disease has no definitive cure, patients may opt to receive a direct intraarticular hyaluronic acid injections in the hope of reducing pain and improving life quality. Both Regen Flex Starter and Regen Flex Bio-Plus are gels based on HA, a substance not only an important constituent of the SF, but also completely natural as a component of connective tissue in the human body. Through intraarticular injections in the knee joint, both gels have similar yet distinct functions: while Starter mainly provides an analgesic effect by immediate reduction of pain and inflammation, Bio-Plus focuses on viscosupplementation, restoring the viscoelastic properties of the SF as well as lubricating the joint. The composition of both gels are as well different: Starter consists of linear HA while Bio-Plus contains HA with cross-linking agent 1,4-butanediol diglycidyl ether (BDDE) and linear HA that is intercalated and slowly released, forming a more stable compound compared to linear HA, as it reduces HA sensitivity to hyaluronidase-mediated degradation [9]. With such distinct properties between the products, the application of Starter and Bio-Plus as a dual treatment has shown success in suffering patients over a period of time. Such success was suggested by a study conducted from the University studies of Urbino Carlo Bo, where researchers concluded that “the RegenFlex Starter plus Bio-Plus protocol has been

demonstrated to be effective on both mild and high-grade chondropathies, with a clinical improvement in articular function and a slowing of disease progression." [2]

1.3 Aim of Study

Although the findings by University Urbino Carlo Bo did show the effectiveness of the dual treatment, the paper mainly involved Caucasians patients. Given the possibility that anthropometric factors or even genetic variations can impact the effectiveness of the treatment, there is a need of conducting a separate research to determine if the results can be generalized to the Chinese population. This study will further validate the effectiveness of the combined protocol of Starter and Bio-Plus to treat knee osteoarthritis in Chinese subjects.

2. METHODS

2.1 Study Design and Subject Recruitment

A descriptive longitudinal study was performed with data collected from medical records of individual subjects and the self-administered Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaires [10] filled in before and after HA injections. The study covered up to 6 months after the first HA injection. Data were pooled from subjects meeting the inclusion criteria: Chinese subjects diagnosed with unilateral or bilateral knee OA; received intraarticular HA injections; completed the KOOS questionnaire and willing to join the study. Exclusion criteria were insufficiency in data from medical records (such as missing date and location of HA injection); and unfilled KOOS questionnaire.

Subjects fulfilling the inclusion criteria were recruited, and basic information was recorded which includes age, sex, type of knee OA (unilateral or bilateral), location of HA injection and the volume of SF. Diagnosis was performed by registered physicians according to the Kellgren-Lawrence Classification of Osteoarthritis [11] with the aid of knee X-ray images. Most subjects were categorized as grade III-IV. Assessments on the range of movement (ROM) and SF volumes (mL), as well as the completion of KOOS questionnaire were done at baseline and after the HA injections respectively. A visual analogue scale (VAS) was used to determine the pain score of subjects at different time points, following up to six months after the second HA injection.

2.2 HA Injections

A total of two intraarticular HA products were sequentially injected, namely RegenFlex Starter and Bio-Plus. While the former contains linear HA of 0.8-1.2 MDa supplied in 32 mg/ 2 mL dosage, the latter consists of two cross-linked HA, 1.0 and 2.0 MDa respectively, intercalated with a linear 0.5 MDa HA and is supplied in 75 mg/ 3 mL form. The second injection was carried out one week subsequent to the first injection.

The injection processes were carried out in the operation theatre of a private clinic with proper aseptic techniques. The medications were injected with the parapatellar approach. Arthrocentesis was performed prior to HA injections for subjects diagnosed with hydrarthrosis, and the volumes of SF withdrawn were recorded in mL. After injection, subjects were instructed with the ways of mild stretching and muscle training of which they should practice on a daily basis for the purpose of relieving joint pain and swelling conditions.

2.3 Knee Function Assessments

Four parameters were used to evaluate the effectiveness of HA injections in improving the knee OA condition. They are the ROM, SF volumes, VAS of knee pain score and KOOS. The ROM was assessed by physicians at baseline and after HA injections using a scale of 0 - 100. SF volumes withdrawn before the first and second HA injections were recorded. A VAS from 1-10 was used to determine the pain scores at baseline, 2 and 24 hours after the first HA injection, and immediately after the second injection. Follow up phone calls were conducted to obtain the pain scores at 1, 3 and 6 months after the second HA injection. Two questionnaires of the same content were filled in by subjects prior and subsequent to the HA injections. Questions were designed according to the KOOS index in which a score out of 0-100 is generated from each of the five aspects, namely Pain, Symptoms, Activities of Daily Living (ADL), Sport and Recreation Function (SportRec) and Quality of Life (QoL) (Appendix 1 & 2).

2.4 Statistical Analysis

Statistical analyses were conducted for the parameters using SPSS (IBM SPSS Statistics for

Mac OS 10.15) with a significance level set at .05. Wilcoxon signed-rank tests were used to compare the ROM, SF volume and KOOS values at baseline and after the second injection. A Kruskal-Wallis test was performed on the VAS pain scores and pairwise comparisons were carried out to determine the difference in pain scores at respective timepoints with baseline values.

3. RESULTS

Data were obtained from a total of 84 subjects among who 41 were males and 43 were females. 48 of them were diagnosed with bilateral knee OA and 36 diagnosed with unilateral knee OA (18 right knee and 18 left knee). The mean age ± standard deviation of the subjects was 62.96 ± 11.55. 50 subjects had SF withdrawn before HA injections while 34 subjects had no SF recorded. Subjects characteristics of the whole study and the sex subgroups are summarized in Table 1.

Wilcoxon signed-rank tests were performed on ROM, SF and KOOS respectively. Median values were reported, as a non-parametric test is preferred for a population not following normal distribution. Results are summarized in Table 2. Except for KOOS QoL, results from all aspects reflect improvement in the knee condition after HA injections. The median SF volume is significantly reduced from 10 mL to 5 mL. Four out of five subcategories of KOOS showed increased scores, with the aspects of Pain, Symptoms and ADL exhibiting significant increments. The median value of change in ROM manifested a 15-mark elevation out of a scale of 100.

A Kruskal-Wallis test was used to test for the difference in VAS pain scores at various timepoints and the mean ranks are summarized in Table 3. Overall, a decreasing trend of pain score was observed, with all individual data points showing statistically significant difference with the baseline value. While apparent decrements of pain scores were observed after the first injection and one month after the second injection, a gradual drop in pain score was observed between the interval of the two injections. The mean rank of pain scores remained low since the third month after the second HA injection.

Several subgroup analyses were also performed on respective sex, type of OA (bilateral or unilateral) and the absence or presence of SF. The results in these subgroups mostly resemble the overall study statistics.

Table 1. Subject characteristics

	Study	Male subgroup	Female subgroup
Subjects	84	41	43
Age (years)	62.96 ± 11.55	62.22 ± 11.17	63.67 ± 11.99
Bilateral OA	48	26	22
Right knee OA	18	10	8
Left knee OA	18	5	13
SF (Yes)	50	26	24
SF (No)	34	15	19

OA, osteoarthritis; SF, synovial fluid
Values are mean ± SD

Table 2. Medians of ROM, SF and KOOS

	Median (before injection)	Median (after injection)	Significance (P values)
ROM	80.00	95.00	.28
SF	10.00	5.00*	.00
KOOS Pain	63.89	69.44*	.00
KOOS Symptoms	64.29	67.86*	.00
KOOS ADL	75.00	81.62*	.00
KOOS SportRec	40.00	50.00	.08
KOOS QoL	37.50	37.50	.19

ROM, range of movement; SF, synovial fluid; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, Function in Daily Living; SportRec, Sport and Recreation Function; QoL, Quality of Life
**Significantly different from baseline*

Table 3. Mean ranks of VAS pain scores

	Before injection	2 hours after first injection	24 hours after first injection	Immediately after second injection	1 month after second injection	3 months after second injection	6 months after second injection
Pain Score	136.65	94.12*	85.19*	82.82*	81.93*	45.60*	45.00*
Significance (p values)		.04	.00	.00	.03	.02	.00

Pain scores are represented as mean ranks
P values are obtained from pairwise comparisons of individual mean rank with baseline
**Significantly different from baseline*

4. DISCUSSION

The present study evaluates the effectiveness of a dual treatment of intraarticular HA injections on the OA conditions within the Chinese population. Follow up investigations up to 6 months generated results that indicate the positive impacts of a sequential injection of linear and crosslinked HA on the improvement of hydrarthrosis, level of pain and symptoms, as well as the ability to perform daily activities with reduced difficulty. The significant drop of VAS pain scores also served as a strong evidence of OA amelioration and patient satisfaction towards the therapy. The results from this study concurred with those from University Urbino Carlo Bo, further strengthening the claim that such a combined therapy is indeed safe and effective in relieving pain and improving functional ability of OA patients [2].

The volume of SF from aspiration is recorded since an elevated SF volume is a characteristic in pathologic knee joints with inflammation [12-14]. The accumulation of SF is also commonly observed in synovitis, a disease that has close correlation with OA [15]. The significant reduction in SF volume suggests that RegenFlex HA supplements are useful in reducing inflammation and swelling conditions induced by OA. Such a proposal is indeed supported by the knowledge that high molecular weight HA has the ability to bind with receptors like CD44 and down-regulate the production of inflammatory markers [16,17].

Although biochemical analyses were not performed like similar studies [2, 18], it is hypothesized that Starter (linear HA) and Bio-Plus (crosslinked HA) brings anti-inflammatory effects by reducing the production of inflammatory molecules, thus controlling inflammation and lowering the level of fluid accumulation in the synovial cavity. The observations from the present study provides a potential direction for future research with similar settings to make investigations on the inflammatory modulators, so as to further validate the suggested effect of RegenFlex injections on SF volume in Chinese subjects.

Apart from having the SF volume as an objective parameter, another self-reported score was adopted in the study. Being recognized as a reliable parameter for the judgement of treatment success for knee OA [19], the VAS pain score showed a continuous significant reduction up to six months after the injection, suggesting that RegenFlex intraarticular regimens are indeed effective in relieving joint ache. A pattern of pain score reduction is observed where remarkable decrement of pain scores appeared shortly after the first injection and three months after the second injection.

The two notable changes can be explained by the respective effects of RegenFlex Starter (linear HA) and Bio-Plus (crosslinked HA). While the long recognized pain reducing efficacy of linear HA [20-22] contributed to the first notable improvement in pain score, the second drop may be attributed to the long term chondroprotective and viscosupplementation effect of crosslinked HA [22], which is made possible due to its higher resistance against hyaluronidase mediated degradation, and the ability to release HA molecules in a much slower speed [2, 23]. Given the positive results obtained here, there seems to be much value of continuing this investigation for further follow-ups up in order to understand the long-term effect of RegenFlex injections on the Chinese population.

Coherent with the changes in VAS pain scores, the KOOS survey Pain subcategory, another parameter for pain determination, showed appreciable reduction as well. Two other subcategories of the KOOS survey, namely Symptoms and ADL, also improved significantly. The results are as expected since the symptoms modifying ability of HA on OA is well recognized in literature [17, 24]. With ameliorated disease symptoms, essentially the ADL score improves parallelly, as symptoms like stiffness and numbness are in fact great obstacles towards performing even simple actions like walking and climbing stairs.

Despite having positive results for the three subcategories, insignificant changes were reflected in the SportRec and QoL subcategories. Similarly, the improvement in ROM was found to be statistically insignificant. A possible reason for the findings may be due to the difference in patient expectations prior to treatment. As a type of self-reported data, some may claim a score much lower because the intervention outcomes have failed their expectations. This does not necessarily mean the medication *per se* is of no use. In fact, past studies have reported that patients receiving placebos also claimed an improvement in their knee condition [19,25,26], indicating that the definitions of a “successful treatment” or “improvement” to individual patients are rather ambiguous. We infer that the KOOS

survey results may be under the influence of personal anticipations, especially when subjects have different backgrounds and nature of work. The same level of knee deterioration may pose distinct physical and psychological obstructions on an office worker and an athlete. That said, further studies and follow-ups for a longer period will be necessary before one can fully judge the effectiveness of RegenFlex products.

There were a few limitations of this study, including the lack of a control group and biochemical assessments, both of which would allow a more objective evaluation of HA product effectiveness. The placebo effect should also be tested, without which may lead to a biased conclusion on the pain relieving and functional improving power of the tested medication. There were also varying basic care received by subjects, including current medications, physical therapies and the habit of stretching.

5. CONCLUSION

This study proved that the sequential injection of RegenFlex Starter and Bio-Plus as a dual treatment for Chinese patients with OA is effective in relieving the experience of pain and symptoms, reducing the accumulation of SF as well as improving the ability of individuals performing daily functions. It is believed that the results from the current study serves as a preliminary version for the full assessment of RegenFlex products on Chinese subjects, which is to be performed in more in-depth studies in the future.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Appendix 1 KOOS survey

Anonymous. Knee Injury And Osteoarthritis Outcome Score, Ewa Roos. Koos.nu. 2012. Accessed 28 December 2020. Available: http://www.koos.nu/index.html.

KOOS Scoring 2012

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a patient reported survey used to determine patient's thoughts on the condition of their knees, and the results are adopted for the measurement of OA treatments. The questionnaire is used for the evaluation of both short term and long term knee condition of OA patients. It consists of 42 questions and is divided into five subcategories, namely KOOS Pain, KOOS Symptoms, Function in Daily Living (KOOS ADL), Function in Sport and Recreation (KOOS SportRec), and Knee-related Quality of Life (KOOS QoL). Each question is designed with five choices where patients put a tick in the box that fits the description the most.

☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
0	1	2	3	4

The responses collected are subsequently converted to numerical values and a score is calculated for each subcategory. Each subcategory score is calculated independently. Apply the mean of the observed items within the subcategory, divide by 4 (the highest possible score for a single answer option), and multiply by 100; this number is then subtracted from 100, and the final score generated is the KOOS subcategory estimate for that individual patient. A score of 100 indicates no problems while 0 indicates extreme problems.

1.	Pain	$100 - \frac{Mean\ score\ (P1-P9) x\ 100}{4}$ = KOOS Pain
2.	Symptoms	$100 - \frac{Mean\ score\ (S1-S7) x\ 100}{4}$ = KOOS Symptoms
3.	ADL	$100 - \frac{Mean\ score\ (A1-A17) x\ 100}{4}$ = KOOS ADL
4.	SportRec	$100 - \frac{Mean\ score\ (SP1-SP5) x\ 100}{4}$ = KOOS SportRec
5.	QoL	$100 - \frac{Mean\ score\ (Q1-Q4) x\ 100}{4}$ = KOOS QoL

Missing data is handled according to the 2012 version of the KOOS guideline. If a mark is placed outside a box, the closest box is chosen. If two boxes are marked, that which indicates the more severe problem is chosen. As long as at least 50% of the subcategory items are answered for each subscale, a mean score can be calculated. If more than 50% of the subscale items are omitted, the response is considered invalid and no subcategory score should be calculated. For the subcategory Pain, this means that 5 items must be answered; for Symptoms, 4 items; for ADL, 9 items; for SportRec, 3 items; and for QoL, 2 items must be answered in order to calculate a score. Subcategory scores are independent and can be reported for any number of the individual subcategories, i.e. if a particular subcategory is not considered valid (for example, the SportRec 2 weeks after total knee replacement), the results from the other subcategories can be reported at this time-point.

Appendix 2 KOOS questionnaire

Pain

P1	How often is your knee painful?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

What degree of pain have you experienced the last week when...?

P2	Twisting/pivoting on your knee	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P3	Straightening knee fully	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P4	Bending knee fully	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P5	Walking on flat surface	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P6	Going up or down stairs	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P7	At night while in bed	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P8	Sitting or lying	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
P9	Standing upright	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Symptoms

SY1	How severe is your knee stiffness after first wakening in the morning?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SY2	How severe is your knee stiffness after sitting, lying, or resting later in the day?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SY3	Do you have swelling in your knee?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SY4	Do you feel grinding, hear clicking or any other type of noise when your knee moves?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SY5	Does your knee catch or hang up when moving?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SY6	Can you straighten your knee fully?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SY7	Can you bend your knee fully?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Activities of Daily Living

What difficulty have you experienced the last week...?

A1	Descending	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A2	Ascending stairs	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A3	Rising from sitting	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A4	Standing	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A5	Bending to floor/ picking up an object	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A6	Walking on flat surface	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A7	Getting in/ out of car	☐	☐	☐	☐	☐

		Never	Mild	Moderate	Severe	Extreme
A8	Going shopping	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A9	Putting on socks/ stockings	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A10	Rising from bed	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A11	Taking off socks/ stockings	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A12	Lying in bed (turning over, maintaining knee position)	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A13	Getting in/ out of bath	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A14	Sitting	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A15	Getting on/ off toilet	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A16	Heavy domestic duties (shovelling, scrubbing floors, etc)	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
A17	Light domestic duties (cooking, dusting, etc)	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Sport and Recreation Function

What difficulty have you experienced the last week...?

SP1	Squatting	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SP2	Running	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SP3	Jumping	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SP4	Turning/ twisting on your injured knee	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
SP5	Kneeling	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Knee-related Quality of Life

Q1	How often are you aware of your knee problems?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Q2	Have you modified your lifestyle to avoid potentially damaging activities to your knee?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Q3	How troubled are you with lack of confidence in your knee?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme
Q4	In general, how much difficulty do you have with your knee?	☐ Never	☐ Mild	☐ Moderate	☐ Severe	☐ Extreme

Peer-review history:
The peer review history for this paper can be accessed here:
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