

The Effect of Silicon Dioxide on Knee Osteoarthritis: A Randomized Clinical Trial

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Received: 03 Jun. 2022; Accepted: 09 Apr. 2023

Abstract- Osteoarthritis (OA) is the most common type of arthritis and although there is no definitive cure for it, there are treatments for symptom management. The present study was conducted to evaluate the effects of silicon dioxide (SiO₂) on clinical symptoms of knee OA and compare it with avocado soybean unsaponifiable (ASU) and placebo. This study is a double-blind randomized clinical trial on 104 patients with knee OA referred to Rheumatology Clinic, Rasoul Akram Hospital, Tehran. Patients were randomly divided into three groups, including patients treated with ASU, SiO₂, and placebo for 3 months. Subsequent referral was performed at weeks 4, 8, and 12, and the stiffness, physical function, and pain scores were recorded based on the WOMAC questionnaire. In this study, the effect of treatment of placebo and SiO₂ and ASU in patients with knee OA based on WOMAC questionnaire showed a significant reduction in terms of pain, joint stiffness, physical function, and total scores of WOMAC in the cases of the SiO₂ group compared with the other two groups. The findings of this study showed that the therapeutic effects of SiO₂ in patients with knee OA in terms of pain and stiffness and physical function scores were more than the ASU and placebo groups.

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Acta Med Iran 2023;61(6):341-346.

Keywords: Knee osteoarthritis; Silicon dioxide; Avocado soybean unsaponifiable; WOMAC

Introduction

Osteoarthritis (OA) is the most common form of arthritis in the world and is strongly associated with aging. This is a complex disease of joints, characterized by degradation of articular cartilage and changes of the subchondral bone and inflammation, leading to pain and stiffness of the joints (1). Knee and hip OA have significant effects on mobility, and this is the reason for most joint replacement surgeries. Considering the increasing age of societies and the prevalence of obesity, it can be expected that the incidence of OA continues to rise. In addition to clinical manifestations of disease such as pain and joint movement restriction, OA leads to other complications. Also, disability due to OA may cause psychological problems such as depression, anxiety, and

irritability (2).

Currently, there is no safe treatment for OA to improve concurrently the clinical symptoms and improve the articular structure (3). Common treatments include exercise and physiotherapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and surgical procedures (4). However, other treatments such as intra-articular injection of hyaluronic acid and oral medications such as glucosamine, ginger compounds and avocado soybean unsaponifiable are also used, but their effectiveness remains to be clarified (2). Some studies have confirmed the efficacy and safety of ASU but these beneficial effects have not been observed in all patients alike (4).

Silicon is an element that is effective in bone metabolism and its deficiency in animals causes bone defects. Silicon increases the production of type I

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collagen in tissues (5). Several studies have shown the effect of silicon on increasing bone mass density (6,7). Also, silicon compounds could reduce pain in patients with knee OA and improve their functional status (8,9). A study investigated the effect of silicon in OA treatment in Iran that silicon dioxide was used and reduced pain and improved functional status of patients with knee OA (9). Considering the lack of effective and accepted drug treatment and increasing the number of patients, we aimed to investigate the effect of SiO₂ on the clinical symptoms of knee OA compared with ASU and placebo.

Materials and Methods

This double-blind randomized clinical trial was performed on patients with knee OA. Patients were randomly divided into three groups, including patients treated with SiO₂, ASU, and placebo for three months.

The inclusion criteria were defined as patients between 50 and 70 years with a diagnosis of primary knee OA according to the American College of Rheumatology (ACR) criteria (10), including knee pain plus at least three of the following characteristics: age >50 years, morning stiffness <30 min, crepitus on active motion, bony enlargement, bony tenderness, no palpable warmth of the synovium. Another inclusion criterion was a radiographic confirmed Kellgren and Lawrence grade I-IV (11). In patients with both knees OA, the knee with the highest pain score was considered the target knee. This study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran with Ethics code IR.IUMS.FMD.REC1396.9611288001 and registered with IRCT number IRCT20180316039112N2.

The exclusion criteria were as follows: a history of inflammatory arthritis such as gout, rheumatoid arthritis or spondyloarthropathy; secondary OA of the target knee; morning stiffness >30 min; significant trauma in the target joint within 12 months before the start of the trial; a history of arthroplasty and joint surgery of the target knee. Patients did not receive any other treatment, such as oral or injectable steroid medications, NSAIDs, glucosamine, hyaluronic acid, as well as physiotherapy within this period. Acetaminophen was used to control pain if needed, but 48 hours before each visit, they should not consume acetaminophen. Osvalin contains SiO₂ which was used as 150 mg per 25 kg body weight daily. The placebo was similar to the SiO₂ in terms of

appearance and taste and was administered with the same method. ASU was used as a capsule of piascledine 300 mg and once daily. Patients were divided into three groups by blind randomization.

Patients were visited every four weeks by one rheumatologist in the clinic. Physical function and pain and joint stiffness scores were recorded according to Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire based on symptoms in the target knee in the preceding 48 h. WOMAC questionnaire consists of three parts: pain, stiffness, and physical function. In this study, Persian-validated WOMAC form was used (12).

Statistical analyses were done with SPSS software version 21. In descriptive analysis, central indicators such as mean and percentage of frequency and coefficient of dispersion such as Standard Deviation (SD) were used. Independent t-test and Mann-Whitney U test were used to compare quantitative variables and Chi-square or Fisher's exact test was used to compare qualitative variables. The significance level was considered less than 0.05.

Results

In this study, 130 patients were divided into three different groups. During the study, 26 patients were excluded as follows: 18 people were reluctant to continue cooperation and 8 patients were excluded due to complications. The reasons for leaving the study were as follows: three individuals left because of nausea and abdominal pain and one person owing to skin rash in the SiO₂ group, and one patient because of dyspepsia in the ASU group, and one of the patients because of palpitation and two persons because of nausea in the placebo group.

Finally, 104 patients (females=89, males=15) were evaluated. There was no significant correlation between demographic and clinical characteristics in all three groups that showed the similarity of these parameters in all three groups (Tables 1 and 2). There was no significant relationship between radiological grading and therapeutic effects in all three groups.

In general, WOMAC indices showed a significant reduction in the scores of stiffness (Figure 1), pain (Figure 2), and physical function (Figure 3) in all three groups, but the SiO₂ group had a higher reduction than the other two groups (Tables 3-6).

Table 1. Distribution of demographic characteristics of patients participating in the study

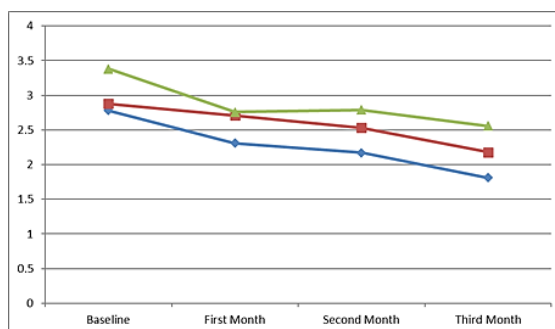
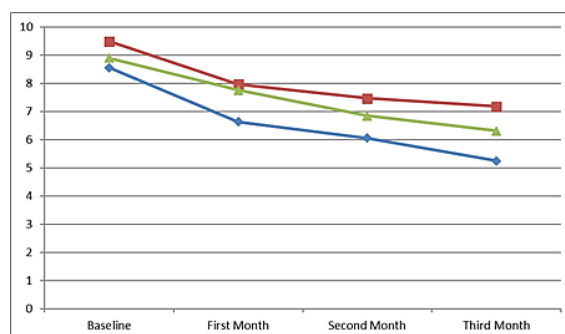
Demographic characteristics	Groups			P
	SiO2 (N=36)	ASU (N=34)	Placebo (N=34)	
Age (year)	58.8	57.32	57.29	P=0.944
Gender	Male	7(19.4%)	3(8.8%)	P=0.449
	Female	29(80.6%)	31(91.2%)	
Weight (Kg)	76.31	74.97	73.41	P=0.403
Height (meter)	1.58	1.57	1.56	P=0.572
BMI (kg/m ²)	30.55	30.33	29.95	P=0.766
Education	Illiterate	3	10	P=0.052
	Elementary	2	8	
	Intermediate	13	6	
	Diploma	9	5	
	Associate Degree	4	3	
	Bachelor Degree	3	2	
Master Degree	2	0	1	

Abbreviations; SiO2: silicon dioxide; ASU: avocado soybean unsaponifiable

Table 2. Distribution of clinical characteristics of patients participating in the study

Clinical characteristics	Groups			P
	SiO2	ASU	Placebo	
Disease duration(years)	8.63	7.55	9.17	P=0.562
Medical history	Positive	18(50%)	23(67.6%)	P=0.285
	Negative	18(50%)	11(32.4%)	
Family history	Positive	21(58.3%)	24(70.6%)	P=0.311
	Negative	15(41.7%)	10(29.4%)	
Kellgren-Lewrence grading	1	11(30.5%)	9(26.4%)	P=0.098
	2	14(38.8%)	13(38.2%)	
	3	8(22.2%)	9(26.5%)	
	4	3(8.3%)	3(8.8%)	

Abbreviations; SiO2: silicon dioxide; ASU: avocado soybean unsaponifiable

**Figure 1.** Mean change from baseline to third month in terms of stiffness score.**Figure 2.** Mean change from baseline to third month in terms of pain score.

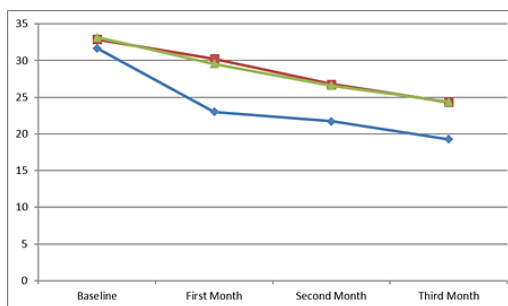


Figure 3. Mean change from baseline to third month in terms of physical function score.

Table 3. Frequency distribution of mean stiffness score in patients participating in the study based on WOMAC questionnaire

	Groups			P
	SiO2	ASU	Placebo	
Baseline	2.78	2.88	3.38	P=0.108
First Month	2.31	2.71	2.76	P=0.264
Second Month	2.17	2.53	2.79	P=0.133
Third Month	1.81	2.18	2.56	P=0.026
P	P=0.001	P=0.001	P=0.001	

*ANOVA test was used. P<0.05 was considered significant. Abbreviations; SiO2: silicon dioxide; ASU: avocado soybean unsaponifiable

Table 4. Frequency distribution of mean pain score in patients participating in the study based on WOMAC questionnaire

	Groups			P
	SiO2	ASU	Placebo	
Baseline	8.56	9.50	8.91	P=0.344
First Month	6.64	7.97	7.76	P=0.114
Second Month	6.06	7.47	6.85	P=0.151
Third Month	5.25	7.18	6.32	P=0.022
P	P=0.001	P=0.001	P=0.001	

*ANOVA test was used. P<0.05 was considered significant. Abbreviations; SiO2: silicon dioxide; ASU: avocado soybean unsaponifiable

Table 5. Frequency distribution of mean physical function score in patients participating in the study based on WOMAC questionnaire

	Groups			P
	SiO2	ASU	Placebo	
Baseline	31.67	32.88	33.15	P=0.827
First Month	23.00	30.26	29.53	P=0.011
Second Month	21.72	26.79	26.59	P=0.093
Third Month	19.28	24.33	24.35	P=0.089
P	P=0.001	P=0.001	P=0.001	

*ANOVA test was used. P<0.05 was considered significant. Abbreviations; SiO2: silicon dioxide; ASU: avocado soybean unsaponifiable

Table 6. Frequency distribution of mean overall WOMAC score in patients participating in the study

	Groups			P
	SiO2	ASU	Placebo	
Baseline	43.00	45.26	40.44	P=0.703
First Month	31.94	40.94	40.06	P=0.015
Second Month	29.94	36.79	36.24	P=0.088
Third Month	26.33	33.68	33.24	P=0.058
P	P=0.001	P=0.001	P=0.001	

*ANOVA test was used. P<0.05 was considered significant. Abbreviations; SiO2: silicon dioxide; ASU: avocado soybean unsaponifiable

Discussion

Silicon has shown a positive role in bone mineralization in mice (13) and calcium metabolism in humans (14). Hott *et al.*, showed that silicon increased osteoblast levels, meanwhile decreasing osteoclast levels in the bone of mice (15). This led to an increase in bone mass in the silicon-treated group. Eisinger *et al.*, administered silicon (50 mg) twice weekly for four months in women with osteoporosis, which showed silicon significantly increased bone mineral density in the treatment group (16). Musik *et al.*, evaluated the association of plasma silicon, magnesium, and calcium with knee OA. They showed silicon concentration of plasma increased in patients with OA (17).

Geusens *et al.*, investigated the effect of choline-stabilized orthosilicic acid (SOA) on patients with symptomatic knee OA. There was no significant change in clinical parameters and serum biomarkers in the total population after 12 weeks of the treatment. Men who received SOA showed overall improvement in WOMAC index, joint stiffness, and physical function. No correlation was observed between the serum silica level and clinical parameters in sex groups (8).

In the present study, patients with knee OA in three groups were treated with SiO₂ and ASU and placebo. Similar to previous studies, the prevalence of OA was higher in women (18). This may be multifactorial and include previous trauma, genetic and hormonal issues. The anatomic differences between males and females that may play a role are comprised of thinner patellae, larger quadriceps angles, narrower femurs, and differences in tibial condylar size (19). Clinical symptoms of OA such as pain and disability do not directly correlate with the intensity of radiographic changes, and radiographic measures as the best way of assessing slow-acting or disease-modifying agents may be insufficient for OA (20).

Moreover, there was no significant difference in the stiffness and pain scores in the first to third visits between the groups. But in the fourth visit (three months after the treatment), there was a statistically significant difference between the placebo and the other two groups; thus, stiffness and pain scores were higher in the placebo group than in the other two groups. At the end of the study, the lowest score of stiffness was in the SiO₂ group, while placebo and ASU had higher scores, respectively (SiO₂=1.81, ASU=2.18, placebo=2.56; $P=0.026$). The SiO₂ group had the lowest pain score compared to the other two groups and this difference was statistically

significant. However, pain score in the placebo group was lower than the ASU group (SiO₂=5.25 placebo=6.32, ASU=7.18; $P=0.022$). These findings show that the most powerful effect of drugs is achieved after three months of treatment. As a result, the minimum treatment period with SiO₂ can be considered for three months.

The results show that patients in the SiO₂ group had an appropriate physical function score in the first month after the treatment; therefore, physical function score in the SiO₂ group was significantly lower than the other two groups. After three months of treatment, the same results were achieved (SiO₂=19.28, ASU=24.32, placebo=24.35; $P=0.089$). It should be noted that stiffness score, pain score, and physical function score in all three groups studied at the end of the study significantly decreased compared to the baseline. In other words, all three drugs improve the symptoms of the disease, but the effect of SiO₂ is superior to the ASU and placebo.

In Geusens study (8), after three months of treatment with choline-stabilized orthosilicic acid, there were no significant differences in terms of pain and joint stiffness and physical function indices in total population, but there were significant changes in men, while the present study showed significant changes in all three indices in the total population of the SiO₂ group at the end of the study. Also, gender did not affect the results.

The interesting point of this study is the appropriate effect of placebo on the improvement of symptoms of knee OA. One randomized controlled trial showed that placebo is effective in the treatment of OA, especially for pain, stiffness and function (21) Pain and disability in patients with OA may be due to fibromyalgia or psychological diseases, and treatment of these disorders may reduce symptoms. Treatment of depression and anxiety, lessons in coping and self-control skills, and manipulation of reinforcements associated with illness behavior are well-established practices for other populations with chronic pain (22).

In Musik *et al.*, study (17), high levels of serum silicon were associated with increased knee OA, and appear to be inconsistent with the results of our study. However, this may be justified, considering that high bone density can be a risk factor for OA and considering the role of silica in bone metabolism and increasing bone density. But to prove this, further studies are needed on bone mineral density and serum silicon levels in patients with osteoarthritis.

This study shows that the therapeutic effects of SiO₂ in patients with knee OA concerning pain and stiffness and physical pain reduction are superior to ASU and

placebo; however, all three drugs were effective in the reduction of symptoms of OA.

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