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Self-education Program for Osteoarthritis Reduces Sodium Intake, Knee Joint pain, and Serum Interleukin-17A level in Osteoarthritis Patients

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Abstract

BACKGROUND: As it has been known that sodium may aggravate joint inflammation through IL-17A pathway and it can cause joint pain.

AIM: The purpose of this study was to determine the effect of the self-education programs for osteoarthritis (SEPO) intervention on sodium intake, knee join pain, and IL-17A level in patients with knee osteoarthritis (OA).

METHODS: This prospective, interventional, and multicenter study was conducted in orthopedic and internal medicine outpatient wards in three hospitals. This research has received ethical approval. Patients were recruited based on accidental sampling, who met the inclusion criteria. SEPO intervention was carried out for 30 days, followed by provision of leaflets, posters, and handbook about OA, daily WhatsApp education chat and/or video. All of SEPO intervention was done by a pharmacist researcher. Patients' demographic, knee joint pain, and sodium intake data was collected during interview, using the semi quantitative food frequency questionnaire, and western ontario mcmaster osteoarthritis index (WOMAC) whereas serum IL-17A was determined using ELISA. The effect of SEPO was analyzed statistically using Mann–Whitney tests ($p < 0.05$).

RESULTS: Total subjects recruited were 80, namely, 30 patients in control group and 50 patients in treatment group. Majority of patients were female (74, 92.5%), age 56–65 years old (32, 40%), obese (54, 67.5%), and senior high school (23, 46%). Statistical results showed that following SEPO intervention daily sodium intake was lower (1289.45 ± 457.98 mg) compared to the control group (2143.94 ± 744.75 mg), $p = 0.04$. WOMAC score of control group (28 ± 12.41) higher than treatment group (23.88 ± 13.61), $p = 0.02$. Serum IL-17A levels were also lower in the treatment group (3.974 ± 1.06 pg/mL) than the control group (5.542 ± 1.99 pg/mL), $p = 0.01$.

CONCLUSION: Education as a non-pharmacological therapy is needed to reduce disease progression. Education is provided according to the patient's needs. Educational models can be offline (face to face) or online (digital). SEPO intervention in patients with knee OA can reduce sodium intake, knee joint pain, and may impact on reduction of serum IL-17A.

Introduction

Osteoarthritis (OA) is a highly prevalent disease worldwide. OA can affect any joint in the fingers, knees, hips, and spine [1]. The knee joint is the most frequently affected by OA [2]. The global prevalence of knee OA alone is (16·0% [95% CI, 14·3%–17·8%]) and incidence (203 per 10,000 person-years [95% CI, 106–331]) [3]. The initiation and progression of OA subtypes are a complex process that at the molecular level probably involves many cell types, signaling pathways, and changes in extracellular matrix [4].

In recent years, among the focused biological factors are cytokines in joint synovial fluid and articular cartilage. Synovial IL-17 levels are reported as significantly higher in OA patients compared with controls, negatively correlated with OA severity and closely related to pain [5]. Human IL-17, a pro-inflammatory cytokine, was identified in 1995 as a product of activated T cells, which involved in the pathogenesis many autoimmune and inflammatory diseases [6]. Since the concept of the IL-17 family, based on molecular homology findings, was introduced, IL-17 was renamed IL-17A [7]. IL-17A alone had relatively modest inflammatory effects; however, when combined

with other cytokines such as TNF or IL-1, IL-17A massively increases the level of inflammation [6], [8]. A systematic review showed that genetically there is an association between IL-17A polymorphism with knee OA and that OA patients showed significantly higher circulating IL-17 levels than the control subjects [9].

IL-17 production, Th17 differentiation, and the balance between pro-inflammatory Th17 cells with Treg cells which have an antagonist effect are influenced by many factors, which may contribute to the appearance and severity of chronic inflammatory diseases [6]. One of such factor is salt, in particular sodium. In murine model, a high-salt diet salt diet alone was found to shift the balance towards Th17 cells [10]. NaCl increased murine and human Th17 cell differentiation in a dose-dependent manner [11]. Such study showed that in mice fed with high salt diet, clinical and histological arthritis were more severe, proportion of Th17 cells among splenocytes and expression of synovial IL-17 was also higher compared to normal salt-diet. The study suggests also that NaCl can aggravate arthritis by affecting Th17 differentiation [11]. A different experimental study involving attenuation of B-cell- and myeloid-cells showed that low salt diet significantly decreased arthritis severity compared to regular and high salt diet [12]. Thus, limiting salt intake as one of non-pharmacological treatment may be helpful for treating and/or preventing inflammatory arthritis, including knee OA.

Non-pharmacological treatment for OA aims to educate patients about the management of OA, reduce pain, improve function, decrease disability, and reduce the progression of the disease [13]. The self-education is a set of educational activities designed to maintain, improve health, or to slow deterioration by increasing participant's perception and/or ability to control various aspects of OA [13]. Group-based and face-to-face self-management education programs facilitated by health professionals can enhance self-efficacy to manage symptoms and functions in patients with knee OA [14]. Studies reported that engagement with self-management necessitates information and understanding about OA and its management, which eventually can minimize the impact of knee OA [15], [16], [17], [18]. Dietary pattern associated with immune-mediated inflammatory disease may be included in OA patients counseling [19]; however, information specifically addressing salt or sodium consumption, low-salt diet recommendation, and its association with knee OA has not been widely included in educational program for OA self-management. Given the role of salt or sodium in pro-inflammatory Th17 cell and IL-17 production, information and recommendation about sodium intake incorporated in a self-education program may be beneficial to prevent and/or improve OA symptoms. In this study, we designed a self-education program for OA (Self-education programs for osteoarthritis [SEPO]) which among other information included information about salt intake. The SEPO was provided by a pharmacist to patients with knee OA. The aim of this study was to determine the SEPO effect on sodium intake and serum IL-17A level in knee OA patients.

Methods

The type of the study was prospective interventional and carried out at the orthopedic and internal medicine outpatient wards in three hospitals. Sample size and sampling were determined using cluster and stratification for the selected hospitals. Two clusters were chosen, that is, Surabaya and Malang, Indonesia. Surabaya is capital city of East Java, Indonesia, whereas Malang is one of Surabaya neighboring cities. The Surabaya cluster consisted of six hospitals of which two were chosen, whereas the Malang cluster consisted of four hospitals of which one was selected as the study site. Selection was based mainly on sites willingness and approval as study sites and size of OA patients population in particular at the orthopedic outpatient wards. Calculation of total sample size was performed using an independent hypothesis test formula, resulted in seventy subjects. The number of subjects sampled in each hospital was determined based on the prevalence of OA patients arrived at the wards 1 year earlier; however, adjusted for COVID-19 visit decrease at 60–80%. Initial recruitment resulted in 119 patients; however, after drop-outs, the remaining was 80. Subjects sampled from Surabaya cluster, hospital 1 Brawijaya Surabaya 32 patients and hospital 2 Airlangga Surabaya 11 patients, whereas from Malang cluster hospital 1 Aisyiyah Islamic 27 patients.

The recruited subjects met the inclusion and exclusion criteria, willing to participate in this study and signed informed consent. The inclusion criteria were aged 45–70 year, diagnosed with OA Kelgreen Lawrence level 1 or 2 which were determined based on X-ray examination results of patients painful knee(s) (it can also be bilateral), did not smoke ≥1 pack/day for the past 1 month, did not consume alcohol ≥1 bottle/day for the past 1 month, whereas the exclusion criteria were OA patients with complications of autoimmune disease, tuberculosis or cancer. All patients diagnosed with OA underwent an X-ray examination at the hospital. Participant recruitment was based on accidental sampling, whereas participant assignments into group with or without SEPO intervention was based on day of patient arrival at outpatients wards, that is, Monday or Wednesday with SEPO, and Tuesday or Friday without SEPO, respectively. Data collection was carried out in May–December 2021 following study ethical approval by the Ethical Committee for Human Research of each hospital involved (No. 44/LE/2021, No. 184/KEP/2021, and No. 234/EC/KEPK/08/2021).

SEPO was an educational model as a non-pharmacological therapy that was given face-to-face at the hospital one time and online for 30 days. The SEPO instrument consists of leaflets, posters, handbooks for OA, WhatsApp chat, and/or videos prepared by the authors. The leaflet contains information about how to avoid and/or reduce sodium intake, the poster about foods with high or low sodium content, handbooks explained the definition, causes, symptoms, clinical signs, and ways to prevent OA. The leaflet, poster, and handbook were given one time during face to face interview with the pharmacist on day 1. WhatsApp chats and videos containing educational materials on how to reduce sodium intake and prevent OA were sent twice a day, every day, except Sundays. SEPO intervention was carried out for 30 days. On Sundays, SEPO intervention was not conducted, instead the sodium intake and symptoms of OA were monitored. All of SEPO intervention was done by one of the researcher team member who was also a pharmacist. The control group, that is, without SEPO intervention, was given leaflets and posters alone and weekly monitoring of OA symptoms.

Patients' demographic data (age, gender, body mass index [BMI], and educational level), knee joint pain, and sodium intake were collected during participants interview on day 1 or pre-SEPO intervention. The sodium intake and knee joint pain data were also collected on day 30. Semi-quantitative food frequency questionnaire (SQ-FFQ) [20] was used to determine sodum intake pre-and post-SEPO intervention. SQ-FFQ consists of list of 68 foods, including staple foods, vegetables, fruits, meats, fish, and beverages. Prior the actual data collection, the SQ-FFQ was validated and met statistical requirements, that is, using Bivariate Pearson >0.05 and Alpha Cronbach >0.8. The SQ-FFQ data for each subject were entered in the Nutrisurvey Indonesia software to calculate total daily sodium (mg) intake. Standard of daily sodium intake for adults was based 2019 guideline of Ministerial Regulations of Health of the Republic of Indonesia, that is, age 36–49 year were 1500 mg, 1500 mg; 50–64 year 1300 mg, 1400 mg; 65–80 year 1100 mg, 1200 mg, for men and women, respectively.

The collection of knee joint pain was carried out through the western ontario mcmaster osteoarthritis index (WOMAC), which is a joint functional questionnaire measured through the subject's ability to perform daily activities at the time of joint pain, stiffness, and difficulty doing activities. The score category uses the Likert scale: 0–24 = Mild, 24–48 = Moderate, 48–72 = Severe, and 72–96 = Very severe. WOMAC is preferred by many health professionals to describe patients' joint pain. Serum IL-17A was determined for both control and intervention groups at the end of the study (day 30) using ELISA (Bio Rad serial No. 12096) using monoclonal antibody anti-IL-17A (Landmax-Bio Legand reagent kit) with a sensitivity of 0.8 pg/mL with yield range value of 3.9–250 pg/mL. The effect of SEPO intervention on sodium intake, knee joint pain, and IL-17A was analyzed using Mann–Whitney, with $p < 0.05$ considered as significantly different. The IL-17A data were carried out only on day 30 for both groups. Researchers did not collect IL-17A data on day 1 due to many bias factors that could affect the results because the initial cytokine measurements could not be conditioned before the study. Changes in IL-17A data due to SEPO intervention can be compared with the control group.

Results

In this study, total patients recruited was 119; however, 39 participants were drop out due to several reasons, for example, patients underwent arthroplasty; referred to or transferred to different hospital; did not show up for follow-up; or did not attend the post-intervention data collection, which mainly because patients' carer did not bring them to hospital. Thus, total participants included in this analyses was 80 patients, that is, 30 subject assigned into control and 50 subject into SEPO intervention (treatment) groups. Matching data on age, sex, BMI, and education level between the control and the treatment groups, there were not significant differences using Mann–Whitney analysis (Table 1). Of note, majority of patients was female (74, 92.5%), aged 56–65 year (32, 40%), and obese (54, 67.5%). The highest education level of participants mostly was senior high school (23, 46%).

Table 1: Biopsychosocial characteristics of patients

Characteristics	Frequency (%)		Mean ± SD		p-value
	Control (n = 30)	SEPO (n = 50)	Control	SEPO	
Gender					
Male	1 (3)	5 (10)			0.28
Female	29 (97)	45 (90)			
Age, year					
46–55	9 (30)	18 (36)	59.67 ± 7.6	59.3 ± 8.7	0.85
56–65	12 (40)	20 (40)			
≥66	9 (30)	12 (24)			
BMI, kg/m^2					
Normal	3 (10)	8 (16)	27.51 ± 4.7	27.79 ± 4.5	0.38
Overweight	6 (20)	9 (18)			
Obese	21 (70)	33 (66)			
Education					
Elementary	4 (13)	4 (8)			0.57
Junior high school	5 (17)	10 (20)			
Senior high school	15 (50)	23 (46)			
Undergraduate	6 (20)	13 (26)			

SEPO: Self-education program for osteoarthritis, BMI: Body mass index.

The mean value of sodium intake in the control and treatment groups, on day 1, was greater than the standard of the Ministerial Regulation of Health of the Republic of Indonesia. In the control group, there was only a slight decrease of mean daily sodium intake on day 30 and still above the standard recommended (Table 2). In contrast, compared with initial sodium intake on day 1, the SEPO intervention (treatment) group showed a drastic decrease of sodium intake on day 30, as much as 35% reduction, and achieved the standard recommended. Likewise the results on

Table 2: Association of SEPO intervention on sodium intake, knee joint pain, and IL-17A

Variables	Control		Treatment
	Mean ± SD	Mean ± SD	p-value
Sodium intake, mg/d			
Pre-intervention	2239.45 ± 730.37	2001.58 ± 1085.43	0.04*
Post-intervention	2143.94 ± 744.757	1289.45 ± 457.98	
WOMAC, score			
Pre-intervention	33 ± 12.47	32.44 ± 16.28	0.02*
Post-intervention	28 ± 12.41	23.88 ± 13.61	
IL-17A, pg/mL			
Post-intervention	5.542 ± 1.99	3.974 ± 1.06	0.01*

*Significant ($p < 0.05$). SEPO: Self-education program for osteoarthritis, WOMAC: Western ontario mcmaster osteoarthritis index.

the WOMAC and IL-17A decreased in the treatment group.

When combined analysis of daily sodium intake, knee joint pain, and IL-17A level, the statistical analysis results showed that model of SEPO gave positive significant results for sodium ($p = 0.01$), knee joint pain ($p = 0.02$), and IL-17A ($p = 0.01$) (Table 2). These results confirm that model of SEPO has a significant effect on reducing sodium, knee joint pain, and IL-17A levels.

Discussion

In this study, female gender and age of 56–65 year were the most prevalent characteristic of OA patients, which probably female at this specific age group female associated with menopause. Menopause may affect the occurrence of OA through estrogen deficiency [21] and its receptor dysregulated expression also involved in OA pathogenesis [22]. Estrogen deficiency, shown in an experimentally postmenopausal rat model, resulted in resorption of subchondral bone and degeneration of articular cartilage [23]. Dysregulated expression of estrogen-related receptors family resulted also in the dysfunction of cytokines, induce articular cartilage ECM degradation, synovial hyperplasia, osteophyte formation, and other pathological manifestations in the occurrence and development of OA, as well as affect the duration of symptoms [22].

Other characteristics commonly found in this study were low level education and obesity. Percentage of patients with high school education was 50% and 46% in control and treatment groups, respectively. Overweight and obese were found in 90% and 84% patients in control and treatment groups, respectively. Low level of educations affects lifestyle and understanding of science [24]. Unhealthy lifestyle including the choice of consumed foods could led to overweight or obesity the biggest risk factors for OA, which resulted in excessive load to joints and cartilage damage [25]. Sodium is a micronutrient found in various foods and beverages consumed. The high sodium content in processed materials and industrial packaging reaches 10 times that of processed natural materials in households [26]. There has never been a monitoring program for sodium intake in OA patients. As a comparison, avoiding excessive sodium intake is included as non-pharmacological intervention in dietary approaches to stop hypertension (DASH) for hypertensive patients through DASH [27]. An increase in body sodium can induce IL-17A cytokine, the pro-inflammatory mediator that plays an important role in the occurrence of OA. IL-17 secretion is closely related to the process of increasing cartilage catabolism [28], decreasing chondrocyte secretion, inhibiting the formation of aggregation, degradation of collagen II, and upregulation of MMPs [29].

The joint pain is an acute or chronic condition that can attack suddenly with many causes. The increase in serum or synovial sodium did not affect knee joint pain and even OA levels according to Kellgreen Lawrence [9] but there were also studies that reported that an increase in IL-17A had a positive effect on knee joint pain but not on the degree of Kellgreen Lawrence [30], [31]. In this study, the SEPO intervention reduced knee joint pain and IL-17A serum. Increased joint pain can be affected by IL-17A [31]. Pain receptors in the skin are influenced by biopsychosocial factors, there are intramolecular interactions when changes in biopsychosocial factors occur. Biopsychosocial factors allow disease to be seen as the result of the interaction of mechanisms at the cellular, tissue, organismal, interpersonal, and environmental levels [32]. Education for OA patients is needed so that joint pain does not occur, especially education about lifestyle.

Programs to reduce sodium intake can be provided by counseling or counseling methods. It aims to increase patient knowledge about OA. Counseling to patients is one component of pharmaceutical care carried out by pharmacists. Self-management OA is a non-pharmacological therapy among other therapies such as exercise, weight loss, and joint protection [33]. Model of SEPO is part of a self-management action in an effort to change behavior with techniques or a combination of therapeutic techniques. Learning given at home in the form of structured and continuous psychoeducation in addition to face to face counseling is an effective support for OA therapy [34]. Thus, in this study, the SEPO model applied as a non-pharmacological therapy program was effective in reducing intake sodium pattern, knee joint pain, and IL-17A level. Although the IL-17A data on day-1 were not measured due to possible factors that could confound the results as the initial cytokine could not be conditioned prior the study, the differences in IL17a level post-SEPO intervention can be compared with the control group. Compared with pharmacological intervention targeting IL-17A pathway with biologics such human monoclonal antibody that targets IL-17A secukinumab; a humanized IgG4 specific for IL-17 ixekizumab and a fully human antibody that targets the IL-17 receptor A

brodalumab, SEPO targeting modification of sodium intake is considerably cost-effective.

Conclusion

Education as a non-pharmacological therapy is needed to reduce disease progression. Education is provided according to the patient's needs. Educational models can be offline (face to face) or online (digital). SEPO intervention in patients with knee OA can reduce sodium intake, knee joint pain, and may impact on reduction of serum IL-17A. Further studies evaluate the effect of the SEPO intervention on the degree of OA and other clinical and laboratory parameters.

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