THE STUDY OF EFFECTIVENESS OF HIGH-FIBER MULTIGRAIN SUPPLEMENTATION AMONG RHEUMATOID ARTHRITIS PATIENTS IN HOSPITAL USM KUBANG KERIAN: A RANDOMIZED OPEN LABEL CLINICAL TRIAL.

DR. THAMARAI A/P SUPRAMANIAM

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE

(INTERNAL MEDICINE)

UNIVERSITI SAINS MALAYSIA

2021

ACKNOWLEDGEMENT

First and foremost, praises and thanks to God, the Almighty, for his shower of blessing throughout my research work to complete the research successfully. I would like to express my sincere gratitude and appreciation to the following individuals who have contributed and supported me in many ways in conducting this study:

1. This work would not have been possible without the support and encouragement from my supervisor, Associate Professor Dr. Wan Syamimee Wan Ghazali. I am forever grateful for her expertise, kindness and patience in making this research possible. As a Consultant Rheumatologist of the School of Medical Sciences, USM, she has continuously provided me with invaluable support.

2. My special thanks to my co-supervisor Dr. Siti Nurbaya Mohd. Nawi, Geriatrician of the School of Medical Sciences, USM, who have helped me tremendously in this study with her ideas and expertise.

3. My gratitude also goes to Dr Lee Lai Kuan (principal investigator) and Miss Farzana Atirah Binti Abdul Latif (clinical nutritionist) for their exceptional teaching and guidance regarding medical nutrition. Last but not least, many heartfelt thanks to all my rheumatology patients who were involved in this study.

Dr. Thamarai A/P Supramaniam

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LIST OF ABBREVIATIONS

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

BMI: Body mass index

CVD: Cardiovascular disease

CI: Confidence interval

CRP: C-reactive protein

DAS 28: Disease activity score

csDMARDS: Conventional synthetic DMARDS

ESR: Erythrocyte sedimentation rate

FBC: Full blood count

FBS: Fasting blood sugar

HAQ-DI: Health assessment questionnaire disability index

IL-6: Interleukin 6

LFT: Liver function test

RA: Rheumatoid arthritis

SD: Standard deviation

T2T: Treat to target

QoL: Quality of life

ABSTRAK

Latar belakang: Artritis reumatoid (RA) adalah sejenis penyakit radang autoimun kronik yang menyerang sendi-sendi manusia, akhirnya menyebabkan kemusnahan sendi. Rawatan awal boleh membantu melambatkan pemusnahan sendi dan mengekalkan fungsi sendi. Ubat-ubatan anti-reumatik yang mengubahsuai penyakit sintetik konvensional (csDMARDs) dan DMARDs biologik (bDMARDs) adalah asas rawatan RA. Walau bagaimanapun, ia telah dikaitkan dengan pelbagai kesan sampingan. Bukti menunjukkan bahawa faktor pemakanan memainkan peranan yang penting dalam pengurusan RA. Oleh itu, terapi pemakanan harus dipertimbangkan sebagai sebahagian daripada regimen rawatan untuk pesakit RA. Kajian ini bertujuan untuk menyelidik kesan suplemen serbuk pelbagai bijirin sebagai terapi pelengkap terhadap tahap keparahan aktiviti penyakit, molekul darah keradangan dan status nutrisi pesakit RA berbanding mereka yang menerima terapi ubat konvensional.

Kaedah:

Kajian ini adalah ujian suplemen secara rawak terbuka yang dijalankan antara Mac 2019 hingga Jun 2019 pada pesakit RA yang membuat pemeriksaan susulan di klinik Reumatologi Hospital Universiti Sains Malaysia (HUSM). Sejumlah 51 pesakit telah direkrut dalam kajian ini. Maklumat pesakit seperti umur, komorbiditi, ubat yang sedang diambil, indeks jisim badan (BMI), lilitan pinggang, tempoh RA, aktiviti penyakit (skor aktiviti penyakit [DAS]), skor indeks kecacatan soal selidik penilaian kesihatan (HAQ-DI), skala penilaian kekakuan pagi, skor skala analog visual (VAS), serta parameter biokimia seperti ujian fungsi ginjal, ujian fungsi hati, kolesterol keseluruhan, kadar pemendapan eritrosit (ESR) dan kiraan darah penuh diperoleh

(WBC). Nilai pra dan pasca DAS 28, skor VAS, skor HAQ-DI, skala penilaian kekakuan pagi dan parameter biokimia dinilai.

Hasil kajian: Umur min peserta dalam kumpulan intervensi dan kawalan masing-masing adalah 54.68 (SD=8.28) dan 51.88 (SD=14.09). Data yang dikumpulkan menunjukkan bahawa majoriti peserta dalam kumpulan intervensi dan kawalan adalah wanita, masing-masing mempunyai 19 (37.2%) dan 24 (47.1%) peserta wanita. Data juga menunjukkan bahawa tidak ada perbezaan yang signifikan dalam ciri-ciri asas antara kumpulan intervensi dan kumpulan kawalan. Untuk kedua-dua kumpulan intervensi dan kawalan, analisis ciri klinikal menunjukkan bahawa 29.4% peserta mempunyai aktiviti penyakit yang rendah (DAS antara 2.6 hingga 3.2), 54.9% mempunyai aktiviti penyakit yang sederhana (DAS antara 3.2 hingga 5.1) dan 15.7% mempunyai aktiviti penyakit yang tinggi (DAS lebih tinggi daripada 5.1).

Hasil ujian pra dan ujian pasca kumpulan intervensi dan kawalan dibandingkan untuk menilai keberkesanan suplemen pelbagai bijirin tinggi serat dalam menurunkan penanda keradangan dan aktiviti penyakit klinikal di kalangan pesakit RA yang mengambil bahagian dalam kajian ini.

Bagi kumpulan intervensi, diperhatikan bahawa skor min BMI ($p<0.001$), lilitan pinggang ($p=0.005$), DAS 28 ($p<0.001$), HAQ-DI ($p=0.034$), skala kekakuan pagi ($p=0.010$) dan skala kesakitan VAS ($p=0.003$) untuk ujian pra mempunyai perbezaan yang signifikan berbanding dengan ujian pasca.

Walau bagaimanapun, tidak ada perbezaan yang signifikan dalam skor min pemboleh ubah dalam ujian pra dan pasca antara kumpulan intervensi dan kawalan, kecuali untuk skor HAQ-DI (p=0.009), skala kekakuan pagi (p=0.035) dan skala kesakitan VAS (p=0.003) dalam ujian pasca. Skor min HAQ-DI kumpulan intervensi dalam ujian pasca lebih rendah sebanyak 0.32 (95% CI=-0.56, -0.08) daripada kumpulan kawalan. Untuk skala kekakuan pagi, skor min kumpulan kawalan lebih tinggi sebanyak 1.42 (95% CI=-2.75, -0.10) berbanding dengan kumpulan intervensi. Bagi skala kesakitan VAS, skor min kumpulan intervensi lebih rendah sebanyak 2.03 (95% CI=-3.34, -0.72) daripada kumpulan kawalan.

Bagi penilaian kesan sampingan suplemen pelbagai bijirin tinggi serat , diperhatikan bahawa dua puluh peserta mengalami rasa kenyang, enam peserta mengalami perut kembung, tiga peserta mengalami loya, tiga peserta mengalami sakit kepala, tiga peserta mengalami pedih ulu hati dan sebilangan kecil peserta mengalami gemuruh usus dan sembelit. Tidak ada peserta daripada kumpulan kawalan yang mengalami cirit-birit.

Untuk penilaian kepatuhan, semua peserta dalam kumpulan intervensi mencapai peratusan pematuhan sasaran sebanyak 80%.

Kesimpulan: Kesimpulannya, fungsi fizikal dan kualiti hidup (QoL) pesakit RA yang mengambil bahagian dalam kajian ini meningkat secara signifikan dengan suplemen serbuk yang diperkaya dengan pelbagai bijirin. Selanjutnya, data kajian ini telah jelas menunjukkan potensi suplemen serbuk yang diperkaya dengan pelbagai bijirin sebagai terapi pemakanan perubatan untuk menyokong terapi standard semasa untuk pesakit RA. Walaupun data kajian mungkin tidak cukup konklusif, nasihat pemakanan penting dalam reumatologi sebagai sebahagian daripada pendekatan bersepadu untuk pesakit RA.

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that attacks human joints, leading to joint destruction. Early treatment can help to delay joint destruction and maintain joint function. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs) are the cornerstones of RA treatment. However, they are associated with various side effects. Evidence suggests that dietary factor plays an important role in RA management. Therefore, dietary therapy should be considered as part of the treatment regimen for RA patients. This study intended to explore the complementary effects of multi-grained powder supplementation on the clinical severity of the disease activity, inflammatory blood molecules and the changes in the nutritional status of RA patients , and to monitor general well being of participants compared to those who are receiving conventional drug therapies.

Methods:

This study was an open randomized supplementation trial conducted between March 2019 and June 2019 on RA patients who followed up at the Hospital Universiti Sains Malaysia (HUSM) Rheumatology clinic. A total of 51 patients were recruited in this study. Patient information such as age, comorbidities, drug history, body mass index (BMI), waist circumference, duration of RA, disease activity (disease activity score [DAS]), health assessment questionnaire disability index (HAQ-DI) score, morning stiffness rating scale, visual analogue scale (VAS) score, as well as biochemical parameters such as renal function test, liver function test, total cholesterol, erythrocyte sedimentation rate (ESR) and full blood count was obtained. The pre and post-DAS

28, VAS score, HAQ-DI score, morning stiffness rating scale and biochemical parameters were assessed.

Results: The mean ages of the participants in the intervention and control groups were 54.68 (SD=8.28) and 51.88 (SD=14.09) respectively. The collected data showed that the majority of the participants in both the intervention and control groups were female, with 19 (37.2%) and 24 (47.1%) female participants respectively. There were no significant differences in the baseline characteristics between the two groups. For both the intervention and control groups, the analysis of the clinical characteristics showed that 29.4% of the participants had low disease activity (DAS between 2.6 to 3.2), 54.9% had moderate disease activity (DAS between 3.2 to 5.1) and 15.7% had high disease activity (DAS higher than 5.1).

The results of the pre and post-tests of the intervention and control groups were compared to evaluate the efficacy of high-fiber multigrain supplementation in reducing inflammatory markers and clinical disease activity among the participating RA patients.

For the intervention group, it was observed that the mean scores of the BMI ($p<0.001$), waist circumference ($p=0.005$), DAS 28 ($p<0.001$), HAQ-DI ($p=0.034$), morning stiffness scale ($p=0.010$) and VAS pain scale ($p=0.003$) in the pre-test were significantly different from those of the post-test

However, there were no significant differences in the mean scores of the variables in both the pre and post-tests between the intervention and control groups, except for the HAQ-DI score ($p=0.009$), morning stiffness scale ($p=0.035$) and VAS pain scale ($p=0.003$) in the post-test. The mean score of the HAQ-DI of the intervention group in the post-test was lower by 0.32 (95% CI=-0.56, -0.08) than that of the control group. For the morning stiffness scale, the mean score of the control group was higher by 1.42 (95% CI=-2.75, -0.10) as compared to the intervention group.

As for the VAS pain scale, the mean score of the intervention group was lower by 2.03 (95% CI=-3.34, -072) than the control group.

As for the assessment of side effects of high-fiber multigrain supplement , it was observed that twenty participants developed satiety, six participants had flatulence, three participants developed nausea, three participants experienced headache, three participants suffered from heartburn and a small number of participants experienced intestinal rumbling and constipation. None of the participants from the control group developed diarrhea.

As far as compliance assessment was concerned, all the participants in the intervention group achieved a target compliance percentage of 80%.

Conclusion: In conclusion, the physical functioning and quality of life (QoL) of the participating RA patients in this study were significantly improved with the multigrain-enriched powder supplementation. Furthermore, the data of this study has clearly demonstrated the potential of multigrain-enriched powder supplementation as nutritional medicine to support current standard therapies for RA patients. Although the data might not be conclusive enough, dietary advice has its place in rheumatology as part of an integrated approach for RA patients.

CHAPTER 1: INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects small joints in the human body. To date, about 1% of the global adult population is affected by RA. However, the prevalence of RA ranges from 0.2% to 0.3% in the Southeast Asian population to 6.0% in the native American Indian population (Silman and Pearson, 2002)[1]. Elderly, people with a family history of RA and females are reported to have a higher risk of RA, although the gender gap is less pronounced among older patients.

The primary aetiology of the disease remains unknown as yet, but environmental factors have been observed to cause RA by triggering the response of immune cells in genetically predisposed individuals. This is because the triggered immune system will produce a number of pro-inflammatory cytokines (Firestein GS *et al.*, 2012)[2], which will then give rise to an inflammatory cascade. The tumour necrosis factor alpha (TNF-α) expressed in the inflammatory cascade is the protein that is responsible for synovitis and joint destruction. Besides, it also causes overproduction of other cytokines, especially interleukin (IL)-6 which, in turn, lead to worsening inflammation and joint destruction.

The clinical characteristics of RA can be divided into two types, namely articular and extra-articular manifestations. Extra-articular manifestations may involve a number of organs, including the skin, eyes, lungs and blood vessels. Besides, RA can be associated with other connective tissue conditions and chronic non-inflammatory pain such as fibromyalgia. Also, it is

an independent risk factor for heart disease or cardiovascular disease (CVD) and osteoporosis.

The main symptoms of RA are:

- articular pain and swelling
- early morning stiffness (EMS) that lasts 60 minutes or longer
- symmetrical polyarthritis involving metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, interphalangeal joint of thumbs, wrists and elbow, or metatarsophalangeal (MTP) joints
- Symptoms of articular inflammation should be present for a minimum of six weeks.

Clinical manifestations as below are usually examined for the diagnosis of RA:

- clinical synovitis
- joint tenderness
- boggy swelling (may be subtle in early RA)
- limited range of motion
- joint deformities, e.g., radial deviation of the wrist, ulnar deviation at the MCPs, “swanneck” deformities, hyperextension of PIP and “boutonniere” deformities

Besides clinical manifestations, the diagnosis of RA is supported by laboratory parameters which include rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA , erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as radiological assessment for

soft tissues swelling, narrowing of joint space and bone erosion. Generally, these changes are symmetrical and do not involve distal IP joints.

Patients with RA are at higher risk of mortality compared to the general population. The increase in mortality rate among RA patients may be largely attributed to its associated risk of CVD (Gabriel, 2008)[3]. The chronic inflammatory component in RA patients is one of the primary reasons for the increased risk of CVD as CVDs such as atherosclerosis also has an inflammatory aetiology (Nurmohamed, 2009)[4]. Therefore, early diagnosis and prompt treatment of RA are crucial not only to prevent irreversible joint damage but also to reduce the CVD risk among RA patients (Kaplan, 2010)[5].

Measurements of disease activity are helpful in RA as they reflect patients outcomes and response to treatment in clinical care and clinical trials. Disease activity, which is reflected by tender and swollen joint counts, levels of acute phase reactants, and patient's and physician's global assessments, is a good predictor of damage and physical disability, and an outcome measure, which is used to evaluate health outcome in clinical studies of patients with RA(Prevoo *et al.*, 1995) [6]. Commonly used disease activity scale are DAS -28 score ,CDAI score and SDAI score . DAS 28 includes both joint counts and inflammatory index, which makes it an important standard for RA disease activity assessment and is recommended by EULAR (Vangestel et al., 2006) . American college of rheumatology (ACR) recommends DAS -28 as a tool to assess disease activity as it is an accurate reflection of disease activity , sensitive to change ,discriminate between low ,moderate and high disease activity states and are feasible to perform in clinical setting [Jaclyn Anderson ,ACR ,2012) [7]. When disease activity is not maintained in remission, DAS28 can be used for clinical criteria (Smolen1 and Aletaha, 2010) [8.]

Whereas when the activity of the disease is maintained in remission, SDAI and CDAI are more accurate. (Takanashi, Kaneko and Takeuchi, 2020) [9].

In addition, the HAQ-DI questionnaire is used to evaluate the functional capability of patients with rheumatoid arthritis, it is the most commonly used tool to assess disability in patients with rheumatoid arthritis (RA). Because it demonstrated sensitivity to change, the HAQ-DI was chosen by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and the American College of Rheumatology (ACR) to be incorporated into the core set of outcome measures of RA disease activity(Felson *et al.*, 1993; Boers *et al.*, 1998) [10]. In addition to being an essential measure of disability in patients with RA in clinical trials, HAQ-DI is also used in clinical practice. Furthermore , there are several scales available to assess pain intensity among rheumatoid arthritis patients . Among these, the Numerical Rating Scale (NRS), the Visual Analog Scale (VAS) and the Verbal Rating Scale (VRS) are frequently used in clinical practice. Based on a study conducted by (Alghadir *et al.*, 2018) [11] a test-retest reliability , and validity of VAS , NRS,VRS has showed that all the three scales had excellent test–retest reliability. However, the VAS was considered the most stable with the smallest error in measurement.

Management of RA usually involves a comprehensive approach that includes both non-pharmacological and pharmacological therapies. Pharmacological therapy should start as soon as the RA diagnosis is established in order to preserve joint function and quality of life (QoL). The aim of RA management is to achieve clinical remission or at least low disease activity within six months with a treat-to-target (T2T) treatment strategy. The treatment goals in RA management include:

- alleviate pain and control inflammation
- maintain joint function and QoL

- minimise systemic complications and manage comorbidities

The T2T treatment strategy was developed in 2010 and have been proven to be able to improve the disease activity of RA. The following elements are usually included as part of the T2T treatment strategy (Smolen *et al.*, 2010) [7]

- a definite treatment goal (clinical remission or at least low activity of the disease)
- shared decision making
- evaluation of disease activity
- regular adjustment of medication

Approaches for RA management

Non-Pharmacological Therapy	Pharmacological Therapy
Patient Education	Non-Steroidal Anti-Inflammatory Drugs
Occupational Therapy	Corticosteroids
Physiotherapy	Conventional Synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs), Targeted Synthetic DMARDs (tsDMARDs)
Podiatry	Biologic DMARDs (bDMARDs)/Biosimilar
Dietetics	Traditional and Complementary Medicines

Generally, DMARDs are used as the first line of RA treatment to suppress disease activity and reduce joint damage. Buch *et al.* (2004)[12] stated that the development of better treatment strategies involving biologics like anti-tumour necrosis factor (TNF)-α or a combination of DMARDs with biologics allow complete remission to be achieved in a greater proportion of patients, although a small proportion of patients may continue to experience frequent relapse after discontinuation of TNF-α therapy. Regarding this, continuous administration of biologics is the only option for extended remission. However, biologics treatment remains out of reach for most people in urban and rural areas due to its high cost (Soini *et al.*, 2013)[13] .

Though there are a variety of drugs that may be used to treat RA, they are all associated with significant side effects, including steroid-induced toxicity, methotrexate-induced liver injury and mucositis, hydroxychloroquine (HCQ)-induced maculopathy and biologic agents-induced flare of tuberculosis and hepatitis. Furthermore, it is common for RA patients to experience gastrointestinal symptoms, particularly dyspepsia (bloating, postprandial fullness, nausea, early satiety, epigastric pain, and burning and belching), mucosal ulceration and altered bowel habits (constipation/diarrhea) (Wolfe *et al.*, 2000)[14], which then result in a reduced QoL. Moreover, observational studies reported that the nutritional status of RA patients was generally poor (Gómez-Vaquero *et al.*, 2001)[15]. A number of contributing factors were identified, including:

i) Diminished intake – articular disease diminishes the ability to self-feed and prepare food, and early morning stiffness may decrease appetite.

ii) Inadequate nutrient uptake – drug therapy (e.g., MTX, SSA, NSAID) may inhibit enzymes of intermediary metabolism and reduce folate uptake.

Aside from drug treatment, numerous randomized control trial (RCT) had reported that certain foods can improve RA symptoms (Haugen *et al.*, 1991)[16]. For instance, Tedeschi *et al.* (2017)[17]conducted a dietary survey among 300 RA patients and almost one-quarter of the patients reported that diet had an effect on their RA symptoms. That is the reason why RA patients often seek specific dietary advice from their physician. Even though some studies had investigated the role of different diets in improving RA symptoms, the mechanisms of action remain unclear still. Nevertheless, it was generally observed that fruits, vegetables, fiber, fish and dietary antioxidants are helpful in alleviating RA symptoms, whereas red meat, alcohol, soft drinks and foods with saturated fatty acids are examples of those that worsen the symptoms.

Thus, dietary manipulation is common in the management of RA symptoms (Hagen *et al.*, 2009)[18], mainly to reduce inflammation, increase antioxidant levels, change lipid profiles in favour of lipids that provide anti-inflammatory benefits and potentially, modify gut flora. This is because when inflammation happens, immune cells (neutrophils) will produce pro-oxidants such as reactive oxygen species (ROS) (Pattison and Winyard, 2008)[19]. The generated ROS, especially mitochondrial ROS(MtROS), will then involve in the secretion of proinflammatory cytokines (Li *et al.*, 2013)[20], and may cause damages to the DNA, proteins and membrane lipids (Filippin *et al.*, 2008)[21]. Constant generation of ROS in the joints will also cause the depletion of antioxidant systems (Li *et al.*, 2013)[20].

Moreover, it was reported that the levels of some antioxidants were lower in the serum (Cerhan *et al.*, 2003)[22] and synovial fluid (Pattison and Winyard, 2008)[19] of RA patients compared to those of healthy individuals. The lower levels of antioxidants were found to be associated with inflammation and the resulting joint erosion. Therefore, this study was conducted to examine the

complementary effects of multigrain-enriched powder supplementation on the level of clinical disease severity measures, blood inflammatory molecules,of RA patients, as compared to conventional drug treatments.

In general, dietary fiber consumption among Malaysians is lower than that of the Western population. According to a study conducted by (Lee and Muda, 2019) [23] among adults living in Kota Bharu and Penang, a 3 days 24hour recall dietary intake of 422 participants showed that the consumption of fruits (< 1 serving) and vegetables (< 2 servings) .It was substantially lower than the levels suggested by the Malaysian Dietary Guideline (MDG), which recommended two daily servings of fruits and three daily servings of vegetables(Vertegaal and Poupyrev, 2010) [24]. This has contributed to low dietary fiber consumption among participants.

A secondary data extracted from the Malaysian Adult Nutrition Survey (MANS) 2003,assessment of food intake by 24-hour recall of food diary method and nutrient calculator to quantify intake of macronutrients and dietary fiber (DF) revealed low mean DF intakes of 10.7±1.0 g/day these data sets did not meet the goal of 20-30 g DF/day

(Ng *et al.*, 2010) [25]. Therefore, in this study, we have provided high fibre multi-grain supplements that contain 15.6 g of total fiber in addition to the usual fiber consumption by participants to meet the recommended DF consumption by MDG.

CHAPTER 2: OBJECTIVES OF THE STUDY

General objective:

To investigate the effects of high-fiber multigrain oats supplementation on RA patients.

Specific objectives:

i) To evaluate the effects of high-fiber multigrain supplementation on the disease activity score (DAS), visual analogue scale (VAS) score and HAQ-DI score.

ii) To evaluate the effects of high-fiber multigrain supplementation on blood inflammatory molecules.

- WBC(white blood cell)

- ESR- erythrocyte sedimentation rate

iii) To determine the safety and tolerability of high-fiber multigrain supplementation in terms of side effects and derangement in liver function test (LFT) and renal function test (RFT).

iv)) to evaluate changes general well-being among participants – anthropometric measurements

-BMI
-waist circumference
-BP

CHAPTER 3: MANUSCRIPT

JOURNAL: Malaysian Journal of Medical Sciences

TITLE: Effectiveness of multigrain-enriched powder supplementation among rheumatoid arthritis (RA) patients: An open-label clinical trial.

Author: Thamarai Supramaniam

Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kota Bharu, Kelantan, MALAYSIA

Corresponding author: Prof. Wan Syamimee Wan Ghazali

Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kota Bharu, Kelantan, MALAYSIA

Email:

Disclosure of finding: none of the authors receives any financial support for this study.

ABSTRACT

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects small joints in the human body. To date, about 1% of the global adult population is affected by RA. However, the prevalence of RA ranges from 0.2% to 0.3% in the Southeast Asian population to 6.0% in the native American Indian population (Silman and Pearson, 2002)[1]. Elderly, people with a family history of RA and females are reported to have a higher risk of RA, although the gender gap is less pronounced among older patients.

The primary aetiology of the disease remains unknown as yet, but environmental factors have been observed to cause RA by triggering the response of immune cells in genetically predisposed individuals. This is because the triggered immune system will produce a number of pro-inflammatory cytokines (Firestein GS *et al.*, 2012)[2], which will then give rise to an inflammatory cascade. The tumour necrosis factor alpha (TNF-α) expressed in the inflammatory cascade is the protein that is responsible for synovitis and joint destruction. Besides, it also causes overproduction of other cytokines, especially interleukin (IL)-6 which, in turn, lead to worsening inflammation and joint destruction.

The clinical characteristics of RA can be divided into two types, namely articular and extra-articular manifestations. Extra-articular manifestations may involve a number of organs, including the skin, eyes, lungs and blood vessels. Besides, RA can be associated with other connective tissue conditions and chronic non-inflammatory pain such as fibromyalgia. Also, it is an independent risk factor for heart disease or cardiovascular disease (CVD) and osteoporosis.

The main symptoms of RA are: articular pain and swelling, early morning stiffness (EMS) that lasts 60 minutes or longer, symmetrical polyarthritis involving metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, interphalangeal joint of thumbs, wrists and elbow, or metatarsophalangeal (MTP) joints,symptoms of articular inflammation should be present for a minimum of six weeks.

Clinical manifestations as below are usually examined for the diagnosis of RA:

- clinical synovitis
- joint tenderness
- boggy swelling (may be subtle in early RA)
- limited range of motion
- joint deformities, e.g., radial deviation of the wrist, ulnar deviation at the MCPs, "swanneck" deformities, hyperextension of PIP and "boutonniere" deformities

The 2010 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) diagnostic criteria is currently used to diagnose RA (Kay and Upchurch, 2012)[2]. Besides, the most established laboratory markers for RA diagnosis are RF and ACCPA. Patients with RA are at higher risk of mortality compared to the general population. The increase in mortality rate among RA patients may be largely attributed to its associated risk of CVD (Gabriel, 2008)[3]. The chronic inflammatory component in RA patients is one of the primary reasons for the increased risk of CVD as CVDs such as atherosclerosis also has an inflammatory aetiology (Nurmohamed, 2009)[4]. Therefore, early diagnosis and prompt treatment of RA are crucial not only to prevent irreversible joint damage but also to reduce the CVD risk among RA patients (Kaplan, 2010)[5].

Patients with RA are at higher risk of mortality compared to the general population. The increase in mortality rate among RA patients may be largely attributed to its associated risk of CVD (Gabriel, 2008)[3]. The chronic inflammatory component in RA patients is one of the primary reasons for the increased risk of CVD as CVDs such as atherosclerosis also has an inflammatory aetiology (Nurmohamed, 2009)[4]. Therefore, early diagnosis and prompt treatment of RA are crucial not only to prevent irreversible joint damage but also to reduce the CVD risk among RA patients (Kaplan, 2010)[5].

Measurements of disease activity are helpful in RA as they reflect patients outcomes and response to treatment in clinical care and clinical trials. Disease activity, which is reflected by tender and swollen joint counts, levels of acute phase reactants, and patient's and physician's global assessments, is a good predictor of damage and physical disability, and an outcome measure, which is used to evaluate health outcome in clinical studies of patients with RA(Prevoo *et al.*, 1995) [6]. Commonly used disease activity scale are DAS -28 score ,CDAI score and SDAI score . DAS 28 includes both joint counts and inflammatory index, which makes it an important standard for RA disease activity assessment and is recommended by EULAR (Vangestel et al., 2006) . American college of rheumatology (ACR) recommends DAS -28 as a tool to assess disease activity as it is an accurate reflection of disease activity , sensitive to change ,discriminate between low ,moderate and high disease activity states and are feasible to perform in clinical setting [Jaclyn Anderson ,ACR ,2012) [7]. When disease activity is not maintained in remission, DAS28 can be used for clinical criteria (Smolen1 and Aletaha, 2010) [8]. Whereas when the activity of the disease is maintained in remission, SDAI and CDAI are more accurate. (Takanashi, Kaneko and Takeuchi, 2020) [9].

In addition, the HAQ-DI questionnaire is used to evaluate the functional capability of patients with rheumatoid arthritis, it is the most commonly used tool to assess disability in patients with rheumatoid arthritis (RA). Because it demonstrated sensitivity to change, the HAQ-DI was chosen by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and the American College of Rheumatology (ACR) to be incorporated into the core set of outcome measures of RA disease activity(Felson *et al.*, 1993; Boers *et al.*, 1998) [10] . In addition to being an essential measure of disability in patients with RA in clinical trials, HAQ-DI is also used in clinical practice. Furthermore , there are several scales available to assess pain intensity among rheumatoid arthritis patients . Among these, the Numerical Rating Scale (NRS), the Visual Analog Scale (VAS) and the Verbal Rating Scale (VRS) are frequently used in clinical practice. Based on a study conducted by (Alghadir *et al.*, 2018) [11]a test-retest reliability , and validity of VAS , NRS,VRS has showed that all the three scales had excellent test–retest reliability. However, the VAS was considered the most stable with the smallest error in measurement.

Management of RA usually involves a comprehensive approach that includes both non-pharmacological and pharmacological therapies. Pharmacological therapy should start as soon as the RA diagnosis is established in order to preserve joint function and quality of life (QoL). The aim of RA management is to achieve clinical remission or at least low disease activity within six months with a treat-to-target (T2T) treatment strategy. The treatment goals in RA management include : alleviate pain and control inflammation, maintain joint function and QoL and to minimise systemic complications and manage comorbidities

The T2T treatment strategy was developed in 2010 and have been proven to be able to improve the disease activity of RA. The following elements are usually included as part of the T2T treatment strategy (Smolen *et al.*, 2010)[7.]

- a definite treatment goal (clinical remission or at least low activity of the disease)
- shared decision making
- evaluation of disease activity
- regular adjustment of medication

Generally, DMARDs are used as the first line of RA treatment to suppress disease activity and reduce joint damage. Buch *et al.* (2004)[12] stated that the development of better treatment strategies involving biologics like anti-tumour necrosis factor (TNF)-α or a combination of DMARDs with biologics allow complete remission to be achieved in a greater proportion of patients, although a small proportion of patients may continue to experience frequent relapse after discontinuation of TNF-α therapy. Regarding this, continuous administration of biologics is the only option for extended remission. However, biologics treatment remains out of reach for most people in urban and rural areas due to its high cost (Soini *et al.*, 2013)[13].

Though there are a variety of drugs that may be used to treat RA, they are all associated with significant side effects, including steroid-induced toxicity, methotrexate-induced liver injury and mucositis, hydroxychloroquine (HCQ)-induced maculopathy and biologic agents-induced flare of tuberculosis and hepatitis. Furthermore, it is common for RA patients to experience gastrointestinal symptoms, particularly dyspepsia (bloating, postprandial fullness, nausea, early satiety, epigastric pain, and burning and belching), mucosal ulceration and altered bowel habits (constipation/diarrhea) (Wolfe *et al.*, 2000)[14], which then result in a reduced QoL. Moreover, observational studies reported that the nutritional status of RA patients was generally poor (Gómez-Vaquero *et al.*, 2001)[15]. A number of contributing factors were identified, including:

i) Diminished intake – articular disease diminishes the ability to self-feed and prepare food, and early morning stiffness may decrease appetite.

ii) Inadequate nutrient uptake – drug therapy (e.g., MTX, SSA, NSAID) may inhibit enzymes of intermediary metabolism and reduce folate uptake.

Aside from drug treatment, numerous randomized control trial (RCT) had reported that certain foods can improve RA symptoms (Haugen *et al.*, 1991)[16]. For instance, Tedeschi *et al.* (2017)[17]conducted a dietary survey among 300 RA patients and almost one-quarter of the patients reported that diet had an effect on their RA symptoms. That is the reason why RA patients often seek specific dietary advice from their physician. Even though some studies had investigated the role of different diets in improving RA symptoms, the mechanisms of action remain unclear still. Nevertheless, it was generally observed that fruits, vegetables, fiber, fish and dietary antioxidants are helpful in alleviating RA symptoms, whereas red meat, alcohol, soft drinks and foods with saturated fatty acids are examples of those that worsen the symptoms.

Thus, dietary manipulation is common in the management of RA symptoms (Hagen *et al.*, 2009)[18], mainly to reduce inflammation, increase antioxidant levels, change lipid profiles in favour of lipids that provide anti-inflammatory benefits and potentially, modify gut flora. This is because when inflammation happens, immune cells (neutrophils) will produce pro-oxidants such as reactive oxygen species (ROS) (Pattison and Winyard, 2008)[19]. The generated ROS, especially mitochondrial ROS(MtROS), will then involve in the secretion of proinflammatory cytokines (Li *et al.*, 2013)[20], and may cause damages to the DNA, proteins and membrane lipids (Filippin *et al.*, 2008)[21]. Constant generation of ROS in the joints will also cause the depletion of antioxidant systems (Li *et al.*, 2013)[20].

Moreover, it was reported that the levels of some antioxidants were lower in the serum (Cerhan *et al.*, 2003)[22]and synovial fluid (Pattison and Winyard, 2008)[19] of RA patients compared to those of healthy individuals. The lower levels of antioxidants were found to be associated with inflammation and the resulting joint erosion. Therefore, this study was conducted to examine the complementary effects of multigrain-enriched powder supplementation on the level of clinical disease severity measures, blood inflammatory molecules, oxidative stress and nutritional status of RA patients, as compared to conventional drug treatments.

In general,dietary fiber consumption among Malaysians is lower than that of the Western population. According to a study conducted by (Lee and Muda, 2019) [23]among adults living in Kota Bharu and Penang, a 3 days 24hour recall dietary intake of 422 participants showed that the consumption of fruits (< 1 serving) and vegetables (< 2 servings) .It was substantially lower than the levels suggested by the Malaysian Dietary Guideline (MDG), which recommended two daily servings of fruits and three daily servings of vegetables(Vertegaal and Poupyrev, 2010) [24]. This has contributed to low dietary fiber consumption among participants.

A secondary data extracted from the Malaysian Adult Nutrition Survey (MANS) 2003,assessment of food intake by 24-hour recall of food diary method and nutrient calculator to quantify intake of macronutrients and dietary fiber (DF) revealed low mean DF intakes of 10.7±1.0 g/day these data sets did not meet the goal of 20-30 g DF/day

(Ng *et al.*, 2010) [25] Therefore, in this study, we have provided high fibre multi-grain supplements that contain 15.6 g of total fiber in addition to the usual fiber consumption by participants to meet the recommended DF consumption by MDG.

MATERIALS AND METHOD METHODOLOGY

Participant recruitment and data collection

A total of 51 RA patients who attended the Rheumatology Clinic at the Hospital Universiti Sains Malaysia (HUSM) between March 2019 and July 2019 were recruited as the participants in this study. The patients were considered eligible for this study if they aged between 20 to 80 years old and fulfilled the 2010 ACR/EULAR RA classification criteria (Kay and Upchurch, 2012)[26]. Patients with the following features were excluded from this study: liver, kidney or haematological disorders, active gastric/duodenal ulcer, psychiatric disease/mental retardation, malignancy, uncontrolled diabetes mellitus, uncontrolled hypertension, endocrine disorders, alcohol and drug abuses, other autoimmune/inflammatory diseases, pregnancy/lactation and under hormone replacement therapy.

The data that were collected and analyzed in this study are as follows:

(1) Demographic data: age and gender.

(2) Clinical data: weight, height, BMI, waist circumference, blood pressure (BP), heart rate (HR), duration of RA, comorbidities and drug history (sulfasalazine, methotrexate, hydroxychloroquine, leflunomide, folic acid, pantoprazole, celecoxib, ibuprofen, etoricoxib, omeprazole, prednisolone, paracetamol).

(3) Laboratory results of the pre and post-tests: RFT, LFT, full blood count (FBC), fasting blood sugar (FBS), total cholesterol, uric acid and ESR.

(4) Baseline diet were obtained using diet history questionnaire to determine patients daily fiber.

The disease activity of RA was assessed using the 28-joint DAS (DAS 28) (Wells *et al.*, 2009)[27] A DAS 28 that is greater than 3.2 implies active disease while a score that is lower than or equal to 3.2 indicates low disease activity. This study was approved by the Human Research Ethics Committee under the School of Medical Sciences, University Sains Malaysia (USM/JEPeM/19010081). Also, this study complied with the acceptable international standards, including the Declaration of Helsinki.

Participant recruitment

Permuted block randomization (blocks of 4) was used in this study to randomly assign the recruited participants to control and intervention groups. The algorithm used in the random permuted blocks was stratified by age, gender and BMI. The participants in the intervention arm were provided with multigrain powder supplement sachets (Oat King Sport) and were required to consume two sachets (each sachet 40.0g) which were equivalent to 15.6g total fiber per day (6.8g beta-glucan and 8.8g insoluble fiber)daily for three months on top of their prescribed conventional medications,. The Malaysian Dietary Guideline recommends a dietary fiber intake of 20g to 30g a day from plant foods, including both soluble and insoluble fiber. According to Malaysian Adult Nutrition Survey (MANS),dietary fiber (DF) intakes among Malaysian adults are 10.7±1.0 g/day these data sets did not meet the national population intake goal of 20-30 g DF/day(Ng *et al.*, 2010) [25]. Therefore, in this study, we have provided high fiber multi-grain supplements that contain 15.6 g of total fiber in addition to the usual fiber consumption by participants to meet the recommended DF consumption by MDG.

On the other hand, the participants in the control arm were required to just continue with the medications provided by their rheumatologist, without the multigrain powder supplementation

were advised not to consume high fibre ,antioxidant and anti-inflammatory supplements throughout this study. Participant's medication remained unchanged throughout this study. Phone interviews were conducted throughout the 90-day study period to assess if the participants experienced any side effects. Lastly, the weight, height, BMI, waist circumference, BP, HR, DAS, VAS, HAQ-DI, morning stiffness scale of the participants were assessed again at the end of the study period. Also, blood tests for RFT, LFT, FLP, ESR, uric acid and FBC were repeated and the results were recorded in a data collection sheet. The participants were advised to bring the remaining high-fiber multigrain supplement sachets during the follow-up visit to assess the adherence.

Statistical analysis

The collected data were analysed using IBM SPSS Statistic Version 26.0 (IBM, Armonk, NY, USA). Descriptive statistics of the variables were determined, including demographic and physical characteristics (age, gender, weight, height and BMI), DAS, HAQ-DI score, VAS score, morning stiffness scale score and blood test results.

The data obtained for numerical variables were expressed as mean with standard deviation (SD) while the categorical variables were expressed as frequency (n) and percentage (%), as tabulated in Table 1. The mean scores of the related numerical variables of the pre and post-tests of both the intervention and control groups were compared using paired t-test. A p value less than 0.05 is considered to be statistically significant. The results were reported with their 95% confidential interval (CI). The differences in the mean score of each variable of both the pre and post-tests

between the intervention and control groups were analyzed using independent t-test. A p value less than 0.05 is statistically significant.

RESULTS

Clinico-demographic characteristics

A total of 51 samples were recruited for this study. The demographic characteristic of participant involved in this study were summarized in Table 1. The mean age of samples in intervention and control group was 54.68(SD=8.28). The result of the data showed that predominantly there were more female in both groups (intervention group=(n=19, 37.2%),vs control group=(n=24, 47.1%)) among all the samples in the present study. There was no significant difference in baseline characteristics between the two groups. For clinical characteristic , 29.4% of patients had low disease activity (DAS score 2.6-3.2) , 54.9 % had moderate disease activity (3.2-5.1) , and 15.7% had high disease activity (>5.1) .

Comparison of the pre and post-tests results among the RA participants.

The comparison between pre and post result for each group is to evaluate efficacy of high fiber multigrain supplementation among RA patients in reduction of inflammatory markers and clinical disease activity. Based on Table 2, there were significant mean differences of mean score between pre and post test for comparison in each intervention and control group. For intervention group, there were significant mean difference for BMI ($p<0.001$), waist circumference ($p=0.005$), DAS 28 ($p<0.001$), HAQ ($p=0.034$), morning stiffness scale ($p=0.010$), and VAS pain scale ($p=0.003$), between pre and post test . For BMI, the mean score of pre-intervention was