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Efficacy of mediterranean diet on pain and knee range of motion in patients with rheumatoid arthritis: A randomized controlled trial

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***Abstract*---**Objective: To investigate the combined effect of the Mediterranean diet and designed exercise program on pain, knee Range of motion, and body weight in patients with rheumatoid arthritis. Methods: Forty females with rheumatoid arthritis were allocated randomly to experimental and control group. The experimental group (A) received a Mediterranean diet plane plus exercises while the control group (B) received exercises only. The treatment protocol continued for three months. All patients were examined by numerical pain rating scale (NRS) for pain intensity, Digital weighing scales (DWS) for weight measuring, and Universal goniometers (UG) for knee Range of motion (ROM). All outcomes were measured at two levels: pre-treatment and after three months of intervention. Results: un-paired t-test reported statistically significant difference between both groups after three months of intervention at

all outcome measures (P< 0.05) with more favor to experimental group (A). Conclusion: Mediterranean Diet combined with exercise improved pain, knee ROM, and weight reduction than exercise alone in female patients with rheumatoid arthritis.

***Keywords*---**rheumatoid arthritis, mediterranean diet, knee range motion.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by systemic inflammation, joint pain, and destruction of the synovial membranes (Aletaha et al., 2010). It affects approximately 1% of the population and is more common in women (0.75%) than men (0.15%) (Rudan et al., 2015). Additionally, the knee joint is affected by about 30% because hyperplastic synovium causes major damage to the cartilage in RA through directed adhesion (McInnes and Schett, 2011) and is considered a major factor that leads to functional impairment and disability (Kapetanovic et al., 2015).

Rheumatoid arthritis's risk of occurrence increases related to obesity (Crowson et al., 2013; Wesley et al., 2013; Lahiri et al., 2014). It is associated with increased pain, comorbidity, and risk of physical disability in RA (Baker et al., 2014). Also, functional disability significantly increases in obese as compared with normal-weight RA patients (Ajeganova et al., 2013). Moreover, Obesity is a common and critical factor that impacts the treatment of patients with RA (Hitt et al., 2007). It is likely that obesity contributes to elevated disease activity through obesity-related symptoms (Kramer et al., 2012).

Rheumatoid arthritis is an inflammatory condition, so the first-line therapy includes medications that suppress inflammation, such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids as act rapidly to improve pain and swelling (Bas et al., 2002). However, these medications develop serious treatment-related adverse effects including infections, tumors, and gastrointestinal toxicity (Turesson et al., 2002).

Rheumatoid arthritis is considered inflammation as a driving pathophysiological process (Galland, 2010). It is strongly influenced by nutrition because nutrients have the ability to modulate the inflammatory status (Calder et al., 2013) and elucidate the link between obesity and inflammatory arthritis (Giuseppe et al., 2014). Since obesity has an impact on disease activity and structural progression, it may modulate the response to treatments (Sparks et al., 2014). Mediterranean diet (MD) is considered one of the healthiest dietary models and is characterized by high consumption of fruits, vegetables, tree nuts, legumes, whole grains, fish, and unsaturated fatty acids (Bach-Faig et al, 2011). Besides its anti-inflammatory properties, MD has a positive effect on chronic disease activity (Barrea et al., 2019).

Exercise and diet interventions have been used as a critical element associated with a decrease in the risk of developing chronic diseases. Therefore, the

implementation of these interventions has gradually increased in the management of RA patients (Jahanbin et al., 2014). But to date, there is limited evidence suggesting the efficacy of MD in the treatment of RA (Oliviero et al., 2015; García-Morales et al., 2020). Additionally, obesity management represents an important issue in RA management, but it is poorly studied (Sparks et al., 2014). So, the aim of this study was to explore the combined effects of MD and exercise programs on pain, knee joint ROM, and body weight in females with RA.

Materials

Study design

The single masking (assessor), prospective, randomized controlled experimental trial was carried out at the outpatient clinic of the Faculty of Physical Therapy, Cairo University, Egypt from February 2020 to May 2021. All females were enrolled from Cairo University hospitals, Al Mataryya and Om El-Masryeen in Cairo.

Subjects

All female were diagnosed with RA and referred by a rheumatologist. Patients were enrolled in this study if they were between 35 and 50 years old, had RA classes I and II, had a disease history less than 5 years ago, and had a body mass index (BMI) between 25 and 40 kg/m^2. Females were excluded from this study if they had chronic heart failure, cancer, chronic kidney disease, infection, any autoimmune disease, unstable ischemic heart disease or arrhythmia, joint surgery within the previous six months, or if they were receiving biological therapy for rheumatoid arthritis. Ten females were excluded for not meeting the inclusion criteria (Figure 1).

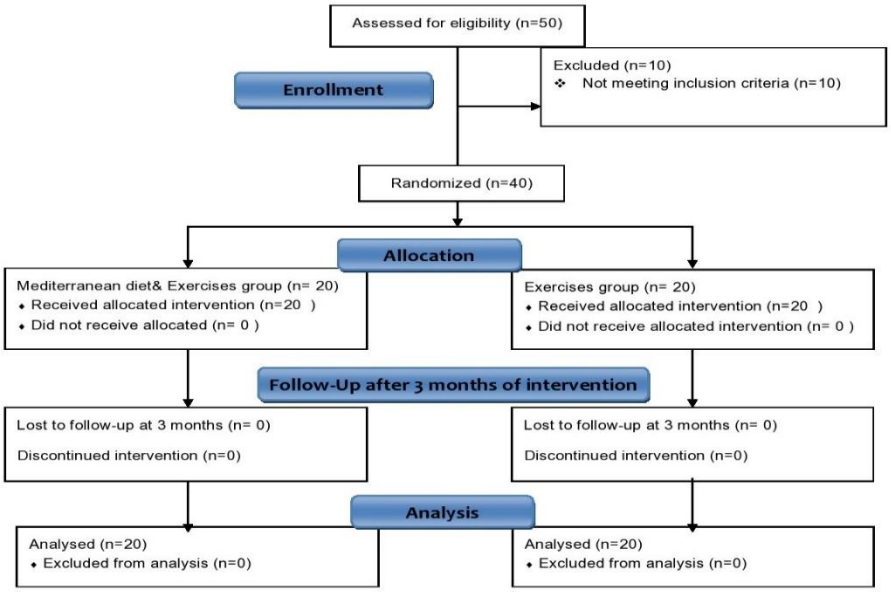

Fig (1): CONSORT flow chart

Sample size and randomization

Sample size calculated by G*Power (version 3.1.9.2). The process of calculation based on F test: repeated measures, between factors, type I error rate was set at 5% (alpha-level=0.05), type II error rate at 0.8 and the effect size = 0.43 of the main outcome variables (pain intensity) obtained from a pilot study on ten patients. The appropriate minimum sample size for this study was 34 subjects. To account for the drop-off, a 15% increase in the calculated sample size, so the study sample would be 40 patients. Forty females were allocated randomly by permuted block into two equal groups; group A received MD and exercise, and group B received exercise only. The first author, who was not involved in participant recruitment, data collection, or treatment, carried out the hidden allocation using sealed, opaque envelopes. The fifth author applied the baseline measurements, and the fourth author opened the envelopes after the measurements and continued the treatment in accordance with group allocation.

Dependent variables

The Numeric Pain Rating Scale (NRS) was used to measure pain intensity. It has good validity and reliability for assessing pain intensity. The NRS is a verbally administered scale that measures pain. For pain intensity, 0 = "no pain at all" to 10 ="worst possible pain" (Von et al., 2009). The patient was asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours. The average of the 3 ratings was used to represent the patient's level of pain over the previous 24 hours (Hjermstad et al., 2011).

A universal goniometer (UG) (Chattanooga©), with a plastic 360 goniometer face, and 10-inch movable arms was used to measure knee joint ROM. The universal goniometer is valid and has good overall intra- and inter-tester reliability (Brosseau et al., 2001). The measurements on the UG were blinded by the examiners. the goniometer axis rested over the lateral epicondyle of the femur. The stationary goniometer arm was aligned parallel to the longitudinal axis of the femur, aligned with the greater trochanter; the recorder documented the angle in whole degrees by examining the non-blinded side of the UG (Clarkson, 2000). Three measurements were undertaken by each examiner and the average was recorded (Milanese et al., 2014).

A digital weighing scale (DWS) (AND FG-150 Platform Scale) was used to assess body weight. DWS is reliable and valid to measure body weight (Walsh et al., 2008; Kumar et al., 2014). DWS was placed on a hard, flat surface. Participants were asked to stand with bare feet placed centrally on DWS to ensure even weight distribution on load cells and were instructed to stand with feet placed shoulder-width apart with their hands at their sides (Adegoke et al.,2012). They were instructed to look straight ahead throughout their stance on the DWS. Stood in their habitual standing posture for 10 s, and then measurements were recorded (Grass et al., 2011). The calibration of the DWS was carried out between each trial when the participants stepped off from the DWS and the display was ensured to read 0 kg (Adegoke et al., 2012).

Intervention

The intervention began with an individual meeting to discuss exercise goals and how the Mediterranean diet intervention should be carried out. For the intervention group's first meeting, both weight and height were calculated to estimate the diet plan based on estimated energy expenditure. The following equation is used to calculate basal energy expenditure by Harris and Benedict (Frankenfield et al., 1998).

BMR for Females= (10 × weight in kg) + (6.25 × height in cm) - (5 × age in years) – 161

Patients were informed about the Mediterranean diet. The macronutrient distribution was as follows: 50 percent carbohydrates, 30 percent fats, and 20 percent proteins (Estruch et al., 2010). Individual verbal instructions from the dietitian were given to each patient, as well as a nutritional handbook with 5 menu options divided into breakfast, morning snack, lunch, afternoon snack, and dinner. Patients were asked to come in once a week to ask questions about the nutritional regimen.

Exercise program

Both groups participated in an aerobic and resistance exercise program three times per week for three months under the supervision of physiotherapists. Walking is the prescribed aerobic exercise for rheumatoid arthritis (Lange et al., 2019), and resistance exercise utilizes a standardized protocol that included leg press, knee extension, biceps curl with free weights, and core stability exercises (Rausch et al., 2018). To reduce the risk of exacerbating symptoms, the exercise load was introduced and increased gradually.

Statistical analysis

The data concerning measured variables (NRS, knee flexion and extension ROM and body weight) and demographic data (age, weight, height and BMI) were collected and analyzed statistically by using SPSS version 25 (IBM Corp, New York, United States). The data were subjected to the Shapiro Wilk test for assessment of normality. All variables were normally distributed. So, all variables were analyzed by parametric test (t-test: paired and un-paired). The level of significance was controlled at 0.05. The adjusted P value for multiple comparisons was 0.0125[level of significance (0.05)/the number of outcomes (4)].

Results

Demographic data: Unpaired t-test revealed no statistically significant difference between two groups at age, weight, height, BMI as ($p > 0.05$) Table (1).

Table (1)
Demographic data of both groups

	Group (A) Mean ± SD	Group (B) Mean ± SD	T-value	P-value
Age (years)	39.9±5.38	40.95±4.35	-1.06	0.29 **
Weight (kg)	84.5±15.92	86.2±15.18	-0.34	0.73 **
Height (cm)	161.75±5.9	163.8±4.96	-1.18	0.24 **
BMI (kg/m ^{2})	32.27±5.73	32±4.81	0.15	0.84 **

**: no significance difference; SD: Standard deviation; BMI: body mass index; kg:kilogram; P-value: significance level

Within group analysis

Paired t-test revealed statistically significant difference between pre and post treatment in NRS, knee flexion and extension ROM and body weight in group (A) (P< 0.05). Also, there was statistically significant difference in group (B) in all measured variables (P< 0.05) except body weight (P> 0.05) as shown in Table (2).

Between group analysis

Un-paired t-test revealed no statistically significant difference between pre-treatment of both groups at all measured variables (P< 0.05). However, there was statistically significant difference between both groups at post-treatment of all measured variables (P< 0.05) with more favor to group (A).

Table (2)
Within and between group analysis of all measured variables

Variables	Group A	Group B	P-value (between groups)
NRS (cm)			
Pre-treatment	6.55±1.39	6.4±0.99	0.69 **
Post-treatment	3±0.9	4.4±0.86	0.006*
MD (95% CI)	3.5 (2.84 to 4.25)	2 (1.11 to 2.88)	
p-value (within	0.0001*	0.0001*	
Knee flexion (degree)			
Pre-treatment	123±1.86	122.45±2.01	0.3**
Post-treatment	129±1.16	125.35±1.72	0.0001*
MD (95% CI)	5.9 (6.93 to 4.86)	2.9 (4.05 to 1.74)	
p-value (within	0.0001*	0.0001*	
Knee extension (degree)			
Pre-treatment	3.6±0.88	3.85±0.9	0.53**
Post-treatment	1.45±0.6	2.45±0.84	0.001*
MD (95% CI)	2.15 (1.51 to 2.78)	1.4 (0.52 to 2.27)	
p-value (within	0.0001*	0.003*	
Body Weight (kg)			
Pre-treatment	84.5±15.92	86.2±15.18	0.73**
Post-treatment	76.05±8.82	85.35±13.73	0.01*

MD (95% CI)	8.45 (3.49 to 13.71)	0.85 (2.73 to 4.43)
p-value (within)	0.002*	0.62**

**: no significance difference; *: significant difference; SD: standard deviation; p-value: significance level; NRS: numerical pain rating scale; kg: kilogram; CI: confidence interval; MD: mean difference.

Discussion

The purpose of the current study was to investigate the efficacy of adding a Mediterranean diet to an exercise program on pain, knee joint ROM, and body weight in patients with RA. The main finding of this study showed a statistically significant difference between both groups regarding all outcome measures after three months of intervention in favor for group A.

The Numeric Pain Rating Scale was used to examine the effect of the Mediterranean diet on pain intensity in a female with rheumatoid arthritis. The results reported statistically significant differences between both groups in pain intensity level after three months of intervention. Oxidative stress and inflammation have been linked to the development of chronic pain (Kaushik et al., 2020). It's assumed that MD has the ability to decrease pain intensity by increasing the antioxidant levels and decreasing the production of anti-inflammatory mediators (McKellar et al., 2007; Hagen et al., 2009; Forestie et al., 2009). The results of this study come in agreement with other studies (Sköldstam et al., 2004; González et al., 2014; Garcia-Morales et al., 2020).

One of the key outcomes and measurable variables for any procedure around the knee is the range of movement. Sixty-seven degrees of flexion is required for a normal gait, 83° for ascending and 90° for descending stairs, 93° to stand from a seated position, and 105° to tie shoes (Dietz et al., 2017). The UG was used to assess knee joint ROM. The result of the current study showed a statistically significant difference between groups after three months of intervention in favor of group A. The refinement in knee ROM is attributed to a decrease in inflammatory parameters (Chrysohoou et al., 2004) that play a pivotal role in the destruction of knee cartilage (Rainbow and Zeng, 2012). This effect seems to be the most important factor in the link between the Mediterranean diet and knee ROM. Similarly, following a Mediterranean diet seems to lower oxidative stress markers which may influence the onset of symptomatic arthritis by enhancing collagen type II levels and inhibiting apoptosis-related protein expression (Scoditti et al., 2012). Finally, the Mediterranean diet seems to have a role in improving the extracellular matrix (ECM) (Scoditti et al., 2012) therefore, promoting the effective repair of a structure that is frequently reduced in people developing RA (Musumeci et al., 2013). The results of the current study were in line with other studies (Dyer et al., 2017; Veronese et al., 2019).

Obesity leads to a significant deterioration in functional capacity and health-related quality of life, and there seems to be a direct proportional relationship between body mass index (BMI) and the degree of quality-of-life deterioration (Spreckley et al., 2012; Taylor et al., 2013). A digital weighting scale was used to examine the effect of the Mediterranean diet on body weight in females with

rheumatoid arthritis. The results reported statistically significant differences between groups in body weight after three months of intervention in favor of group A. Previous studies have pointed out that obese individuals, undergoing medical nutritional treatment based on the Mediterranean diet, substantially decrease their body weight, and other anthropometric measurements (Bach-Faig et al., 2011; Buscemi et al., 2020). The reduction in body weight in the MD group may be attributed to the high level of dietary fiber, which is a key to appetite regulation, such as prolonged mastication, increased gastric detention, and enhanced release of cholecystokinin (Schröder et al., 2007). So, adherence to an MD significantly decreased body weight (Goulet et al., 2003; Bautista-Castano et al., 2004; Vincent-Baudry et al., 2005; Andreoli et al., 2007).

Moreover, Energy density has an important role in weight gain. MD has a low energy density and a low glycemic load compared with many other dietary patterns. These characteristics together with its high-water content lead to increase satiation and a lower calorie intake and thus help to prevent weight gain (Willett and Leibel, 2002). Additionally, diets rich in monounsaturated fat have been found to improve glucose metabolism and increase postprandial fat oxidation, diet-induced thermogenesis, and overall daily energy expenditure (Sanchez-Villegas et al., 2006; Due et al., 2008). This study's results comes in agreement with other studies (Bach-Faig et al., 2011; Agnoli et al., 2018; Poulimeneas et al., 2020; Buscemi et al., 2020).

On the other hand, group B has improvements in pain levels. This result may be attributed to exercising muscle stimulating cellular immune changes that have a significant anti-inflammatory effect. More specifically, exercise decreases induced muscle-derived (IL-6), which is predominantly described as a pro-inflammatory cytokine in RA (Pedersen et al., 2007). Moreover, exercise is able to attenuate inflammation indirectly by reducing adiposity (Metsios et al., 2010). The results of the current study come in agreement with other studies (Perandini et al., 2012: Ertek et al., 2012: El Kabbaj et al., 2016).

Finally, group B has an improvement in knee ROM. This result may be attributed to the that resistance training at partial ROM has been suggested as a good strategy to reduce neural inhibition and improve the coordination of primary and stabilizing muscles (Clark and Bryant, 2008; Kompf and Arandjelović, 2016). Additionally, the dynamic exercise program improved muscle flexibility since it increased the ROM (Steultjenset al., 2004). This study results come in agreement with (Häkkinen et al., 2004; Bloomquist et al., 2013; Kubo et al., 2019).

Limitation

This study had some limitations. First, the small sample sizes could alter the statistical power to detect significant associations. So, studies with a bigger sample size are needed. Second, the MD diet compares with the no diet. so, MD interventions should compare with another diet, if the aim is to assess which diet is more effective for weight loss. Finally, Longer interventions, which also assess compliance, are required to evaluate the long-term efficacy of the MD for promoting and preventing overweight/obesity.

Conclusion

Mediterranean Diet combined with exercise improved pain score, knee ROM, and weight reduction than exercise alone in female patients with rheumatoid arthritis.

Clinical implication

Adding the Mediterranean diet to the exercise program might help in improving pain, knee ROM and obesity management more than the exercise program alone in patients with Rheumatoid arthritis.

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