ORIGINAL ARTICLE

Exercise Intervention for Chronic Pain Management, Muscle Strengthening, and Functional Score in Obese Patients with Chronic Musculoskeletal Pain: A Systematic Review and Meta-analysis

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ABSTRAK

Latar belakang: *obesitas dan Osteoartritis memiliki hubungan yang kuat dengan mekanisme multifaktorial yang menyebabkan rasa sakit dan mengarah pada penurunan kualitas hidup. Latihan telah diidentifikasi sebagai pencegahan dan manajemen terhadap obesitas dan nyeri sendi. Tinjauan systematic review ini diusulkan untuk menilai efek antara latihan dibandingkan dengan kelompok diet untuk manajemen nyeri kronis, fungsi fisik dan mental pada pasien obesitas dengan masalah muskuloskeletal kronis.* ***Metode:*** *kami melakukan penelusuran sistematis dari Randomized Control Trial di Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EBSCO; SCIENCEDIRECT (Elsevier); SCOPUS, laporan penelitian terdahulu, trial registry, studi yang sedang berlangsung untuk studi yang diterbitkan, dan dari ClinicalTrial.gov, tesis kedokteran rehabilitasi medik di RSCM, dan buku prosiding untuk studi yang tidak dipublikasikan yang terakhir kali diperbaharui pada bulan November 2016. Risiko bias dinilai dengan menggunakan tool risiko bias Cochrane dan data dianalisis menggunakan Review Manager 2014.* ***Hasil:*** *satu penelitian menunjukkan tidak ada perbedaan dalam perbaikan kualitas nyeri yang dinilai menggunakan VAS antara dua kelompok. Dua penelitian menunjukkan peningkatan fungsi fisik diukur menggunakan 6MWT dalam kelompok latihan pada 6 dan 18 bulan dengan perbedaan rata-rata 28,12 [11,20,45,04] dan 26,21 [9,01,43,41]. Tidak ada efek yang signifikan yang diamati untuk fungsi mental dan fisik berdasarkan SF-36 setelah 6 bulan (1 studi) dan 18 bulan (2 penelitian) pengamatan dengan perbedaan rata-rata 1,10 [-0,79, 2,99] dan 0,08 [-1,53, 1,70] nilai untuk tiap skor fungsi mental dan -0,30 [-2,54, 1,94] dan -0,36 [-2.30, 1,57] untuk skor fungsi fisik.* ***Kesimpulan:*** *efek latihan dapat meningkatkan fungsi fisik secara objektif, tetapi tidak dapat mengurangi rasa sakit pada pasien obesitas dengan masalah muskuloskeletal kronis secara subyektif.*

Kata kunci: *exercises intervention, tata laksana nyeri kronis, functional score, kualitas hidup, systematic review.*

ABSTRACT

Background: *obesity and osteoarthritis have strong inter-relationship with multi-factorial mechanism that caused pain and leads to decreased quality of life. Exercise has been identified as prevention and management against obesity and joint pain. This systematic review aims to assess the effect between exercises compared to diet group for chronic pain management, physical and mental function in obese patients with chronic musculoskeletal problem.* ***Methods:*** *we performed a systematic search of Randomized Control Trial studies from Cochrane Central*

Register of Controlled Trials (CENTRAL); MEDLINE; EBSCO; SCIENCEDIRECT (Elsevier); SCOPUS, grey literature, trial registry, ongoing study for published studies, and from the ClinicalTrial.gov, thesis of rehabilitation medicine in RSCM, and proceeding books for unpublished studies that was last updated on November 2016. Risk of bias was assessed using Cochrane risk-of-bias tool and data were analyzed using Review Manager 2014. ***Results:*** *one study showed no difference in pain reduction (assessed using VAS) between two groups. Two studies showed improvement in physical function measured using 6MWT in exercise group at 6 and 18 months with mean difference 28.12 [11.20, 45.04] and 26.21 [9.01, 43.41]. There was no significant effects observed for Mental and Physical Function based on SF-36 after 6 months (1 study) and 18 months (2 studies) observation, with mean difference 1.10 [-0.79, 2.99] and 0.08 [-1.53, 1.70] respectively for Mental Function score and -0.30 [-2.54, 1.94] and -0.36 [-2.30, 1.57] respectively for Physical Function score.* ***Conclusion:*** *exercise can improve physical function objectively, but could not reduce pain in obese patients with chronic musculoskeletal problem subjectively.*

Keywords: *exercises intervention, chronic pain management, functional score, quality of life, systematic review.*

INTRODUCTION

Obesity is a global public health issue.[1] Data from WHO showed that worldwide obesity has nearly tripled since 1975.[2] In 2016, more than 1.9 billion adults with population aged 18 years and older were overweight.[2] Data from Riskesdas 2013 showed that in Indonesia, prevalence of obesity keeps increasing since 2007.[3] Percentage of obese male and female population from 2007 until 2013 was increased 5,8% and 19% respectively.[3]

Excessive weight shifts the center of gravity and increase mechanical stress to the joints and tissues of the body and induces physical limitations, impairment and significant disturbance to the quality of life due to pain.[4] Depending on the location of pain and the severity, several medications may be used to reduce pain.[4] Procedural treatments such as intra-articular injections may be used for immediate and long term pain relief.[4,5] However other treatment options are needed to be considered.[6]

Regular exercise has been identified as a primary preventive and management for obesity, joint pain-related diseases, anxiety and depression.[4] Exercise can positively impact chronic pain mediators by exerting anti-inflammatory effects, increasing muscle coordination caused by muscle imbalance, and improving psychological outlook.[4]

Recent studies mostly focuses only on the effect of therapeutic exercise on single musculoskeletal pain region.[4] Based on those reasons, this systematic review propose to assess the effect of exercise for chronic pain management, muscle strengthening, physical function and quality of life in obese patient with chronic musculoskeletal pain.

METHODS

Review authors (TZ and NM) independently selected and assessed the articles and recorded the selection process in sufficient detail to a complete PRISMA flow diagram.[7]

We did systematic literature search using Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EBSCO; SCIENCEDIRECT (Elsevier); and SCOPUS, and grey literature, trial registry, ongoing study for published studies, and from the ClinicalTrial.gov, thesis of rehabilitation medicine in RSCM, and proceeding books for unpublished studies. These were last updated on 16th November 2016.

Search was conducted using the appropriate MeSHterms and textword: "Obese" OR "Obesity" OR "Overweight" OR "Excessive Weight" OR "Osteoarthritis" AND "Low back pain" OR "Musculoskeletal Problem" OR "Musculoskeletal Impairment" OR "Musculoskeletal Dysfunction" AND "Exercise" OR "Exercise Training" OR "Exercise Intervention" OR "Aerobic" OR "Cardiorespiratory Exercise" OR "Strengthening" OR "Progressive Resistance Exercise" OR "Resistance Exercise" AND "Muscle strengthening" OR "Pain" OR "Pain Scale" OR "Pain Score" OR "Pain Reduction" OR "Functional Score" OR "Functional Capability" OR "Functional Evaluation" OR "Functional Assessment" OR "Functional Test".

Eligibility Criteria

We focused on randomized clinical trials articles. The characteristics of the patients are: 1) Body Mass Index great the very least 25.0 kg/m^2, 2) Age between 18-70 years old, 3) No compelling disease other than musculoskeletal problem, 4) Minimum 6 months of pain (chronic pain) and has undergone aerobic and resistance exercise. The comparators of this study are drugs (Anti-obesity drugs, NSAIDs, and/or intra-articular injection) or diet with earliest weight reduction target is ±10% of previous body weight, or 1-2 lbs. (0.5-1 kg)/ week for 6 months period. This target should be achieved along by reducing calories 500-1000 Cal/day). The primary outcome is reducing pain score assessed by Visual Analogue Score (VAS). The secondary outcomes are muscle strength with hand held-dynamometer, physical functional score with 6-minute walk test, quality of life with Short Form-36 (SF-36) which includes physical score and mental score.

Data Extraction and Management

Reviewing authors independently extracted data on the study characteristics as follow: the study's methods, participants (number, age, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria), interventions and comparison and also the outcomes (primary and secondary). We resolved disagreements by consensus.

The reviewing authors (TZ and NM) input the data into Review Manager software (RevMan 2014). The methodologists (YP and EDS) double-checked that the data were entered correctly and spot-checked the study characteristics data for accuracy against the trial report.

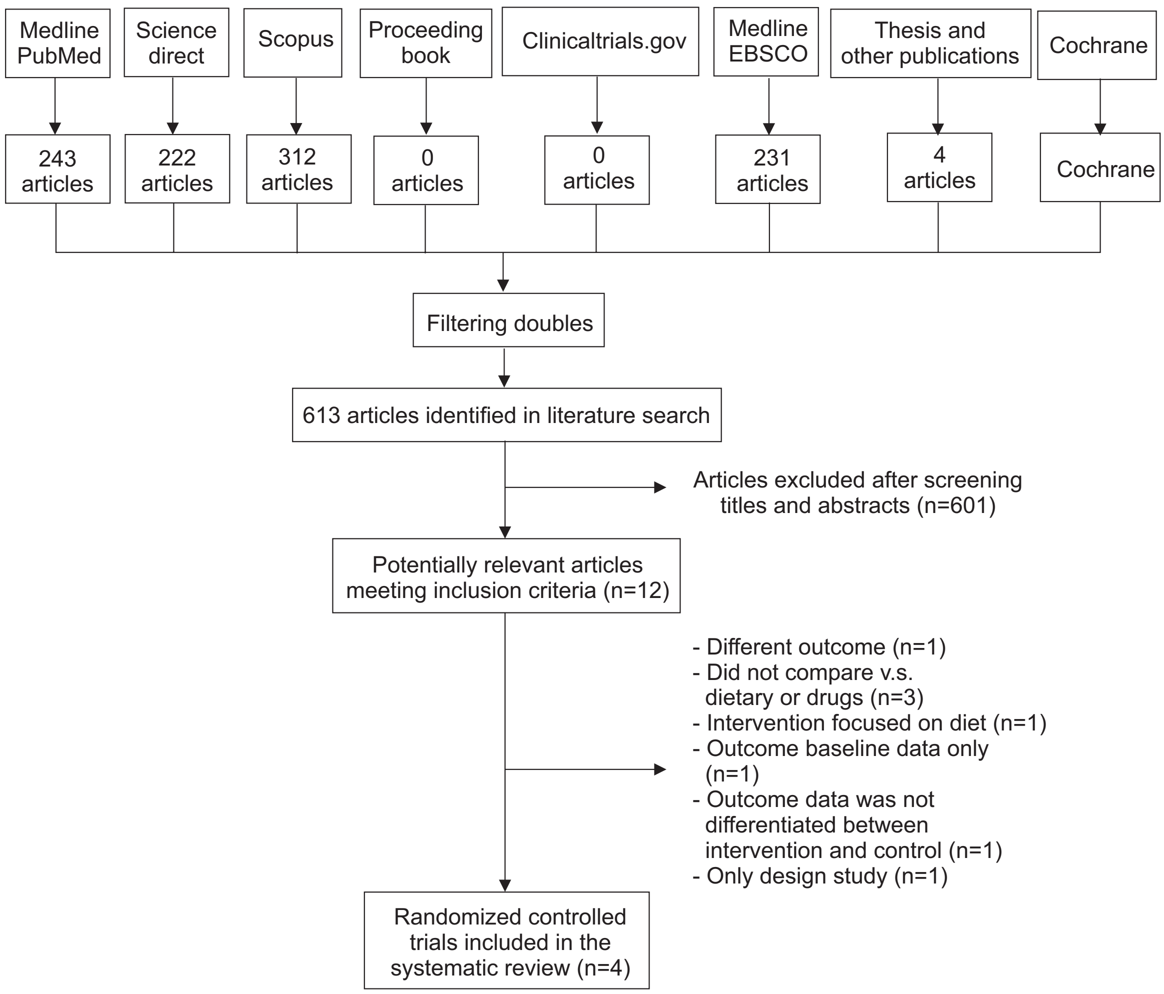

Figure 1. Collecting and selection process of articles

Assessment of Risk of Bias in Included Studies

We assessed risk of bias using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[8] We graded each potential source of bias as high, low, or unclear.

Statistical Analysis

Continuous outcome data was recorded using the same measurement scale, data was converted into mean differences (MDs). In regards to missing data, we tried to contact the author to obtain data or formulas to get the standard deviation. We used Chi square test and the I^2 statistic to measure heterogenity.

Data Synthesis

We pooled data that we judged to be clinically homogeneous using RevMan 2014, with a fixed-effect model. If a single true effect was not plausible, due to variation in populations and interventions or substantial heterogeneity, we would use a random-effects model instead (DerSimonian and Laird method).[8] If more than one study provided usable data in any single comparison, we would perform a meta-analysis.

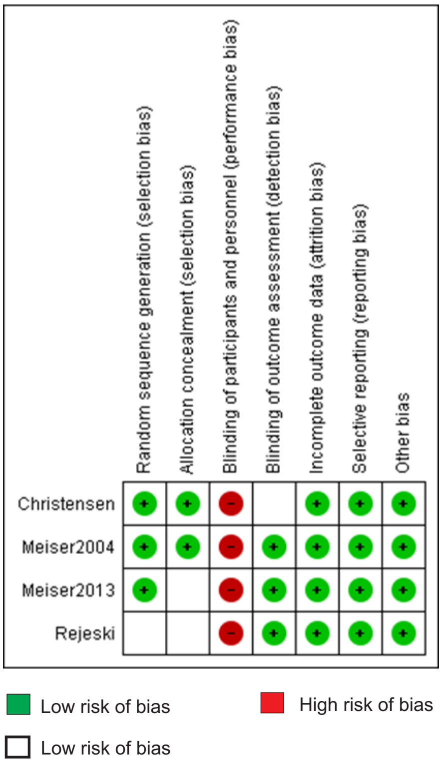

Figure 2. Risk of bias in included studies.

RESULTS

Two reviewers assessed 613 papers independently based on titles and abstracts. We found 12 papers that suited our inclusion criteria. We further reviewed the full-text papers based on the eligibility criteria. We excluded 8 papers. We did the last search on 16th November 2016.

Study Characteristics

We included four studies with a total of 734 participants aged 18-70 years old, BMI >25 kg/m² with chronic musculoskeletal disorder (Christensen 2015; Messier 2004; Rejeski 2002; Messier 2013). Methods, participants, interventions and outcomes of the included studies were described in characteristics of included studies (**Table 1**).

Risk of Bias in Included Studies

We had identified the risk of bias from all included studies. The random sequence generation in Christensen (2015), Messier (2004), and Messier (2013) were 75% low risk, while in Rejeski (2002) was 25% unclear risk of bias. The allocation concealment were 50% low risk in Christensen (2015), Messier (2004), while in Messier (2013) and Rejeski (2002) were 50% unclear risk of bias. The blinding of participants and personnel in all study were 100% high risk of bias. The blinding of outcome assessment were 75% low risk in Messier (2004), Messier (2013) and Rejeski (2002), while in Christensen (2015), 25% was unclear. The incomplete outcome, the selective reporting and other bias in all study were 100% low risk.

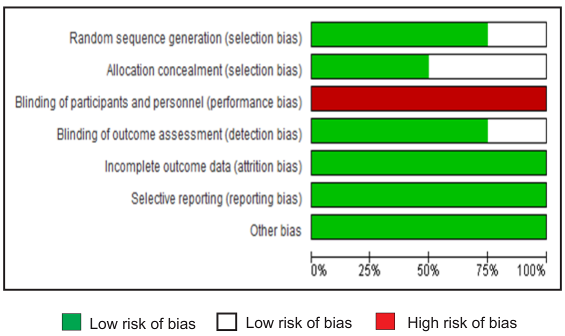

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 1. Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes
Christensen 2015[9]	RCT	- Age ≥ 50 years old	In 1st phase, all participants were randomly assigned to 1 of 3 groups and began a dietary regimen of 400 kcal/day, 810 kcal/day, and 1250 kcal/day for 16 weeks to achieve a major weight loss.	Primary outcome: self-reported pain on 100-mm Visual Analog Scale (VAS)
		- BMI ≥ 30 kg/m^2	The 2nd phase consisted of 52 weeks maintenance in either group diet, exercise, or control.	
		- Confirmed knee OA with clinical symptom and radiograph	Diet program group Participants met once a week to attend session for 1 hour, got weighted, and were handed out formula product. The participants were advised to use the formula product once a day (choose between liquid shake or a snack bar).	Secondary outcome: symptoms of knee OA with Knee Injury and Osteoarthritis Outcome Score (KOOS), health related quality of life with Short Form-36 (SF-36), physical function by 6-minute walk test (6MWT).
			Exercises program group Participants met 3 days per week to do exercises program which consist of warm up phase (10 minutes), a circuit-training phase (45 minutes), and a cool down/ stretching exercises phase (5 minutes). The exercises intervention divided into 4 periods of 12 weeks and 1 period of 4 weeks (total 52 weeks)	
			Control group No attention was provided to the participants after the first 16 weeks of therapy. The participants were contacted after 52 weeks for evaluation.	
Rejeski 2002[10]	RCT	- Age ≥ 60 years old - BMI ≥ 28 kg/m^2 - Knee pain on most day of the month	Diet program group The group consisted of 3 diet programs. The first one is intensive program for the first 4 months, followed by the transition program from month 5-6, and the maintenance program from month 7-18. This program aimed to increase the awareness of the necessity to modify the eating habits lower the intake of calories through self-regulatory abilities.	Health status measured by SF-36, BMI, demographic and comorbidities and satisfaction with physical function and appearance
		- Sedentary activity pattern with less than 20 min of formal exercises once per week for the past 6 months - Self-reported difficulty in at least one of the following activity ascribed to knee pain	Exercises program group 3 days per week exercises program consisted of an aerobic phase (15 minutes), a resistance-training phase (15 minutes), a second aerobic phase (15 minutes), and a cool-down phase (15 minutes). The first 4 months were facility based, then 2 months of transition phase (altered between the facility and the home), and 12 months of home based program.	
		- Radiographic evidence of tibia-femoral osteoarthritis	Healthy Lifestyle control This group was given healthy lifestyle session monthly for 1 hour for the first 3 months, followed by monthly phone contact during months 4-6, and bimonthly phone contact during months 7 – 18.	

Table 1. Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes
Messier 2004[11]	RCT	- Age $\geq$ 60 year old - BMI $\geq$ 28 kg/m^2 - Knee pain on most days of the month - Sedentary activity with duration of formal exercises exercises less than 20 minutes per week in the last 6 months - Patient report difficulty in doing ≥ 1 activites attributed to knee pain - Radiographic showed of tibio-femoral or patella-femoral OA	Exercises group The first 4 months was facility based, followed by 2 months of transition, and 12 months of home based program. The exercises program was consisted of aerobic exercise (15 minutes), resistance-training exercise (15 minutes), the second aerobic exercise (15 minutes), and cool down phase (15 minutes) for 3 days per week. Aerobic exercise consisted of walking until 50-75% of heart rate reserve was reached. Resistance-training consisted of 2 sets of 12 repetitions of leg extension, leg curl, heel rise, and step up Aerobic exercise: walking within heart rate range of 50-75% of heart rate reserve. Resistance-training portion: 2 sets of 12 repetitions of leg extension, leg curl, heel rise, and step up Dietary weight loss group Dietary intervention was done according to the principles from the group dynamic literature and social cognitive theory; divided into 3 phases: 4 months of intensive phase, 2 months of transition phase, and 12 months of maintenance phase. The main purpose of the intensive phase was to increase the awareness of the importance of and the need for changing eating habits in order to reduce caloric intake. Dietary Weight loss plus exercises group Combination of both exercises and dietary weight loss program described above. Both interventions were done consecutively on the same day and at the same location. Healthy lifestyle group This group was given attention, social interaction and health education. They met every month or 1 hour for the first 3 months. From month 4-6 they were followed up by phone calls. Followed by phone calls every 2 months from month 7-18. The patients were suggested to follow the ACR and EULAR recommendation for weight loss and were given exercises for OA treatment.	Primary outcome: self-reported physical function (WOMAC function test). Secondary outcome: weight, measures of mobility (6MWT), pain (WOMAC pain score), and knee radiographs.
Messier 2013[12]	RCT	- Age $\geq$ 55 years old - Radiographic evidenced of tibio-femoral OA or tibio-femoral plus patella-femoral OA - Pain on most days due to knee OA - BMI 27 – 41 kg/m^2 - Sedentary life style (< 30minutes per week of formal exercises for the past 6 months)	Intensive weight loss intervention This group was given partial meal replacement. Two meal replacements shakes were given each day (lean shake: General Nutrition Center). The participants were given a weekly menu plan for for the third meal. The meals were 500 to 750 kcal, low in fat and high in vegetable. The daily diet plan aims for energy intake deficit of 800-1000kcal/day based on energy expenditure estimation (resting metabolism x 1.2 activity factor) with minimum of 1100 kcal for women and 1200 kcal for men. The nutrients composed of 15-20% protein, <30% fat, and 45-60% carbohydrates, in accordance with the Dietary Reference Intake for Energy and Macronutrient and successful weight loss program. Exercises intervention The exercise program lasted for 18 months, with 1 hour session for 3 days/ week. The exercise was held center based for the first 6 months, then continued by transition phase for 2 weeks before the home phase. The programs included aerobic walking for 15 minutes, strength/resistance training for 20 minutes, then followed by a second aerobic phase for 15 minutes, and finished by cool down session for 10 minutes). Diet and exercises intervention Combination of both exercises and dietary weight loss program described above.	Primary outcome: knee joint compression force and plasma IL-6 level. Secondary clinical outcome: Self-reported pain (WOMAC pain score), function, mobility , and health related quality of life (6MWT and SF-36 physical function score)

Effects of Interventions

- Primary outcome

  There was only one study (Christensen 2015) about the effect of exercise on the reduction of pain score assessed according to VAS. This study was reported by a randomized trial consisted of 2-phase, parallel group trial, with a total of 192 obese participants. This study compared the VAS of obese patients with knee osteoarthritis (OA) after 18 months of intensive weight loss regimen, 1 year of either dietary support program or knee exercise program, to the control group. Changes in VAS score from baseline in this study showed no significant difference between exercise and diet group.
- Secondary outcome

  There were two studies about the effect of exercise on physical function score that assessed according to 6MWT compared to diet group after 6 and 18 month follow up. Also, there were two studies about the effect of exercise on quality of life (mental health and physical function) score assessed using SF-36 compared to diet group after 18 month follow up.

Assessment of physical function score according to 6MWT after 6 month follow up (**Figure 4**) and 18 month follow up (**Figure 5**) showed that exercise was more effective compared to diet with the mean difference 28.12 (95% CI, 11.20-45.04) and 26.21 (95% CI 9.01-43.41), respectively.

Assessment of mental function score with SF-36 after 18 months follow up (**Figure 6**) showed no difference in the effect of both group with mean difference of 0.08 (95% CI -1.53 – 1.70).

Physical function score according to SF-36 after 18 month follow up (**Figure 7**) showed no difference, in the effect of both group with mean difference -0.36 (95% CI -2.30 – 1.57).

DISCUSSION

We included four studies with a total of 734 participants. All studies were single-blind randomized clinical trial. Physical function score according to 6MWT after 6 month follow-up and 18 month follow-up showed that exercise group was more effective compared to diet group. In comparison to diet, exercise was more effective for in increasing physical function as assessed using 6MWT.[5] Aerobic exercises increase muscle mass and fat burning which result in increase of the muscle strength and endurance.[13,14] It leads to the decrease of disabilities that were caused by

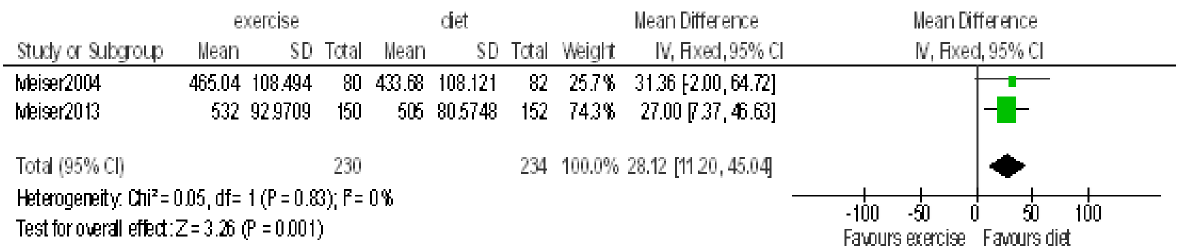

Figure 4. Mean difference in physical function score with 6MWT after 6 months follow up between exercises and diet program.

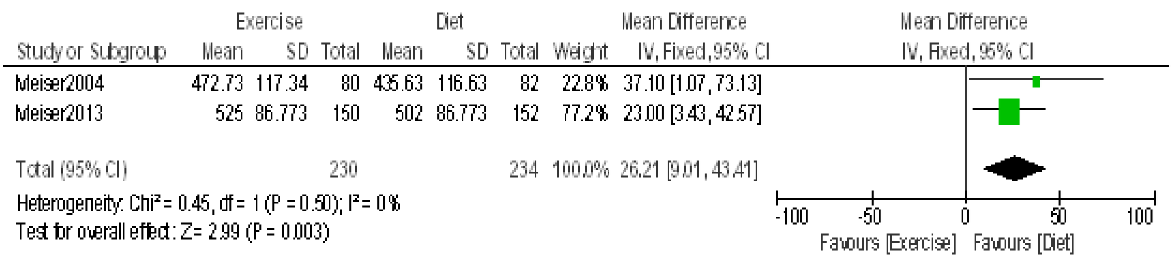

Figure 5. Mean difference in physical function score with 6MWT after 18 months follow up between exercises and diet program.

physical problem. Resistance exercises improve gait performance and aerobic exercises increase the cardiopulmonary capacity.[15] Resistance exercises may act by correcting muscle strength deficits and knee instability, thereby allowing the affected individual to engage in more activity with less pain.[4] Improving muscle strength is important because it increases the shock absorbing capacity in joints and increases joint stability.[16] The biochemical changes as a response of aerobic exercises also influence muscle.[14,15] Myoglobin concentration in the muscle has a role in oxygen diffusion during physical activity. It increases oxygenation of carbohydrate as a result of the increase of quantity, size, and surface area of mitochondrial membrane of the skeletal muscle. It also increase activity or concentration level of enzyme involved in Krebs cycle and electrical transport system. It also increases fat oxidation, and muscle fiber type I and II.[14,15] Increased number of muscle fiber type I, along with increased size and number of mitochondria on the muscle increases the muscle endurance.[14] Aerobic exercises have a systemic effect and local effect.[15] Its systemic effects increase the muscle endurance.[4] Its local effect on muscle increases the aerobic metabolism of muscle, increase surface area of muscle (i.e. muscle hypertrophy), increases total number of the muscle fiber (i.e. muscle hyperplasia) as a reaction and degeneration to injury or overuse.[14,15] This mechanism affected by the intensity of aerobic exercise.[14,15]

No significant effects were observed in Mental Function Score based on SF-36 after 6 month (1 study) and 18 month observation (2 studies). SF-36 Quality of Life (QoL) Scoring System is a self-administered questionnaire that was constructed to fill the gap between much more lengthy surveys and relatively coarse single-item measures of the QoL.[17] The scales of SF-36 are summarized into two dimensions.[17] The first five scales make up the "physical health" dimension, and the last five form the "mental health" dimension. Vitality and general health are parts of both dimensions.[17] Aerobic exercise and resistance exercise increase adrenalin and endogenous morphine-like hormone activity that facilitate the stress adaptive response.[18] Endorphins is an endogenous morphine like chemical in both structure and effect and it also has the same binding site in brain cells or receptor to reduce pain signals, calm the brain in stress full situations, and bring feeling of happiness.[18] It is produced and released from the pituitary

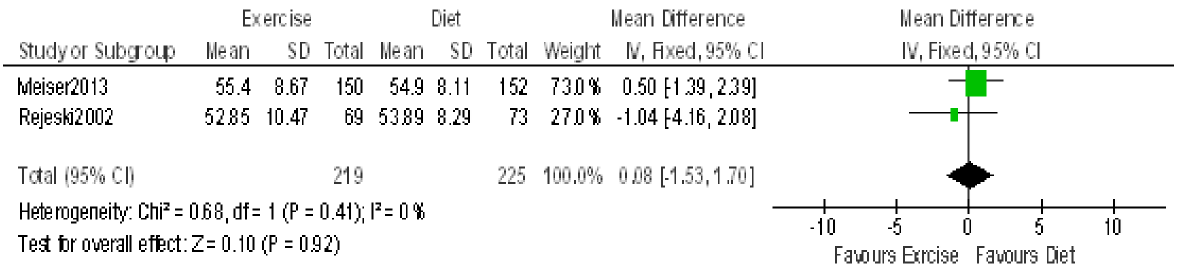

Figure 6. Mean difference in mental function score with SF-36 after 18 months follow up between exercises and diet program.

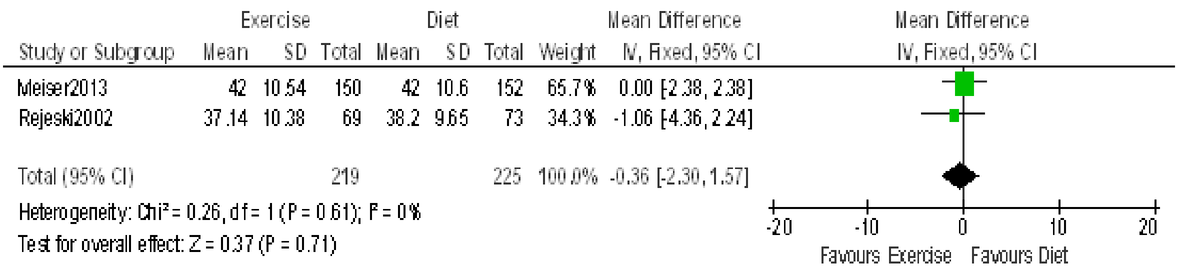

Figure 7. Mean difference in physical function score with SF-36 after 18 months follow up between exercises and diet program.

gland during continuous exercises for more than 30 minutes.[18] The effect is called "a runner's high".[18] In addition, exercises increase sense of control and self-sufficiency, a meditation like state, social reinforcement, and diversion from pain or anxiety.[18] However exercise and diet showed no significant effect on mental health assessed using SF-36. Obesity is associated with general and specific musculoskeletal pain.[4] There is an interrelationship between mechanical loading, chronic pain, inflammation, and psychological status in obese patients.[4] Dietary restriction for 16 weeks reduces the joint loading and pain as well as habituates patient to the way of healthy and low-calories diet which leads to a better compliance of exercise and diet program compared to directly administering either exercise, diet control, or both exercise and diet.[9] Physical function score in SF-36 shows the impact of health problem in restricting daily living activities such as walking, climbing stairs, lifting things, cleaning home as well grooming and bathing.[17] Walking and climbing stairs is related to cardiopulmonary function and posture control.[17] Decreasing load in joints increase the physical function of the patients.[1,4,19] Besides, ingestion of approximately 25–30g of protein per meal maximally stimulates muscle protein synthesis in both young and older individuals.[13] However, there was no significant effect on physical function score based on SF-36 after 6 month (1 study) and 18 month (2 studies) observation. In this study, we observed that there was no significant differences between exercises and diet in obese patients with chronic musculoskeletal pain as measured using SF-36. Chronic pain is common in people with obesity.[4,5] Chronic pain is subjective experience and varies between individuals depending on the context and psychological state of the person.[20] The perception of pain is influenced by cognitive and emotional factors lies in the area of the brain involved in pain modulation.[21] People who suffers from chronic pain tends to adapt to their pain, since the pain becomes part of their daily life.[21] Chronic pain management need interdisciplinary approach including Cognitive Behavioural Therapy.[20,21] This therapy may improve outcomes with long-term benefits, not only to self management of chronic pain and coping with pain but also increasing health-related quality of life.[20,21]

Limitations of the Study

Since this systematic review only involved knee osteoarthritis (OA) as musculoskeletal problem, the result cannot be generalized for OA of other location such as shoulder or neck OA.

CONCLUSION

In obese adults with chronic musculoskeletal problem, there is no difference between exercise and diet in pain reduction and quality of life. However, exercise is more effective in improving physical function score according to 6 MWT.

ACKNOWLEDGMENTS

We would like to thank Univesity of Indonesia for the grant given to this study. We also would like to thank Rehabilitation Medicine Department of Universitas Indonesia and CEEBM Unit RSCM-FKUI for their support in this study.

FUNDING

This research was funded by Faculty of Medicine Universitas Indonesia.

CONTRIBUTIONS OF AUTHORS

Tirza Z. Tamin (TZ) drafted the protocol and contributed as a primary review author, selected studies for inclusion, extracted data, entered data into RevMan, and carried out and interpreted the analysis.

Nyoman Murdana (NM) drafted the protocol and contributed as a primary review author, selected studies for inclusion, extracted data, entered data into RevMan, and carried out and interpreted the analysis.

Yupitri Pitoyo (YP) and Eka Dian Safitri (EDS) carried out and interpreted the analysis, contributed as the third and fourth review author for disagreements on methodological/statistical issues.

DECLARATION OF INTEREST

Tirza Z. Tamin, Nyoman Murdana, Yupitri Pitoyo, Eka Dian Safitri this review was supported by a grant from the Faculty of Medicine Universitas Indonesia.

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