Original Article

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Lifestyle Interventions and Weight Management in Systemic Lupus Erythematosus Patients: A Systematic Literature Review and Metanalysis

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Background: We aimed to identify and describe different types of lifestyle interventions primarily or secondarily focused on weight loss in SLE patients.

Methods: A systematic search of controlled trials published until June 2021 that assigned adults patients after dietary or exercise intervention resulted in 248 studies initially screened.

Results: Six studies with seven interventions (3 dietary and 4 exercise training programs) fulfilled the eligibility criteria and were included in the meta-analysis with a median of age 35.8 (31.3 to 49.0 years); median of BMI 26.6 (25.2 to 33.6 kg/m^2). After six to twelve weeks of diet or exercise program, no differences were observed in body weight [−1.539 (−4.482 to 1.405) kg (CI 95%), p = 0.306]. Also, a subgroup analysis also revelated no body weight difference following dietary intervention [−3.561 (−9.604 to 2.481) kg (CI 95%), p = 0.248] or exercise intervention [−0.910 (−4.279 to 2.460) kg (CI 95%), p = 0.597].

Conclusion: The results showed that different protocols of exercise intervention or diets were not effective to reduce body weight in patients with SLE. However, only one of the selected trials had a specific study design and protocol focusing on weight loss management.

Key Words: Systemic lupus erythematosus, Weight loss, Lifestyle intervention, Diet, Exercise

INTRODUCTION

Obesity is a public-health condition associated with various comorbidities and disabilities, with an increasing prevalence across the world. In systemic lupus erythematosus (SLE) patients, the frequency of obesity is similar to or higher than in general populations [1], with prevalence ranging from 28% to 50% [2,3].

Considering that obesity may induce a systemic low-grade inflammatory environment, by increasing the production of cytokines [e.g. tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6)] [4], this condition has been associated with the pathogenesis of SLE [2]. Obesity-driven events

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(such as oxidative stress) can initiate inflammation through the transition of adipose tissue macrophages from M2 to M1, leading T cells recruitment [5]. This condition is also associated with lower B-regulatory and invariant natural killer (NK) cells within the adipose tissue [6]. Furthermore, chronic overnutrition-driven adipocyte hypertrophy leads to tissue growth with consequent hypoxia and chronically elevated basal lipolysis, which increased the fat free acids release [7]. Lastly, these mechanisms promote pro-inflammatory cytokine release, adipocyte dysfunction and may lead to insulin resistance [8], which if not appropriately resolved, can underlies or exacerbates autoimmunity [9].

Other mechanisms have been appointed to connect obesity with SLE, such as prolonged use of corticosteroid therapy [10], vitamin D deficiency (which are frequently observed in SLE patients and in obese subjects), hypoactivity [11], and dysbiosis of gut microbiota (Fig. 1) [1]. A high-fat diet is responsible for excess of weight and also for gut microbiota dysbiosis, which per se may lead to a deregulation of intestinal immune responses [6,12]. On the other hand, vitamin D deficiency levels have been related to changes on immune cell differentiation [6,13]. Moreover, regular exercise strengthens the immune system [14] by promoting a release of anti-nflammatory cytokines [14], reduction in neutrophil chemotaxis [15], increasing the concentration of circulating leukocytes [16], decreasing of lymphocyte levels [17] and inhibition of monocyte and/or macrophage infiltration into adipose tissue [18]. Thus, sedentary behavior and low physical activity levels is related to an unfavorable level of adiposity-associated inflammation [19].

In this context, several studies have shown that obesity is an independent risk factor associated with worse SLE disease activity [2], dyslipidemia [20], cumulative organ damage [e.g. nephritis] [21], depression [22], fatigue [22,23] and decreased quality of life [20,23]. A meta-analysis published by Sun et al., 2017 [24] showed that patients with SLE were more susceptible to develop metabolic syndrome compared with healthy individuals.

In view of this, weight loss interventions have been thought to ameliorate symptoms and minimize the need for medications among rheumatic diseases [25]. However, there is large uncertainty regarding the impact of different types of interventions (e.g., diet, exercise, behavior changes) on body weight in SLE patients. Therefore, the objective of this systematic review and meta-analysis was to (1) identify and describe different types of lifestyle interventions primarily or secondarily focused on weight loss in SLE patients and (2) verify if these interventions promote weight loss. Based on the findings, we also pointed out the main gaps in the field.

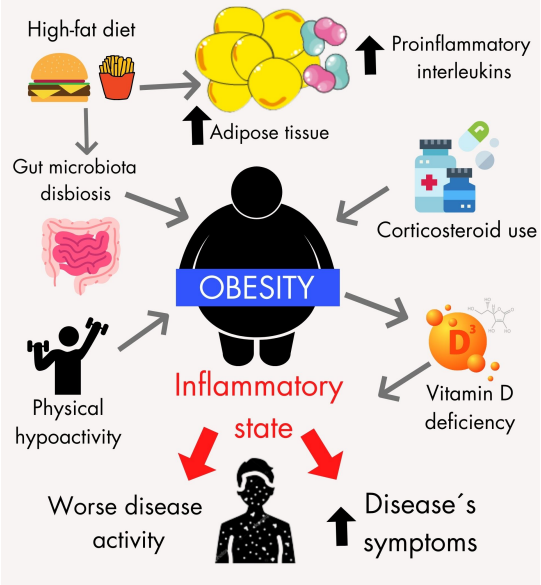

Fig. 1. Representation of the mechanisms that connect obesity with systemic lupus erythematosus.

MATERIALS AND METHODS

1. Protocol

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42021276607) and the protocol was designed and conducted in accordance with the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [26].

2. Search strategy

A systematic search of the literature was independently conducted in electronic databases (PubMed and Web of Science) by two members of the review team (CFN and KG) until June 30th, 2021.

The search strategy consisted of the search terms and descriptors, in combination with Medical Subject Headings (MeSH) terms in PubMed, related to disease (i.e., 'Lupus' OR

'systemic lupus erythematosus') and weight loss ('weight loss', 'weight management', 'nutritional intervention', 'exercise intervention', 'diet', 'hypocaloric diet', 'behavior intervention'). These were combined with a sensitive search strategy in order to identify 'randomized controlled trials' or 'randomized study design' performed in 'humans'. Observational studies and non-randomized and non-controlled trials (quasi-experimental designs) were excluded (Supplementary File 1).

3. Eligibility criteria

Studies were included if they had a randomized controlled design and included adults (≥ 18 years) with SLE disease. Trials should evaluate a lifestyle intervention (diet, exercise or both) and report the effect on body weight or body mass index (BMI) (pre- and/or post-intervention data). Only data from full-text, peer-reviewed publications were considered for inclusion. Filters for language were not applied.

4. Study selection

All identified studies were imported into Rayyan, a specific electronic application for systematic review and meta-analysis (https://rayyan.qcri.org/welcome). Duplicates were identified and removed. According to eligibility criteria, two reviewers independently screened the titles and abstracts of all studies. Disagreements between both reviewers were discussed and resolved by consensus.

5. Data extraction

The following data were extracted: (1) first author's surname, (2) publication year, (3) country, (4) study design, (5) sample size, (6) participant characteristics (mean age, sex and baseline BMI), (7) disease duration, (8) disease activity, (9) intervention characteristics (type, duration, frequency), and (10) body weight data (pre and post intervention). For those studies that met the inclusion criteria but did not report absolute body weight data at pre- and/or post-intervention period, the corresponding author was contacted twice by e-mail over a 15-day period to provide the missing information.

6. Assessment of the quality of the study

Quality assessment of each study was performed using the Cochrane Collaboration Risk of Bias tool (Review Manager 5.3). The Cochrane Risk of Bias Tool was adapted for the study design and consisted of the following items: (1) eligibility criteria described, (2) intervention protocol described, (3) point and variability measure reported for all body weight measurements, and (4) incomplete body weight data. Each criterion was rated by the authors as 'high risk', 'low risk' or 'unclear' risk of bias. Discrepancies were addressed by the re-evaluation of the original article, discussed and solved by consensus. Studies were not excluded based on their quality.

7. Statistical analysis

Statistical analyses were performed with Comprehensive Meta-Analysis software (CMA, version 2.2.064, Biostat, NJ, USA). The primary outcome measure was body weight. Data expressed using the standard error of the mean (SEM) were first converted to standard deviation (SD) by the formula: SD = SEM $\times \sqrt{n}$. We used only pre-to-post data for SLE patients, without including data from healthy individuals when used as control comparator. Individual studies were pooled using random-effect model using $p < 0.05$ (two-tailed) as significance level. Additionally, standardized mean difference (SMD) (mean difference between pre- and post-intervention divided by the pooled SD) was also computed. Descriptive data for each study is reported as mean ± SD and mean weighted difference (95% confidence interval (CI)). I^2 statistics were calculated to provide an estimation of the degree of heterogeneity in effect among studies (25-50% small amounts of inconsistency; 50-75% medium amounts of inconsistency and > 75% large amounts of inconsistency) [27]. Publication bias was examined by visual inspection of the different funnel plots' asymmetry. The effect of publication bias on the results was verified by Duval and Tweedie's Trim and Fill procedure [28]. Finally, sensitivity analysis excluding selected trials with discrepant results from the overall trials were performed to explore results' robustness.

RESULTS

A PRISMA flow diagram of the literature search and selection is presented in Fig. 2. Initial database search identified 248 articles (226 after removing duplicates), of which 206 were excluded by eligibility based on titles and abstracts

analysis (Fig. 2). The full-text was retrieved from 19 articles, and 17 met the inclusion criteria. Four studies reported complete weight data (pre- and post-intervention) and 13 articles reported only baseline data. Two authors provided more detailed information, whereas two others reported the lack of body weight data following the intervention. The other authors (from nine studies) did not reply to the contact. Therefore, six studies were included in the analysis. A total of seven distinct interventions were included in the meta-analyses.

1. Risk of bias within and across studies

Fig. 3 shows the risk of bias for the included studies. A good overall agreement was found between both authors (k = 0.881, 95% CI 0.72-0.94; $p < 0.001$). According to 'eligibility criteria' and 'intervention protocol described' domains, all studies presented a 'low risk' of bias. In the domains 'point and variability measure reported' and 'incomplete data outcome', 50% of the studies were judged as 'high risk'.

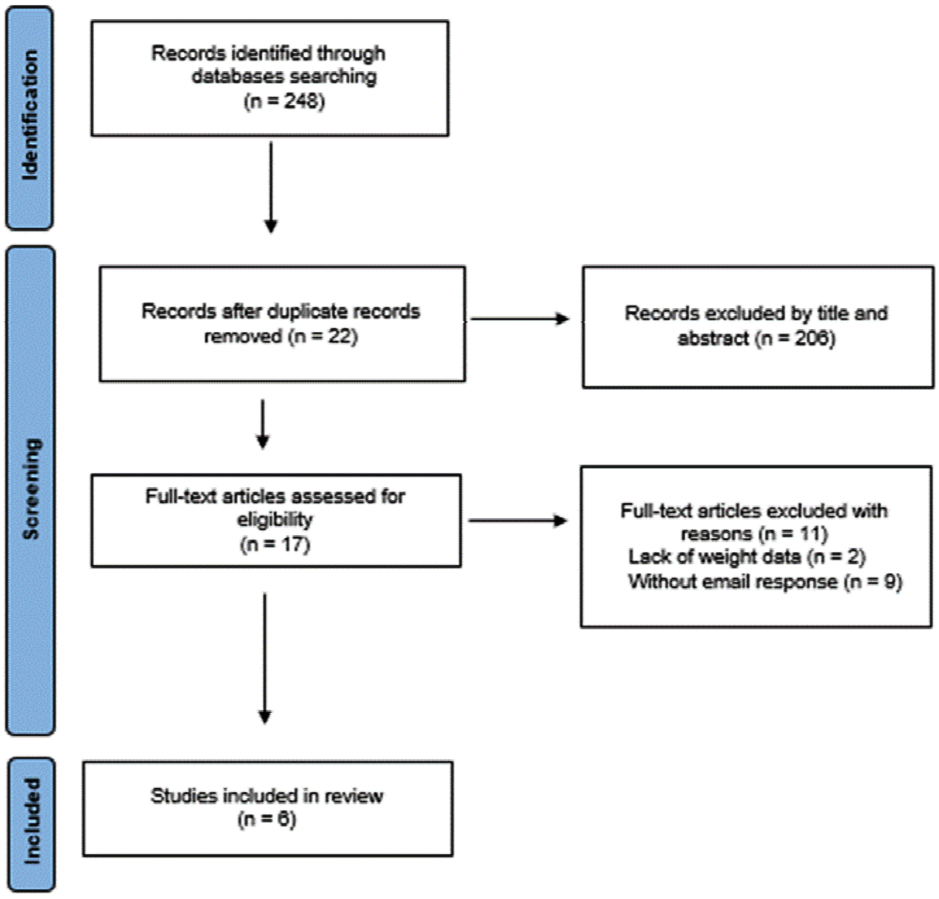

Fig. 2. Flowchart of the selection process of studies of lifestyle interventions and weight management.

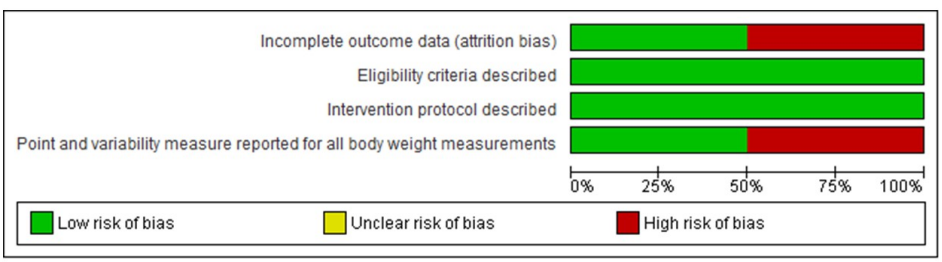

Fig. 3. Risk of bias.

2. Study characteristics

Studies were published between 2002 and 2018 in three countries (Brazil, USA, and UK). A total sample of 71 women median of age 35.8 [31.3 to 49.0 years]; median of BMI 26.6 [25.2 to 33.6 kg/m^2] were included in this meta-analysis (Table 1). Disease duration ranged from 6.1 to 13.7 years. Disease activity was evaluated by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) which varied from 0.2 to 2.0 [29-33]; however, one study used the

Table 1. Characteristics of studies included in the review and meta-analysis

Author, date	Sample size	Sex	Age (years)	BMI (kg/m^2)	Disease's duration (years)	Disease activity (SLEDAI* or SLAM†)	Glucocorticoids use	Intervention type	Intervention duration/ frequency
Benatti, 2018	9	Women	34.8 ± 4.1	26.3 ± 3.4	9.8 ± 4.1	0.22 ± 0.67*	Yes	Exercise	12 weeks/2x/week
Davies, 2012‡	11	Women	44 ± 12	33.6 ± 5.1	-	3.2 ± 5.1*	Yes	Diet	6 weeks
Davies, 2012§	11	Women	49 ± 9	33.6 ± 6.3	-	1 ± 1.2*	Yes	Diet	6 weeks
Perandini, 2014	8	Women	35.8 ± 6.5	25.2 ± 2.6	11.6 ± 6.4	1.3 ± 1.1*	No	Exercise	12 weeks/2x/week
Shah, 2002	8	Women	44.1 ± 9.3	-	13.7 ± 9.2	8.9 ± 2.2†	Yes	Diet	12 weeks
Benatti, 2015	17	Women	31.3 ± 5.9	25.9 ± 5.7	6.1 ± 3	0.9 ± 1.4*	Yes	Exercise	12 weeks/2x/week
Reis-Neto, 2013	18	Women	35.3 ± 6.8	26.9 ± 4.7	6.6 ± 5.4	2 ± 2.1*	Yes	Exercise	12 weeks/3x/week

BMI: Body Mass Index, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLAM: Systemic Lupus Activity Measure. ‡Low glycemic index diet from Davies, 2012; §Low caloric diet from Davies, 2012.

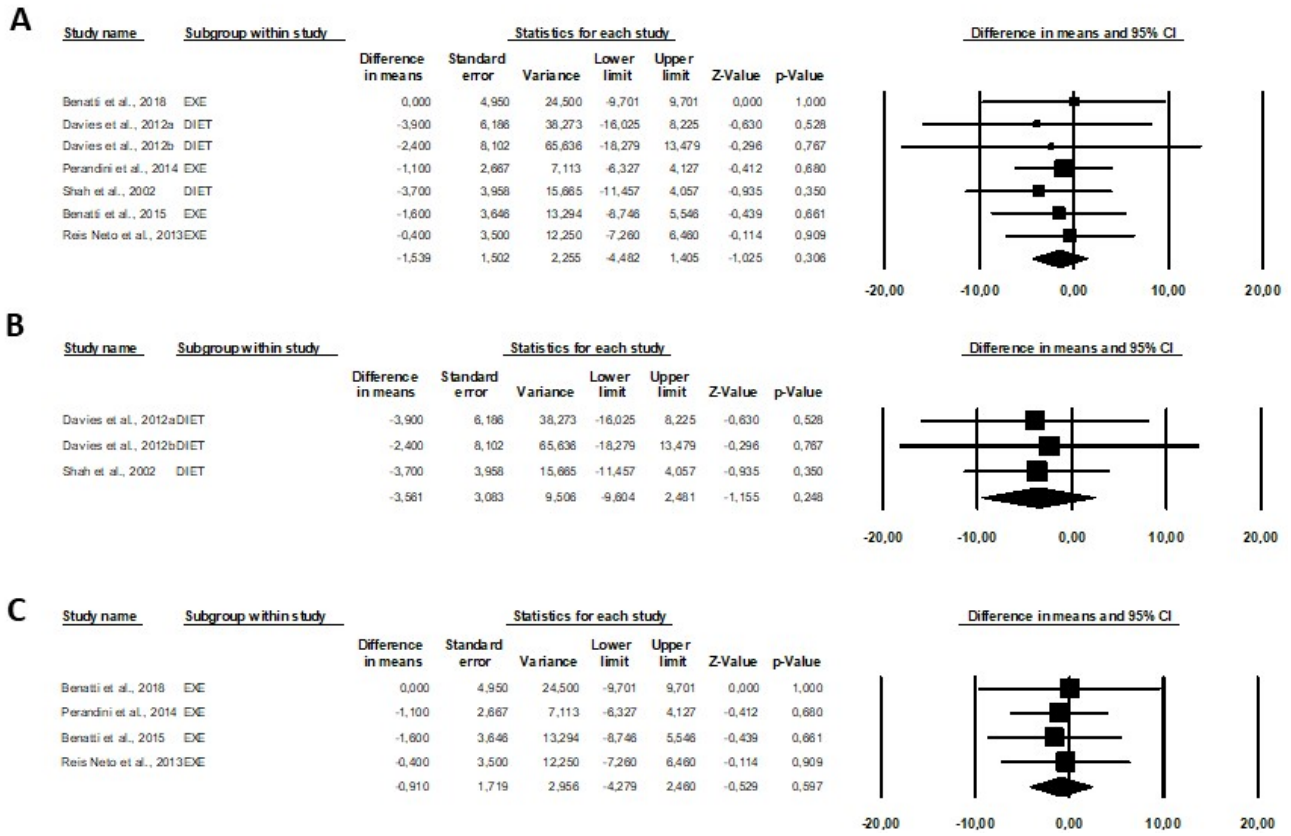

Fig. 4. Forest plots for body weight fowling lifestyle intervention. (A) General analysis after six to twelve weeks of diet or exercise interventions. (B) Subgroup analysis after dietary intervention. (C) Subgroup analysis after exercise intervention. a: low glycemic index diet from Davies, 2012; b: low caloric diet from Davies, 2012.

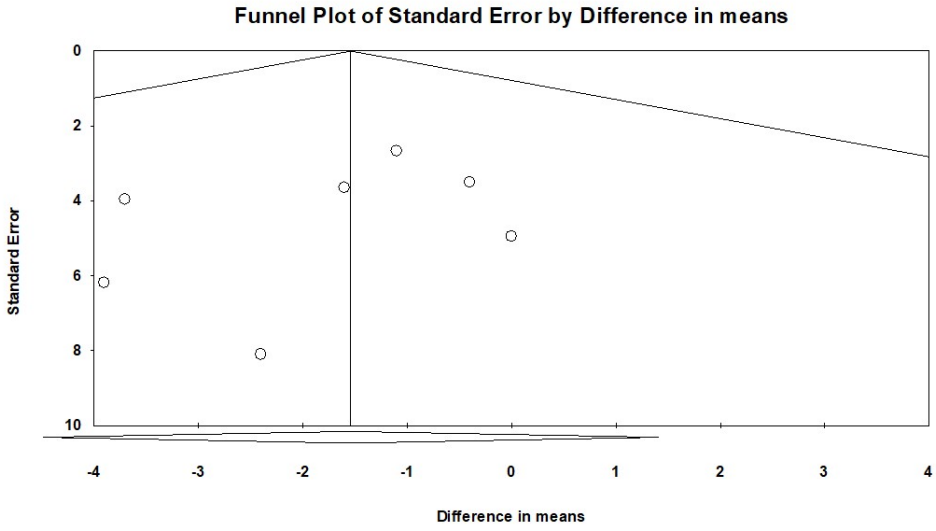

Fig. 5. Funnel plots of risk of publication bias.

Systemic Lupus Activity Measure (SLAM), which ranged between 1.0 and 3.2 [34]. Five studies [29,30,32-34] reported use of glucocorticoids at baseline (1.7 to 11.5 mg/day). One study [31] mentioned that patients were not using glucocorticoids over the study period. No comparisons were made to investigate the use of glucocorticoids before and after interventions.

Four studies assessed supervised exercise interventions (duration was 12 weeks for all studies) [29-32]. Weekly frequency of exercise intervention ranged from 2 to 3 days, with duration between 40 to 60 minutes. Most of the studies including exercise intervention (n = 3) [29-31] performed gym based supervised combined exercises (i.e, strength exercises for the major muscle groups plus aerobic exercise). One study performed an exercise protocol with only aerobic exercise at a public park [32]. Two studies assessed dietary interventions (duration ranged from 6 to 12 weeks) [33,34]. One of them [33] tested two different types of diet (low caloric diet vs. low glycemic index diet). Another study [34] assessed a low cholesterol diet (30% or less calories from fat, in which 7% were from saturated fat, 13% from monounsaturated fat, 10% from polyunsaturated fat, and < 200 mg of cholesterol per day).

All studies had sufficient data to warrant inclusion in the meta-analysis. Fig. 4 shows the forest plots for body weight in each included study. After six to twelve weeks of diet or exercise interventions, no differences were observed in body weight [−1.539 (−4.482 to 1.405) kg (CI 95%), p = 0.306] (Fig. 4A). A small inconsistency was observed. A subgroup analysis also revelated no difference in body weight following dietary intervention [−3.561 (−9.604 to 2.481) kg (CI 95%), p = 0.248] (Fig. 4B) or exercise intervention [−0.910 (−4.279 to 2.460) kg (CI 95%), p = 0.597] (Fig. 4C).

Funnel plots were generated and analyzed by visual inspection, indicating that there was not publication bias (Fig. 5).

DISCUSSION

The objective of this systematic review with meta-analysis was to verify if different lifestyle interventions are capable to promote changes on body weight among patients with SLE. A total of six studies were reviewed and included. The results showed that different protocols of exercise intervention or low-calorie, low-lipid and low-glycemic diets were not effective to reduce body weight in patients with SLE. However, only one of the selected trials had a specific study design and protocol focusing on weight loss management.

Epidemiological studies have consistently demonstrated a predominance of women with lupus compared to men [35,36], highlighting some distinct clinical features between them, such as severest disease form among male patients [37]. Sex-related differences regarding body weight loss also must be taken into consideration when analyzing interventions related to SLE. Of note, men appear to be more likely to lose weight than women [35], which might explain in part the null effect of the interventions on body weight.

It is therefore relevant that all studies included in this meta-analysis involved only women, minimizing this possible confounding variable.

The accelerated development of cardiovascular disease and other comorbidities in SLE is determined by traditional risk factors, including obesity, and disease-specific factors [immunogenetics, immune dysfunction, chronic inflammation, and medication toxicity] [38]. In the studies assessed herein, four of them had patients with overweight [29-32], and two with obesity [33]. In fact, SLE patients present with a high frequency of overweight and obesity [2,39], and the prevalence of excess body weight (BMI > 25 kg/m^2) in Brazilian SLE patients varied from 62.4% to 64.1% [3,39].

The use of corticosteroids was reported in most study [29,30,32-34]. Corticosteroids are often used in SLE treatment [40] and its prolonged use was reported to be related to weight gain (ranged from less than 10 to almost 30 pounds) [41]. Study with a different population (adolescents) reported that some patients became overweight or obese after corticosteroids treatment and weight gain was associated with cumulative medications dose [42]. Indeed, the excess of body weight observed in SLE patients on chronic use of corticosteroids determines higher risk of cardiovascular disease, generating a vicious cycle in which weight gain can maintain disease activity, requiring the maintenance of these medication [43]. Thus, it is plausible to assume that the chronic use of corticosteroids may have accounted for the inefficacy of the lifestyle interventions on weight loss management on this meta-analysis. However, the objective analysis of this confounding variable was not tested, as the studies did not provide consistent medication data.

Excess body weight is a multifactorial condition in SLE and may have several deleterious effects. In fact, obesity condition and excess of adipose tissue could increase the levels of pro-inflammatory cytokines which can intensify the inflammatory process and increase the risk of higher mortality in SLE patients [2,6]. Also, excess weight was associated with an increase in the clinical activity [44]. According to the findings from the Southern California Lupus Registry [SCOLR], obesity could be considered an important target for improving SLE outcomes [2]. Thus, weight control for this population is not important only for traditional risk reductions (i.e. cardiovascular disease) but also for SLE outcomes improvement. Despite this relevance, a small number of studies had investigated weight control in these patients. This is the first systematic review and meta-analysis to assess weight management in these patients and we highlight the relevance to warrant more longitudinal studies investigating strategies for body weight control, including exercise intervention and dietary programs in SLE patients.

In studies including exercise intervention program, the duration ranged from 12 to 16 weeks, 2 to 3 times per week, lasting 40-60 minutes per session of aerobic and strength exercises. Recent publications have pointed exercise as an important therapy for SLE [45], especially because exercise may reduce possible side effects of glucocorticoid treatment, including muscle weakness and overweight [46], and also, may have positive effects on cardiovascular function [47]. In addition, a cross-sectional study evidenced that lower physical fitness (e.g. muscular strength, and flexibility) is associated with higher body weight and central adiposity in women with SLE [48], showing the importance of exercise training for these patients. Recent overview of reviews focusing on the effects of exercise training programs on weight loss in adults with overweight or obesity had shown that exercise training promotes body weight reduction in these patients, but in a relatively small magnitude [49]. More importantly, despite outcomes of weight, exercise training programs promoted fat, and visceral fat loss, which is crucial to enhance cardiometabolic health [49]. However, in this meta-analysis, the different protocols of exercise programs were not able to change body weight.

Concerning studies evaluating dietary treatments, the duration varied from 6 to 12 weeks, however the dietary approach considering calorie restriction or specific nutrient reduction varied among studies. The different types of dietary intervention performed was not able to reduce body weight. There is a lack of literature about dietary management aiming weight control in SLE patients. Many of published studies reported data including only nutrients that may ameliorate the inflammatory state such as antioxidant [50], omega-3, and vitamin D supplementation [51]. For example, anti-inflammatory dietary patterns such as Mediterranean diet are appointed as important factor in disease management, impacting positively disease activity [52]. Some authors demonstrated that the consumption of certain components

of the Mediterranean diet (i.e., olive oil, fruits, vegetables, fish and nuts) as well as the reduction in the red meats, meat products and sugary intake was associated with a lower disease activity scores [52].

The absence of weight changes after exercise or dietary programs probably occurred because most of the included studies did not had weight loss as primary outcome. In other words, both intervention protocol included in this meta-analysis (exercise training and diet) were not designed to weight loss, but focused in others outcomes such as lipid profile, endothelial function and aerobic capacity. Thus, the key point of this meta-analysis is the call of attention for future longitudinal studies, focusing on weight loss management in SLE patients.

From a clinical standpoint, exercise programs with higher volume and/or frequency or different approach considering dietary calories or nutrients content and during a longer time of intervention seem to be necessary to promote weight control/reduction in SLE patients. Thus, despite the high prevalence of obesity among SLE patients, until today, there is not specific studies or recommendations about the weight management for these individuals.

The present review has some limitations to be point out. Firstly, weight loss was not the principal outcome of most of included studies. Thus, we highlight that the protocols used in included clinical trials were not designed for weight-loss or weight-control, which might have an important influence in our results. Secondly, this review involved only six studies which presented relatively small sample sizes. Finally, interventions protocol, mainly those about dietary interventions, were so different, which hamper to summarize the characteristics or recommendations.

Our findings demonstrate that specifics protocol of exercise training and low-calorie, low-lipid and low-glycemic diets are not effective to reduce weight of SLE patients with overweight or obesity. However, most of these protocols were not specifically designed for weight management. Given that obesity is highly prevalent amongst patients with SLE, we highlight the importance of establishment of efficient strategies and guidelines for weight loss and reduction of excessive adipose tissue.

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CONFLICTS OF INTERESTS

None to declare.

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