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Meta-analysis

Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: A meta-analysis of randomized controlled trials

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ABSTRACT

Objective. C-reactive protein (CRP), inflammatory cytokines, and adipokines contribute to atherosclerosis, insulin resistance, and development of late-onset complication in patients with type 2 diabetes. We performed a systematic review to assess effects of exercise interventions on inflammatory markers/cytokines and adipokines.

Materials/Methods. We searched electronic databases (MEDLINE, EMBASE, and Cochrane Controlled Trials Registry) and reference lists in relevant papers for articles published in 1966–2013. We selected studies that evaluated the effects of exercise intervention on inflammatory markers/cytokines and adipokines in adult patients with type 2 diabetes. Weighted mean differences of exercise on outcomes were derived using fixed or random effect models; factors influencing heterogeneity were identified using meta-regression analysis.

Results. Fourteen randomized controlled trials (824 patients) were included in our meta-analysis. Exercise was associated with a significant in CRP = −0.66 mg/l (95% CI, −1.09 to −0.23 mg/l; −14% from baseline) and interleukin-6 (IL-6) = −0.88 pg/ml (95% CI, −1.44 to −0.32 pg/ml; −18% from baseline) but did not alter adiponectin or resistin levels; aerobic exercise program was associated with a significant change in leptin = −3.72 ng/ml (95% CI, −6.26 to −1.18 ng/ml; −24% from baseline). For IL-6, exercise was more effective in those with a longer duration in the program and larger number of sessions during study ($p = 0.001$).

Conclusions. Exercise decreases inflammatory cytokine (CRP and IL-6) in patients with type 2 diabetes. Exercise could be a therapeutic option for improving abnormalities in inflammation levels in patients with diabetes.

Abbreviations: CRP, C-reactive protein; RCT, randomized controlled trial; SD, standard deviation; BMI, body mass index; IL-6, interleukin-6; CI, confidence interval; WMD, weighted mean difference; SMD, standardized mean difference.

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1. Introduction

The prevalence of type 2 diabetes has reached epidemic proportions worldwide. Type 2 diabetes currently affects 170 million people, and the affected population is expected to double to 340 million people by 2030 [1]. The rate of increase in the prevalence of this disease in developing countries is particularly high. By the year 2025, more than three-quarters of all people with diabetes will be from developing countries [2].

The function of adipose tissue is not merely the passive storage of excess energy. Recent evidence suggests that mature adipocytes synthesize and secrete numerous cytokines and hormones involved in overall energy homeostasis [3–5]. Adipokines are involved in the etiology of diabetes, resistance to insulin, and the development of atherosclerosis and late-onset complications [3–7]. In addition, proinflammatory cytokines, such as IL-6 and TNF-α, regulate the release of acute reactant C-reactive protein (CRP) from the liver and increase plasma CRP levels [8]. CRP is a strong independent predictor of cardiovascular disease and the outcome of acute coronary syndromes [9].

Along with dietary and pharmacological interventions, exercise is a key element in diabetes management [10]. Diabetes care guidelines recommend that patients with type 2 diabetes should perform moderate-intensity exercise for at least 150 min per week [11]. Although several studies have evaluated the effects of exercise on the levels of various inflammatory cytokines and adipokines in patients with type 2 diabetes, their findings are inconsistent [12–24]. The aim of this meta-analysis was to systematically summarize the evidence of the effects of exercise on the levels of CRP, inflammatory markers/cytokines, and adipokines in adults with type 2 diabetes.

2. Methods

2.1. Study Selection

Literature searches of MEDLINE (from 1966), EMBASE (from 1980), and the Cochrane Controlled Trials Registry were performed on May 1, 2013, using the search strategy "[physical activity OR exercise OR physical exercise] AND diabetes." Potential missing articles were also sought from experts. Non-English studies were not explored. MEDLINE and EMBASE searches were limited to human studies and were used with a previously validated, sensitive search filter for randomized controlled clinical trials [25].

We included randomized controlled trials (RCTs) that compared any type of supervised exercise (aerobic, resistance, or a combination of both) or physical exercise advice in adult patients with type 2 diabetes, evaluated CRP; inflammatory markers/cytokines; or adipokines levels as an outcome, and reported means (or differences between means) and respective variances of these markers at baseline and after intervention. Because there are many types of inflammatory markers/cytokines and adipokines and some of them have been evaluated in very few studies, we included inflammatory markers/cytokines reported in four or more of the study arms defined by our search strategy. A supervised exercise intervention was defined as a predetermined program of physical activity described in terms of type, frequency, intensity, and duration. Physical exercise advice was defined as an intervention in which patients were partially engaged or not engaged in supervised exercise training but received formal instructions to exercise regularly with or without an individualized exercise prescription. The exclusion criteria were as follows: (1) patients with diabetes other than type 2; (2) duplicate publication or subgroup analysis of the included trials; (3) RCTs that did not report sufficient data for performing a meta-analysis; and (4) studies with less than 1 week of follow-up.

2.2. Data Extraction

Two investigators (Y.H. and T.H.) independently abstracted all data, and disagreements were resolved by discussion. For the variables of interest, we extracted sample sizes as well as baseline and postintervention standard deviations (SDs) for the intervention and control groups following the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions [26]. Additional data abstracted included the year of publication, baseline characteristics (age, sex, and duration of diabetes mellitus), duration of follow-up, characteristics of exercise (type, frequency, duration, and intensity), and concurrent dietary intervention. In cases in which duplicate research was published using the same population, the data from the study with the longest follow-up duration were used for the meta-analysis. If trials compared multiple exercise intervention groups with a single control group within one comparison, we split the shared control group into two groups or more with a smaller sample size [26].

2.3. Quality Assessment

Two authors (F.M. and N.F.) independently evaluated the methodological quality of the included trials according to the criteria by Verhagen [27]. The following nine domains were evaluated: randomization, concealment of treatment allocation, similarity of groups at baseline, eligibility criteria, blinding of outcome assessor, patient and care provider, point estimates, and intention-to-treat analysis. Disagreement was resolved through consensus and by discussion with a third reviewer (Y.H.).

2.4. Statistical Analysis

For each study, the effect size for an intervention was calculated as the difference between the mean changes in parameters between the exercise and control groups during intervention. We performed the analysis using both the random effect and fixed effect models [26,28], and results are shown as the weighted mean difference (WMD) and standardized mean difference (SMD). We statistically assessed heterogeneity using I^2 [29]. We explored the heterogeneity between studies using meta-regression. We initially