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Review

Exercise and ectopic fat in type 2 diabetes: A systematic review and meta-analysis

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A B S T R A C T

Ectopic adipose tissue surrounding the intra-abdominal organs (visceral fat) and located in the liver, heart, pancreas and muscle, is linked to cardio-metabolic complications commonly experienced in type 2 diabetes. A systematic review and meta-analysis was performed to determine the effect of exercise on ectopic fat in adults with type 2 diabetes. Relevant databases were searched to February 2016. Included were randomised controlled studies, which implemented $\geq$ 4 weeks of aerobic and/or resistance exercise and quantified ectopic fat via magnetic resonance imaging, computed tomography, proton magnetic resonance spectroscopy or muscle biopsy before and after intervention. Risk of bias and study quality was assessed using Egger's funnel plot test and modified Downs and Black checklist, respectively. Of the 10,750 studies retrieved, 24 were included involving 1383 participants. No studies were found assessing the interaction between exercise and cardiac or pancreas fat. One study assessed the effect of exercise on intramyocellular triglyceride concentration. There was a significant pooled effect size for the meta-analysis comparing exercise vs. control on visceral adiposity (ES = −0.21, 95% CI: −0.37 to −0.05; P = 0.010) and a near-significant pooled effect size for liver steatosis reduction with exercise (ES = −0.28, 95% CI: −0.57 to 0.01; P = 0.054). Aerobic exercise (ES = −0.23, 95% CI: −0.44 to −0.03; P = 0.025) but not resistance training exercise (ES = −0.13, 95% CI: −0.37 to 0.12; P = 0.307) was effective for reducing visceral fat in overweight/obese adults with type 2 diabetes. These data suggest that exercise effectively reduces visceral and perhaps liver adipose tissue and that aerobic exercise should be a key feature of exercise programs aimed at reducing visceral fat in obesity-related type 2 diabetes. Further studies are required to assess the relative efficacy of exercise modality on liver fat reduction and the effect of exercise on pancreas, heart, and intramyocellular fat in type 2 diabetes and to clarify the effect of exercise on ectopic fat independent of weight loss.

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Introduction

Overweight and obesity contributes to the increased worldwide prevalence of cardiovascular and metabolic morbidity and mortality [1]. Evidence also suggests that the location of excess adiposity, particularly that stored around the organs as visceral adipose tissue (VAT), is of greater importance in determining adverse health outcomes than the larger subcutaneous adipose tissue reserves [2]. More recently, excess adiposity within lean tissues has been associated with the underlying pathophysiological characteristics of type 2 diabetes. For instance, increased fat within the liver is associated with insulin resistance [3], impaired glycaemic control [4] and increased cardiovascular disease risk [2]. Similarly, small amounts of fat within muscle cells, the pancreas and myocardium and have been linked with peripheral insulin resistance [5], impaired insulin secretion [6] and hypertension/cardiomyopathy [7], respectively. Given the association between these "ectopic fats" [8] and adverse metabolic and cardiovascular outcomes, it is important to determine the

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efficacy of interventions, which aim to reduce ectopic fat in type 2 diabetes.

Although there are surgical [9] and pharmaceutical [10] interventions which assist in obesity and ectopic fat reduction, access, cost, and side-effects limit their usefulness for type 2 management at a population level, particularly in the Middle East and North Africa regions where two out of five adults with diabetes are believed to be undiagnosed [11].

Lifestyle modification involving exercise is considered to be the first line of therapy [1] for obesity-related type 2 diabetes, and produces a well-established multiplicity of benefits such as improved insulin sensitivity, and glycaemic control [12]. Although the consensus of evidence demonstrates that regular exercise may benefit body weight reduction, the effect is typically small when compared with other weight loss therapies [13]. Recently, studies have suggested regular exercise may decrease VAT and liver fat and improve cardio-metabolic outcomes [14,15].

As ectopic fat increases the risk for developing type 2 diabetes, and populations with type 2 diabetes may be at a higher risk of excess ectopic fat accumulation independent of BMI [16], we aimed to assess the efficacy of exercise as an intervention to reduce ectopic fat in type 2 diabetes via systematic review and meta-analyses of pooled data from randomised controlled adult human studies.

Materials and methods

Search

Electronic database searches were performed by two researchers (AS and KW) in Medline (Ovid), Cinahl (EBSCO Host), AMED (Ovid), Web of Science (ISI Web of Knowledge), SportDisucs (EBSCO Host), and Embase (Ovid) from earliest record to February 2016. The search was performed using keywords covering the area of exercise and ectopic fat. Specifically, keywords searched were: (aerobic exercise, endurance exercise, aerobic training, endurance training, cardio training, exercise, physical endurance, physical exertion) or (strength training, weight training, resistance training, progressive training, progressive resistance, weight lifting) and (NAFLD, nonalcoholic fatty liver disease, fatty liver, hepatic steatosis, hepatic, liver, steatohepatitis, NASH, aminotransferase, AST, ALT, intrahepatic lipid, IHL) or (VAT, visceral adipose tissue, visceral fat, abdominal adipose tissue, abdominal fat, ectopic fat, ectopic adipose tissue) or (intramyocellular lipid, IMCL, intramuscular fat, intramuscular triglyceride, intramyocellular triglyceride, IMTG) or (myocardial fat, myocardial steatosis, perivascular fat, pericardial fat, pericoronary fat, intra-myocardial fat, epicardial fat, epicardial adipose tissue, cardiac fat, cardiac adipose tissue) or (pancreas lipid, pancreatic lipid, pancreas fat, pancreatic fat) and (Diabetes). Reference lists of all identified papers were manually searched for potentially eligible papers. Randomised controlled trials were included while non-randomised trials, uncontrolled trials, and cross-sectional studies were excluded from the review. Manuscripts were not excluded based on language, however studies were excluded if they were: book sections, theses, film/broadcast, opinion articles, observational studies, reviews, and abstracts without adequate data which was assessed by a reviewer.

Intervention

Studies were included if the exercise training intervention was completed for ≥ 4 weeks. This delineation was used to differentiate studies examining the acute effects of exercise from those examining training adaptations. Trials involving supervised and unsupervised aerobic exercise (AEx) (continuous, intermittent, or high intensity interval training), or progressive resistance exercise training (PRT) alone, or in combination (AEx + PRT) were included in the review. Exercise studies that also utilised a dietary intervention were included if both groups (exercise and comparison groups) undertook the same dietary intervention.

Participants

Studies reporting an adult sample (≥ 18 years) with type 2 diabetes were included.

Outcome measures

Studies were included if the outcome of liver, pancreatic, intramyocellular, cardiac or visceral adipose tissue was quantified by biopsy and histological or biochemical assessment (where relevant) or proton magnetic resonance spectroscopy (^{1}H-MRS), magnetic resonance imaging (MRI) or computed tomography (CT).

Selection of studies

After eliminating duplicates, search results were screened by two independent researchers (AS and KW) against the eligibility criteria, and studies that could not be eliminated by title or abstract were retrieved and assessed for eligibility. Disagreements were resolved by a third researcher (NJ). Reference lists of included papers were searched to identify further studies that were not identified in the database search. In instances where the identified studies reported insufficient data, attempts were made to contact authors to acquire the required information. In instances where data were represented in graphical format [17,18], the data were extrapolated into numerical format. Where required, standard error was converted to standard deviation.

Analyses and meta-analyses

The between-trial standardised mean difference, effect size (ES), 95% confidence intervals (95% CI) and study variability using I^2 measure of consistency were calculated. Pooled estimates of the effect of exercise on ectopic fat were obtained using a random-effects model [19]. Publication bias was assessed by examining asymmetry of funnel plots (precision vs. ES) using the Egger's test [20] and those studies, which indicated potential bias was eliminated. Where possible, sub-analyses were performed to determine the effect of different exercise modalities:

- aerobic vs. control;
- resistance training vs. control;
- combined training vs. control on ectopic fat change.

All analyses were conducted using Comprehensive Meta-analysis [Version 2.2.046, Biostat, Englewood, NJ (2007)].

Study quality assessment

Study quality was assessed by one researcher (AS) using a modified Downs and Black checklist [21]. The scale was modified to include criteria for adequate description of control and whether the exercise sessions were supervised. Where the reviewer was unsure, specific criteria were discussed with a second reviewer (NJ) until consensus was reached. If an item was unable to be determined a 'no' was given.

Results

Identification and selection of studies

The original search identified 10,750 studies. After removal of duplicates and elimination of papers based on the eligibility criteria, 24 studies remained (Fig. 1). Of the 24 studies included, six

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