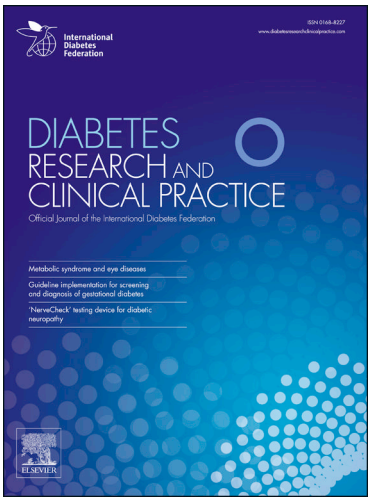

Clinical Outcomes to Exercise Training in Type 1 Diabetes: A Systematic Review and Meta-Analysis

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PII: S0168-8227(17)31108-7
DOI: https://doi.org/10.1016/j.diabres.2017.11.036
Reference: DIAB 7156

To appear in: *Diabetes Research and Clinical Practice*

Received Date: 10 July 2017
Revised Date: 25 August 2017
Accepted Date: 28 November 2017

Please cite this article as: D. Jewiss, C. Ostman, N. King, N.A. Smart, Clinical Outcomes to Exercise Training in Type 1 Diabetes: A Systematic Review and Meta-Analysis, *Diabetes Research and Clinical Practice* (2017), doi: https://doi.org/10.1016/j.diabres.2017.11.036

Clinical Outcomes to Exercise Training in Type 1 Diabetes: A Systematic Review and Meta-Analysis.

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Running head: Exercise training in type I diabetes: meta-analysis

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: None declared

Word count: 5289

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ABSTRACT

Aims To establish the relationship between exercise training and clinical outcomes in people with type I diabetes.

Methods Studies were identified through a MEDLINE search strategy, Cochrane Controlled Trials Registry, CINAHL, SPORTDiscus and Science Citation Index. The search strategy included a mix of key concepts related to exercise training; type 1 diabetes; glycaemic control for trials of exercise training in people with type 1 diabetes. Searches were limited to prospective randomized or controlled trials of exercise training in humans with type 1 diabetes lasting 12 weeks or more.

Results In exercised adults there were significant improvements in body mass Mean Difference (MD): -2.20 kg, 95% Confidence Interval (CI) -3.79 -0.61, p=0.007; body mass index (BMI) MD: -0.39 kg/m^2, 95% CI -0.75 -0.02, p=0.04; Peak VO_2 MD: 4.08 ml/kg/min, 95% CI 2.18 5.98, p<0.0001; and, low-density lipoprotein cholesterol (LDL) MD: -0.21 mmol/L, 95% CI -0.33 -0.08, p=0.002. In exercised children there were significant improvements in insulin dose MD: -0.23 IU/kg, 95% CI -0.37 -0.09, p=0.002; waist circumference MD: -5.40 cm, 95% CI -8.45 -2.35, p=0.0005; LDL MD: -0.31 mmol/L, 95% CI -0.55 -0.06, p=0.02; and, triglycerides MD: -0.21 mmol/L, 95% CI -0.42 -0.0, p=0.04. There were no significant changes in glycosylated haemoglobin (HbA1C%), fasting blood glucose, resting heart rate, resting systolic blood pressure or high density lipoproteins in either group.

Conclusions Exercise training improves some markers of type 1 diabetes severity; particularly body mass, BMI, Peak VO_2 and LDL in adults and insulin dose, waist circumference, LDL and triglycerides in children.

Keywords

Exercise Training, Meta-Analysis, Type I diabetes

Abbreviations

Body Mass Index (BMI)

CI – Confidence Interval

HDL – High Density Lipoproteins

LDL – Low Density Lipoproteins

HbA1C% - Glycosylated Hemoglobin

% HR_{max} - Heart Rate Peak

% VO_2 Peak - Percentage of Peak Oxygen Uptake

MD – Mean Difference

INTRODUCTION

The clinically beneficial effects of lifestyle interventions have been shown in meta-analyses in people with type II diabetes [1]. Substantial pooled data has demonstrated improvements in peak VO_2 [2] and glycaemic control [3] in individuals with type II diabetes. In the general population, high intensity interval training has been shown to be more effective in regulating glucose than continuous training at lower intensity [4]. Moreover, high intensity exercise training has been shown to be superior to lower intensity exercise for improving cardiorespiratory fitness (peak VO_2) in heart failure patients [5-7]. Evidence of beneficial effects of regular exercise training is sparse for people with Type I Diabetes (T1D).

While few trials of exercise training in T1D exits, it has been demonstrated that increased physical activity is associated with an increased life expectancy and a lower risk of

complications in these patients [8]. More alarmingly an estimated 60% of adults with T1D do not undertake the recommended 150 minutes of weekly levels of physical activity at moderate (50-70% HRmax) to vigorous (>70% HRmax) intensity [9]. However, the clinical implications of these guidelines are contentious and their effect on clinical outcomes are yet to be established.

Poor compliance rate may be at least be partially explained by fear of an induced hypoglycaemic episode and fitness levels [10]. While it has been shown that educational interventions improve the associated fear of exercise induced hypoglycaemic event, no appropriate evidence addresses the efficacy of the current recommendations and their relationship to the clinical outcomes [10]. With T1D affecting adult, adolescent and paediatric groups, the recommendations for children and adults in terms of physical activity are very similar. We focused our work on establishing the clinical efficacy of the recommendation for physical activity in all patients with Type 1 Diabetes.

We conducted a systematic analysis of all clinical randomized, controlled, aerobic exercise training trials in people with type I diabetes. We aimed, via systematic review, to establish the relationship between physical activity and its effect on clinical markers of glycaemic control and cardiorespiratory fitness. Secondly, we wished to establish if exercise training program parameters affected the size of change in clinical outcome measures. Finally, we examined if our findings aligned with the current recommendations for physical activity.

MATERIALS AND METHODS

Search Strategy

Studies were identified through a MEDLINE search strategy (1985 to Aug 4, 2016), Cochrane Controlled Trials Registry (1966 to Aug 4, 2016), CINAHL, SPORTDiscus and Science Citation Index. The search strategy included a mix of MeSH and free text terms for the key concepts related to exercise training, type 1 diabetes and glycaemic control for clinical trials of exercise training in people with type 1 diabetes (see PubMed search strategy in Supplementary file). We considered all types of physical training. Studies were included if patients exhibited a diagnosis of type 1 diabetes. Searches were limited to prospective randomized or controlled trials of exercise training in humans, lasting 12 weeks or more. No restrictions were placed on the year, or language, of publication. Reference list of papers and latest editions of relevant journals which were not available online were scrutinised for new references. Full articles were read and assessed by two reviewers (DJ and CO) for relevance and study eligibility. Disagreements on methodology were resolved by discussion, a third reviewer (NS) adjudicated over any disputes. Study authors were contacted and requested to provide further data if required.

Study selection

Included studies were randomized controlled trials of exercise training in people with type 1 diabetes. All published studies included in this systematic review were comparisons between intervention groups and a sedentary control.

In addition to the studies identified through database searching, reference lists of identified studies were scrutinized. Only the principal study with the greatest number of subjects was included where multiple publications existed from the same dataset. After initial screening we removed over-lapping, duplicates, duplicate data and irrelevant articles such as editorials and discussion papers that did not match the inclusion criteria. We excluded studies where

the control group received additional intervention or did not have type 1 diabetes, non-relevant studies; and those reporting only acute exercise testing responses. We excluded studies from specific analyses if incomplete data was reported and the authors did not respond to our requests to provide missing data.

Outcomes measures

We recorded the following data; percentage change in HbA1c%, BMI, body mass, Waist Circumference, peak VO_2, resting heart rate, resting systolic blood pressure, fasting blood glucose, low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides and daily insulin dose. We also recorded exercise training frequency, intensity, duration per-session, length of exercise program, participant exercise adherence and completion rates.

Data Synthesis

From extracted data we calculated patient-hours of exercise training, mean difference change in outcome measures and medical events.

Assessment of study quality

We assessed study quality with regard to: eligibility criteria specified, random allocation of participants, allocation concealed, similarity groups at baseline, assessors blinded, outcome measures assessed in 85% of participants and intention to treat analysis. The study quality was assessed according to the validated TESTex scale which has a maximum score of 15 [11].

Data Synthesis

Revman 5.3 (Nordic Cochrane Centre, Denmark) was used to complete the meta-analysis and generate forest plots. Pooled data are presented as mean differences. A minimum of three intervention groups was required for forest plots. Some studies used more than one intervention group, but the same people were only represented once in our forest plots.

Meta-analyses were completed for continuous data by using the change in the mean and standard deviation of outcome measures. It is an accepted practice to only use post intervention data for meta-analysis but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity etc. Change in post intervention mean was calculated by subtracting baseline from post intervention values. Data required was either (i) 95% confidence interval data for pre-post intervention change for each group or when this was unavailable (ii) actual p values for pre-post intervention change for each group or if only the level of statistical significance was available (iii) we used default p values e.g. $p<0.05$ becomes $p=0.049$, $p<0.01$ becomes $P=0.0099$ and p = not significant becomes $p=0.05$.

Where appropriate data was divided into subgroups according to adults and children (under 18 years); and, pre and post 2000 studies. This was considered important because of developmental changes to insulin formulations and insulin delivery technologies have evolved a great deal over the past two decades. We believe these differences may lead to differences in key parameters such as peak VO_2 and because of possible chronological variations in the technique used to measure some of the variables e.g. peak VO_2. In many cases there was insufficient studies/intervention groups to facilitate a complete analysis of all the experimental groups.

Heterogeneity

Heterogeneity was quantified using the I^2 test [12], as it does not inherently depend upon the number of studies considered. I^2 values range from 0% (homogeneity) to 100% (greater heterogeneity); a *CI* that does not include 0% indicates that the hypothesis of homogeneity is rejected, and an inference of heterogeneity is merited [12]. A random effects model was used throughout.

Publication Bias

Egger plots [13] were provided to assess the risk of publication bias (see supplementary files).

RESULTS

Our initial search identified 36 manuscripts. After removal of duplicates, 33 studies remained, of which 14 were not randomised controlled trials. Out of the remaining 19 studies, two were excluded due to a lack of proper randomisation, 2 were excluded due to a control group consisting of those without diabetes, and another study was excluded for a non-exercise intervention. This left 14 included studies [10, 14-27] for analysis. The search details are provided in the CONSORT Statement, Figure 1.

Our analysis of the 15 studies (16 intervention groups) totalled 596 participants; 360 from exercise groups and 236 from control groups. Five of the studies involved adults and 6 of the studies were completed before 2000. The studies contain data from 9,251 patient-hours of exercise training. Studies ranged in duration from 12-26 weeks (average 18.7 weeks, median 16 weeks), and 1-7 weekly exercise sessions (median =3) and session duration ranged from 20-120 minutes (median =47.5). Table 1. Summarizes the details of the included studies.

Meta-Analyses

All forest plots can be seen in the supplementary file.

HbA1C%

Eleven intervention groups provided data on HbA1C% of which 4 intervention groups were in adults with the remainder in children and 4 studies were carried out prior to 2000. Results show that there was no significant difference between exercise and control for either adults MD: -0.08%, 95% CI: -0.38, 0.22; p = 0.6 (Chi^2 = 13.96, df = 3, p = 0.003; I^2 = 79%); or, children MD: -0.27%, 95% CI -0.73, 0.19; p = 0.25 (Chi^2 = 22.97, df = 6, p = 0.0008; I^2 = 74%). There was also no significant difference between studies that were performed post-2000 MD -0.11%, 95% CI -0.37, 0.16; p = 0.43 (Chi^2 = 32.79, df = 6, p = 0.0001; I^2 = 82%); and, studies that were performed pre-2000 MD: -0.15%, 95% CI -0.76, 0.46; p = 0.62 (Chi^2 = 6.18, df = 3, p = 0.10; I^2 = 51%).

Total daily insulin dose (IU/kg)

There was insufficient studies to pool data for total daily insulin dose in adults and in pre-2000 studies. Four intervention groups studied this parameter in children, which showed that exercise significantly lowered the total daily insulin dose MD: -0.23 IU/kg, 95% CI -0.37 - 0.09; p = 0.002 (Chi^2 = 23.48, df = 3, p < 0.0001; I^2 = 87%). A similar significantly lowering effect with exercise was measured in the 6 post-2000 intervention groups, where MD: -0.16, 95% CI -0.26, -0.05; p = 0.003 (Chi^2 = 84.46, df = 5, p < 00001; I^2 = 94%).

Fasting blood glucose in children (mmol/L)

There was only sufficient intervention groups (3) to perform data pooling on fasting blood glucose in children. Results show that there was no significant effect of exercise MD: -0.71 mmol/L, 95% CI -1.94, 0.52; p = 0.26 (Chi^2 = 19.18, df = 2, p < 0.0001; I^2 = 90%).

Body mass (kg)

Sufficient data was available to perform data pooling in adults (3 intervention groups), children (4 intervention groups) and post-2000 (5 intervention groups) studies. Results show that exercise significantly reduced body mass in adults MD: -2.20 kg, 95% CI -3.79, -0.61; p = 0.007 (Chi^2 = 5.12, df = 2, p = 0.08; I^2 = 61%). In contrast, exercise significantly increased body mass in children MD: 0.95 kg, 95% CI 0.17, 1.73; p = 0.02 (Chi^2 = 2.12, df = 3, p = 0.55, I^2 = 0%). Exercise did not significantly affect body mass in post-2000 studies MD: -0.54, 95% CI = -2.1, 1.02; p = 0.5 (Chi^2 = 17.95, df = 4, p = 0.001; I^2 = 78%).

BMI (kg/m^2)

Sufficient data was available to perform data pooling in adults (3 intervention groups), children (3 intervention groups) and post-2000 (6 intervention groups) studies. Results show that exercise significantly reduced BMI in adults MD: -0.39 kg/m^2, 95% CI -0.75, -0.02; p = 0.04 (Chi^2 = 7.54, df = 2, p = 0.02; I^2 = 73%); but not in children MD: 0.29 kg/m^2, 95% CI -0.03, 0.61; p = 0.07 (Chi^2 = 1.92, df = 2, p = 0.38; I^2 = 0%). Exercise did not exert any significant effect in post-2000 studies MD: -0.11 kg/m^2, 95% CI -0.43, 0.21; p = 0.5 (Chi^2 = 18.83, df = 5, p = 0.002; I^2 = 73%).

Waist circumference in children (cm)

Three intervention groups reported waist circumference in children and in post-2000 studies. In children, results show that exercise significantly reduced waist circumference MD: -5.4

cm, 95% CI -8.45, -2.35; p = 0.0005 (Chi^2 = 92.45, df = 2; p< 0.00001; I^2 = 98%). There was insufficient data to perform pooling for adults and pre-2000 studies.

Peak VO_2 (ml/kg/min)

Peak VO_2 was reported in 4 adult studies and 3 studies on children. Results show that exercise significantly increased peak VO_2 in adults MD: 4.08 $ml.kg^{-1}./min^{-1}$, 95% CI 2.18, 5.98; p < 0.0001 (Chi^2 = 4.88, df = 3, p = 0.18; I^2 = 39%); but, not in children MD: 1.95 $ml.kg^{-1}./min^{-1}$, 95% CI 0.04, 3.85; p = 0.05 (Chi^2 = 0.96, df = 2, p = 0.62; I^2 = 0%). Four pre-2000 and 3 post-2000 studies reported peak VO_2. Results show exercise significantly increased peak VO_2 in both pre-2000 studies MD: 2.22 $ml.kg^{-1}./min^{-1}$, 95% CI 0.88, 3.57; p = 0.001 (Chi^2 = 1.13, df = 3, p = 0.77; I^2 = 0%; and post-2000 studies MD: 3.1 $ml.kg^{-1}./min^{-1}$, 95% CI 0.29, 5.91; p = 0.03 (Chi^2 = 3.47, df = 2; p = 0.18; I^2 = 42%).

Resting heart rate in adults (bpm)

There were insufficient data for pooling in children, pre-2000 and post-2000 studies regarding resting heart rate. Three studies reported resting heart rate in adults. Results show there was no significant difference in exercise compared to control MD: -4.11 bpm, 95% CI -9.01, 0.8; p = 0.1 (Chi^2 = 7.24, df = 2, p = 0.03; I^2 = 72%).

Resting systolic blood pressure in post-2000 studies (mmHg)

There were insufficient data for pooling in adults, children and pre-2000 studies. Results show that there was no significant difference in exercise compared to control MD: -3.89 mmHg, 95% CI -11.61, 3.82; p = 0.32 (Chi^2 = 0.2, df = 2, p = 0.91; I^2 = 0%).

LDL (mmol/L)

LDL was reported in 4 adults studies and in 3 (4 intervention groups) studies in children. Exercise significantly reduced LDL in both adults MD: -0.21 mmol/L, 95% CI -0.33, -0.08; p = 0.002 (Chi^2 = 1.08, df = 3, p = 0.78; I^2 = 0%); and, in children MD: -0.31 mmol/L, 95% CI -0.55, -0.06; p = 0.02 (Chi^2 = 8.75, df = 3, p = 0.03; I^2 = 66%). LDL was also reported in 6 intervention groups post-2000. Results show that exercise led to a significant reduction in LDL MD: -0.24 mmol/L, 95% CI -0.39, -0.09; p = 0.002 (Chi^2 = 9.23, df = 5, p = 0.10; I^2 = 48%).

HDL (mmol/L)

HDL was reported in 4 adults studies and 3 (4 intervention groups) studies in children. Exercise did not affect the plasma HDL concentration in either adults MD: 0.01 mmol/L, 95% CI -0.08, 0.10; p = 0.86 (Chi^2 = 10.86, df = 3, p = 0.01; I^2 = 72%); or children MD: 0.15 mmol/L, 95% CI -0.07, 0.37; p = 0.17 (Chi^2 = 22.13, df = 3, p < 0.0001; I^2 = 86%). HDL was also reported in 5 (6 intervention groups) post 2000 studies, where exercise also did not affect the plasma HDL concentration MD: 0.1 mmol/L, 95% CI -0.07, 0.28; p = 0.26 (Chi^2 = 48.35, df = 5, p < 0.00001; I^2 = 90%).

Triglycerides (mmol/L)

Triglycerides were reported in 4 adult studies and 3 (4 intervention groups) studies in children. Exercise did not affect triglycerides in adults MD: -0.1 mmol/L, 95% CI -0.31, 0.11; p = 0.33 (Chi^2 = 26.27, df = 3, p < 0.00001; I^2 = 89%). In contrast, exercise significantly reduced triglycerides in children MD: -0.21 mmol/L, 95% CI -0.42, -0.01; p = 0.04 (Chi^2 = 649.47, df = 3, p < 0.00001; I^2 = 100%). In addition, triglycerides were measured in 5 (6 intervention groups) post 2000 studies. The MD was -0.25 mmol/L, 95% CI -0.43, -0.08; p = 0.004 (Chi^2 = 649.95, df = 5, p < 0.00001; I^2 = 99%).

Effect of Exercise Time on Selected Outcome Measures

Table 2 shows changes in outcome measures stratified by weekly exercise time. Overall the response was varied with regard to weekly exercise time.

Study Quality

The TESTEX scale of study quality revealed a median score of 10 (out of a possible 15). Study quality items that were not exhibited by more than 50% of studies were, assessor blinding (0 studies), intention to treat analyses (0 studies), relative exercise intensity review (6 studies) and activity monitoring of the control (non-exercise) groups (0 studies) (See Table 3).

DISCUSSION

Our work is the first to conduct a data pooling analysis of the effects of exercise training and associated moderator variables on clinical markers of type I diabetes control. In children our analyses showed improvements in total daily insulin dose, waist circumference, LDL and triglycerides. In adults there were improvements in body mass, BMI, peak VO_2, LDL and triglycerides. Peak VO_2 was also improved in studies carried out both pre- and post-2000, whilst LDL and triglycerides decreased in post 2000 studies. There remains insufficient published data to establish the moderating effect of exercise program duration for most of the reported outcome measures, however it is likely that exercise program duration has a moderating role.

Hba1C% did not show a significant change with exercise training. Given that the median duration of included studies was 13 weeks, which is a similar duration to the life of a red

blood cell, it is possible that only partial changes in HbA1c% via exercise training are possible in such a short timeframe. The pre-enrolment physical activity levels of the participants in many of the included studies were unknown, therefore the expected benefit is difficult to ascertain. However, the importance of sustained lifestyle changes to affect health improvements should be reinforced as previous systematic reviews have suggested sedentary behaviour in youths with Type 1 diabetes [28, 29].

Interestingly, exercise led to a significantly reduced body mass in adults, but a significantly increased body mass in children. A similarly increasing effect on body mass with improved hepatic insulin sensitivity has been reported in obese children in response to resistance training [30]. In that study the increased body mass was associated with increased lean body mass [30]. An increase in muscle mass may also explain the weight gain in studies conducted on children in our analysis, particularly since we also showed a decreased waist circumference in the studies conducted on children and a reduced total daily insulin dose. A small, pooled analysis from 2014 suggests equivocal findings with respect to insulin dose [31].

Our serum LDL results showed improvement in both adults and children with exercise. A recent meta-analysis in participants with type 2 diabetes mellitus reported no change in serum LDL [32], whilst an older meta-analysis reporting on apparently healthy elderly participants had results favouring positive changes in LDL [33]. In contrast, a non-randomised controlled trial has shown a reduction in LDL after exercise in children with type 1 diabetes [34].

The change in Peak VO_2 in adults was in the order of 0.8 METs and this moderate effect is to be expected in a known chronic disease group. Our analyses were however unable to identify

that at least 100 minutes of weekly activity is optimal for change in peak VO_2. Previous work has shown that intensity is the primary stimulus for improved cardiorespiratory fitness in people with cardiac disease [6]. One may expect intuitively that increasing exercise program duration would produce greater improvements in peak VO_2. It is therefore perhaps surprising that studies comparing shorter and longer exercise program durations have produced non-uniform effects on peak VO_2 [5, 6, 35]. The likely explanation for this phenomenon is that it may be more difficult to get patients to continue to adhere to an exercise program in the longer term.

Our sub-analyses produced conflicting results with respect to weekly exercise time, the more time exercising, the better the effect on glycaemic control, however the less time, the better effect on the lipids. It is remarkable that the exercise guidelines for type II diabetes were one of the first to offer a sliding exercise prescription scale, based upon the manipulation of intensity and weekly duration in order to keep work volume relatively constant [36]. These guidelines suggest 270 weekly minutes of moderate intensity exercise but only 90 minutes of vigorous intensity activity. Our work suggests a varied response to weekly exercise duration, so the existence of a two-tiered exercise prescription could be related to total work, or energy expended. Energy expenditure is the product of exercise duration, intensity and frequency. We were unable to calculate energy expenditure in a sufficient number of the included studies to shed more light on this.

Limitations

A major limitation of this work was that considerable heterogeneity meant that data pooling was unjustified in a number of meta-analyses. We systematically attempted to identify reasons for heterogeneity by grouping studies according to similarities in interventions and

exercise programs. We were able to reduce heterogeneity somewhat by limiting data pooling to studies that did not use concurrent dietary interventions.For several of the studies included in this meta-analysis we were unable to determine if medications held steady across the study groups. Even if we knew of medication changes, we would need to assess individual patient data for this to be meaningful. We are therefore unable to gauge the extent to which the observed changes were attributable to any medication changes. A similar issue is true of subjects who exhibited low or high resting heart rate, blood pressure and body mass as at group-level, and not patient level, data analysis we are unable to make adjustments to analyses. The exercise training programs varied greatly between studies with respect to exercise intensity, duration, frequency and modality. The normal distribution of the Egger plots evidenced minimal risk of publication bias.

Measures of lean and fat mass would have shed more light onto the role that body composition plays in improving glycaemic control through exercise. We would like to have conducted more moderator variable analyses but limited extracted data precluded this. We were only able to consider program duration, and high/vigorous versus low/moderate exercise intensity sub-analyses.

Conclusions

Exercise training improves some markers of type 1 diabetes severity; particularly body mass, BMI, Peak VO_2 and LDL in adults and insulin dose, waist circumference, LDL and triglycerides in children.Our analysis support existing guidelines that for those who can tolerate it, we were unable to determine if exercise at any intensity offered superior benefits.

Acknowledgements

None

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Figure Legends

Figure 1: Consort statement

Table Legends

Table 1: Characteristics of Included Studies

Table 2: Change in Outcome Measures Stratified by Weekly Exercise Time.

Table 3: TESTX Assessment of Study Quality of Included Studies

Table 1. Characteristics of Included Studies

Author	Participants	Wks	Freq. (Session. Wk^{-1})	Intensity	Session Time (min)	Country	Participants	Intervention	Outcomes
Brazeau 2014	18-65 yrs	12	1	Not stated	60 PA, 30 Education	Canada	48 Patients with diagnosis of T1D (>12mths) and report less than 150min PA per week were randomised into control (25) and Intervention (23)	60 minutes of various exercise including endurance, flexibility and resistance. 30 minutes of PA counselling and education	Body Weight, BMI, Waist circumference, Physical activity level (kcal), VO_2peak (ml/kg/min), HR, SBP, DBP, HbA1c%
Campaigne 1984	5-11 yrs	12	3	HR>160bpm Vigorous - 76% Max HR	30	USA	19 children, similar SES and geographic location were recruited. All had a diagnosis of T1D (>6mths), all children were on an insulin regime. Children were randomly assigned into control (10) or experimental (9).	Activity included running, movement to music etc.	Peak VO_2, Peak VE, Peak HR, Fasting Blood glucose, Hba1c%

Dahl-Jorgensen 1980	9-15 yrs	20	2	Not Given	60	Norway	22 children who had T1D were enrolled. They were randomised into a control (8) and experimental (14)	No Information given	HbA1c
D'hooge 2011	10-18 yrs	20	2	60% PHR→ 75%PHR (wk 12) Resistance 20RM→12RM (wk12)	70	Belgium	16 adolescents with T1D (>1yr) were recruited into the study and randomised into control (8) and intervention (8)	Each session consisted of a warm up (5min), Strength training of upper and lower limbs and abdominal muscles(30mins), cycling (10mins), running (10mins), stepping (10mins) and a warm down (5mins)	Weight, BMI, waist circumference, Peak VO_2 (ml/min), Peak HR, Blood glucose, HbA1c, total daily insulin dose.
Fuchsjager -Maryl 2002	Adults 40±10 yrs	16	2-3	>60% Max HR Moderate intensity	50	Austria	26 adults were recruited 40±10 yrs who have had T1D for 20±10 years. They were randomised into an intervention arm (18) and a control (8)	stationary cycling training program sessions 2-3 times per week. (twice during first 2 weeks, 3 per week there after)	BMI, Body weight, Rest HR, VO_2max, Lipid Panel, HbA1c%, insulin dose.
Heyman 2007	Adolescent girls	26	3	80-90% MHR reserve	60(x2) and 120(x1)	France	16 adolescent girls with T1D were recruited	These sessions consisted of a combination of	Lipid panel, body mass

							and participants were randomised into an intervention group (n=9) and a control (n=7)	strength and aerobic exercises at a ratio of 2:1.	
Huttunen 1989	8-17yrs	13	1	HR >150bpm Vigorous 72% max HR	60	Finland	34 Children with T1D (>6mths) produced 17 age and sex matched pairs, after drop out they were allocated into control (16) and intervention (16).	The sessions included running, jogging, gymnastics and other active games	VO_2 max, Blood glucose, HbA1c%
Laaksonen 2000	20-40 yrs men	12-16wk	Wk1(3)→ 4-5	Wk 1 20-30min 50-60% VO_2→30-60min at 60-80% VO_2 "Mod Intensity endurance training"	20-60	Finland	42 men with T1D were included and randomized into training (20) and control (22)	First week: 20-30 min running at 50-60% VO_2 mixed with walking as necessary 3 times a week training was gradually increased on an individual basis, with a goal of 30-60 min running at 60-80% VO_2 peak 4-5 times per week	VO_2max, Daily insulin dose, HbA1c, Plasma glucose, BMI, Lipid panel
Landt 1985	Adolescents	12	3	HR>160 for at least 25mins	45	USA	15 adolescents with T1D (>1yr) were randomised into exercise (9) and control (6).	Each session consisted of a 10 min warm up, 25 min aerobic activity to music and 10 min cool down.	Weight, VO_2 max

Maggio 2012	Children 10.5yrs±2.4 yrs	40	2	HR >140	90	Switzerland	27 children with t1D (>5mths) were recruited and randomised into control (12) and exercise (15)	Each session consisted of a 10 min warm up, 10min drop jump, 60 mins of aerobic activity and a 10 min cool down.	Body weight, BMI
Perry 1997	20-69 yrs	26	3-4	Not Given	Not given	NZ	61 people with T1D (>1yr) were recruited and randomised into control (30) and intervention (31)	Sessions included cycling, walking, running and weight training. Patient were given dietary advice.	Weight, SBP, DBP,HbA1c, lipid Panel, VO_2 max (l/min), rest HR
Roberts 2002	14±1.2 yrs	12	3	HR>160	45	Aust	24 adolescents with T1D (5yrs±3.1yrs) of a similar SES background were selected and allocated into control (12) and intervention (12)	Sessions had an aerobic to anaerobic ratio of 7:3	Body mass, BMI
Salem 2010	12-18 yrs	26	Group B-1 Group C-3	THRR = 220-age in years ×(65-85%)	30	Egypt	196 adolescents with T1D (>3yrs) and HbA1c >7.5% for 6mths were allocated into control (48), and two intervention groups, once per week (75) and	Each session lasted for 30 minutes and consisted of warm up (5), training period (20) and warm down (20). Activities included cycling, treadmill and strength and resistance exercises	SBP, waist circumference, Insulin dose, Hypoglycaemia attacks, HbA1c, lipid profile

							three times per week (73). .		
Tunar 2012	14.2±2 yrs	12	3	Not given	45	Turkey	31 Children with a diagnosis of T1D were included and randomised into control (14) and intervention (17)	Mat Based Pilates	HbA1c, Daily insulin dose, Lipid profile, Peak Power (w)
Wallberg-Henriksson 1986	25-45 yrs Women	20	7	1st Month- 60-70% VO_2max →70-80% VO_2max "high intensity cycling"	20	Sweden	21 Female T1D (>5yrs) patients were recruited and were randomised into control (10) and training (11)	Each session had a 5 min warm up and a 15-minute-high intensity cycling	Lipid profile, VO_2 max.

Key: Aust – Australia; BMI - body mass index; DBP – diastolic blood pressure; HR – heart rate; MHR – maximum heart rate; NZ – New Zealand; PA – physical activity; PHR – peak heart rate; RM – repetition maximum; SBP – systolic blood pressure; SES – social economic status; T1D – type 1 diabetes; THRR – training heart rate range; VE – minute ventilation; wks – weeks; yrs - years.

Table 2. Change in Outcome Measures Stratified by Weekly Exercise Time.

	<100 mins per week			100-150 mins/week			>150min/week		
	Mean Difference (95%CI)	No. of Study groups (participants)	P value	Mean Difference (95% CI)	No. of Study Groups (Participants)	P value	Mean Difference (95% CI)	No. of Study Groups (Participants)	P value
HbA1C (%)	-0.13 [-0.31, 0.06]	6 (287)	0.19	0.15 [0.03, 0.28]	4 (92)	0.02	-0.40 [-0.67, -0.13]	1 (42)	0.003
Blood Glucose ($mmol.L^{-1}$).	-1.36 [-5.26, 2.54]	2 (51)	0.50	-0.61 [-0.97, -0.25]	1 (16)	0.0009	-0.20 [-2.46, 2.06]	1 (42)	0.86
Insulin Dose. ($IU/kg\ .d^{-1}$)	-0.38 [-0.78, 0.02]	2 (196)	0.06	-0.11 [-0.16, -0.06]	3 (70)	<0.00001	0.01 [0.00, 0.02]	1 (42)	0.04
BMI ($Kg.m^{-2}$)	-0.30 [-0.58, -0.02]	1(43)	0.04	-0.07 [-0.51, 0.36]	3 (63)	0.74	-0.15 [-0.28, -0.03]	2 (69)	0.02
Body Mass (Kg)	0.09 [-2.19, 2.37]	2 (62)	0.94	-1.21 [-3.71, 1.29]	3 (63)	0.34	0.90 [-0.41, 2.21]	2 (43)	0.18
Peak VO_2 ($mlO_2.kg^{-1}.min^{-1}$)	2.32 [0.64, 4.00]	3 (89)	0.007	2.94 [1.15, 4.72]	3 (88)	0.001	1.30 [-1.21, 3.81]	1 (42)	0.31
LDL ($mmol.L^{-1}$)	-0.43 [-0.64, -0.22]	2 (196)	<0.0001	-0.17 [-0.27, -0.07]	3 (67)	0.006	-0.09 [-0.29, 0.11]	2 (57)	0.38
HDL ($mmol.L^{-1}$)	0.30 [0.26, 0.34]	2 (196)	<0.00001	-0.06 [-0.09, -0.03]	3 (67)	0.0003	-0.04 [-0.10, 0.03]	2 (58)	0.26
TGD ($mmol.L^{-1}$)	-0.34 [-0.61, -0.07]	2 (196)	0.01	-0.08 [-0.29, 0.12]	3 (67)	0.43	-0.14 [-0.40, 0.12]	2 (58)	0.30

Key

LDL – Low density lipoprotein, HDL - High density lipoprotein, TGD – Triglyceride

Table 3. TESTex Assessment of Study Quality of Included Studies

Study	Eligibility Criteria specified	Randomly allocated participants	Allocation concealed	Groups Similar at baseline	Assessors blinded	Outcome Measures assessed >85% of participants #	Intention to treat analysis	Reporting of between group statistical comparisons	Point measures & measures of variability reported*	Activity Monitoring in Control Group	Relative Exercise Intensity Review	Exercise Volume & Energy Expended	Overall TESTEx
Brazeau 2014	YES	YES	NO	YES	Unclear	YES (2)	NO	YES (2)	YES	NO	NO	YES	9
Campaigne 1984	YES	YES	NO	YES	Unclear	YES (1)	NO	YES (2)	YES	NO	NO	YES	8
Dahl-Jorgensen 1980	YES	NO	NO	Unclear	NO	YES (1)	NO	YES (2)	YES	NO	NO	NO	5
D'hooge 2011	YES	YES	NO	YES	Unclear	YES (2)	NO	YES (2)	YES	NO	YES	YES	10
Fuchsjager-maryl 2002	YES	NO	Unclear	YES	Unclear	YES (3)	NO	YES (2)	YES	NO	YES	YES	10
Heyman 2007	YES	YES	YES	YES	NO	YES (2)	NO	YES (2)	YES	NO	YES	YES	10
Huttunen	YES	NO	Unclear	YES	Unclear	YES (2)	NO	YES (2)	YES	NO	NO	YES	8

1989													
Laaksonen 2000	YES	YES	YES	YES	NO	YES (2)	NO	YES (2)	YES	NO	YES	YES	11
Landt 1985	NO	YES	YES	YES	Unclear	YES (2)	NO	YES (2)	YES	NO	NO	YES	9
Maggio 2012	YES	YES	YES	YES	NO	YES (3)	NO	YES (2)	YES	NO	NO	YES	11
Perry 1997	YES	YES	YES	YES	NO	YES (3)	NO	YES (2)	YES	NO	NO	NO	10
Roberts 2002	YES	YES	YES	YES	NO	YES (2)	NO	YES (2)	YES	NO	NO	YES	10
Salem 2010	YES	YES	YES	YES	Unclear	NO (1)	NO	YES (2)	NO	NO	YES	YES	9
Tunar 2012	YES	YES	YES	YES	Unclear	YES (1)	NO	YES (2)	YES	NO	NO	NO	8
Wallberg-Henriksson 1986	YES	YES	YES	YES	Unclear	YES (1)	NO	YES (2)	YES	NO	YES	YES	10
Totals	14	12	9	14	0	14	0	15	14	0	6	12	Median 10

Total out of 15 Points

Three points possible- 1 point if adherence>85%, 1 point if adverse vents reported, 1 point if exercise attendance is reported

*Two points possible- 1 point if primary outcome is reported, 1 point if all other outcomes reported

Highlights

- Meta-analysis investigating exercise training in type 1 diabetes
- Exercise reduced daily insulin, BMI, peak VO_2 and resting heart rate
- Exercise also reduced resting systolic blood pressure, LDL and triglycerides
- No effect on HbA1C%, Fasting Blood Glucose, body mass or HDL
- This could stimulate development of novel treatment regimes for type 1 diabetes

Figure 1. Consort Statement