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META-ANALYSIS

Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis

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Abstract
Aims/hypothesis This study aimed to systematically review randomised controlled trials comparing the effects of aerobic exercise training (AET), resistance training (RT) and combined training (CT) on glycaemic control and blood lipids in patients with type 2 diabetes mellitus.
Methods Searches were performed in MEDLINE, EMBASE and the Cochrane Library. Inclusion criteria were: type 2 diabetes mellitus, adult, supervised training and a minimum intervention period of 8 weeks. Pooled effects were calculated by fixed/random effect pairwise and Bayesian fixed/random effects network meta-analyses.
Results A total of 14 trials enrolling 915 participants were included. AET was more effective than RT in improving HbA_{1c} levels (mean difference [MD] −0.20% [−2.2 mmol/mol]; 95% CI −0.32, −0.08; p=0.0007, 10 trials/515 participants) and fasting glucose (MD −0.9 mmol/l; 95% CI −1.71, −0.09; p=0.03, 8 trials/245 participants). Compared with AET, CT resulted in a significantly more pronounced reduction in HbA_{1c} (MD −0.17% [−1.87 mmol/mol]; 95% CI −0.31, −0.03; p=0.02, 9 trials/493 participants). Compared with RT, the MD of the change in HbA_{1c} (MD −0.62%, [−6.82 mmol/mol]; 95% CI −0.95, −0.30; p=0.0002, 5 trials/362 participants], fasting glucose (MD −1.99 mmol/l; 95% CI −3.07, −0.90; p=0.0003, 3 trials/99 participants) and triacylglycerols (MD −0.28 mmol/l; 95% CI −0.46, −0.10; p=0.003, 4 trials/213 participants) were all in favour of CT. The exclusion of trials with a high risk of bias yielded only non-significant results.
Conclusions/interpretation The present data suggest that CT might be the most efficacious exercise modality to improve glycaemic control and blood lipids. Interpretation with respect to clinical relevance is limited by the low quality of the studies included and the limited information on the clinically important outcomes or adverse effects of exercise.

Keywords Aerobic exercise · Combined training · Network meta-analysis · Resistance training · Systematic review

Abbreviations

AET	Aerobic exercise training
BW	Body weight
CT	Combined training
DBP	Diastolic blood pressure
FG	Fasting glucose
MD	Mean difference
RT	Resistance training
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triacylglycerols

Introduction

Increased physical activity and improved nutritional habits in the form of hypocaloric diets (of varying macronutrient compositions) are of particular importance to decelerate the manifestations of type 2 diabetes [1–3]. The ADA and the

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American College of Sports Medicine have stated that a combination of resistance training (RT) and aerobic exercise training (AET) of at least 150 min of moderate-intensity exercise per week may be more effective in improving glycaemic control than focusing solely on one single training modality (evidence category B) [4].

The isolated effects of either RT or AET, or a combination of both (combined training [CT]), on anthropometric, cardiac and metabolic risk factors have been meta-analysed by Snowling and Hopkins [5] as well as by Chudyk and Petrella [6]. Both studies reported that the reduction in HbA_{1c} and fasting glucose (FG) levels, systolic blood pressure (SBP), waist circumference, HDL and triacylglycerols (TG) was more pronounced following AET and CT compared with RT. In addition, HbA_{1c}- and blood pressure-lowering effects of RT were shown. However, all these systematic reviews included trials in which training modalities were compared with the data from a sedentary control group [7, 8].

To date, no systematic review has compared the direct and indirect effects of these three different training modalities on the outcomes of glycaemic control and blood lipids in patients with type 2 diabetes. A recent pairwise meta-analysis comparing RT (all supervised) with AET (not all supervised) exercise in patients with type 2 diabetes concluded that although differences in some outcome variables reached statistical significance, there was no evidence that they were of clinical relevance [9]. In a recently published network meta-analysis, we were able to demonstrate that CT is ranked as the most likely effective exercise model in the treatment of overweight and obesity [10].

The aim of the present study was to assess the efficacy of AET, RT and CT on glycaemic control, blood pressure and blood lipids in patients with type 2 diabetes mellitus in a systematic review including a pairwise and network meta-analysis of randomised trials. The importance of supervised training has been demonstrated by Umpierre et al, who showed that structured training compared with training advice only significantly improved glycaemic control in patients with type 2 diabetes [11]. Based upon these findings, only trials that conducted an exercise intervention which was guided by supervised training were enrolled in the present systematic review and meta-analyses.

Methods

The review was registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42014007502). However, no study protocol was published before the initiation of the meta-analysis.

Literature search

Queries of the literature were performed using the electronic databases MEDLINE (until 2 May 2014), EMBASE (until 2 May 2014) and the Cochrane Central Register of Controlled Trials (until 2 May 2014) with no restrictions. The following keywords were used: ('strength' OR 'resistance' OR 'aerobic' OR 'endurance' OR 'combined training' OR 'progressive' OR 'walking' OR 'interval training' OR 'weight lifting') AND ('training' OR 'exercise' OR 'physical activity') AND ('diabetes' OR 'glycemic' OR 'glycaemia' OR 'glycaemic' OR 'glycemia' OR 'HbA_{1c}' OR 'A_{1c}' OR 'glycated' OR 'glycosylated' OR 'glucose' OR 'lipids' OR 'body weight' OR 'blood pressure') AND ('randomized controlled trial' OR 'randomized' OR 'clinical trials as topic' OR 'placebo' OR 'randomly' OR 'trial') NOT ('animals' NOT 'humans').

Moreover, the reference lists from the retrieved articles, systematic reviews and meta-analyses were checked to search for further relevant studies. This systematic review was planned, conducted and reported in adherence with standards of quality for reporting meta-analyses [12]. The entire literature search was conducted independently by two authors (L. Schwingshackl and B. Missbach), with disagreements resolved by consensus. The detailed search strategy for MEDLINE is given in the electronic supplementary material (ESM Methods).

Eligibility criteria

Studies were included in the meta-analysis if they met all of the following criteria: (1) a randomised controlled design; (2) a minimum intervention period of 8 weeks; (3) patients with type 2 diabetes; (4) patients' age ≥19 years; (5) a comparison of either AET vs RT and/or CT vs AET and/or CT vs RT; (6) an assessment of at least one of the following outcome markers: HbA_{1c}, blood glucose, body weight (BW), blood pressure or blood lipids (total cholesterol [TC], LDL, HDL and TG); (7) the reporting of changes from baseline value scores with SDs (or data suitable to calculate these variables: SE and 95% CI); if the SDs of the changes from baseline value scores were not available, post-intervention values were imputed, according to the *Cochrane Handbook* [13]; (8) training that was conducted under direct (guided by a physiotherapist in training classes, hospital gyms, etc.) or partial supervision, and was not home-based; and (9) the exclusion of studies with a dietary co-intervention that was not applied in all the intervention groups. All abstracts and full texts were independently assessed for eligibility by two authors (L. Schwingshackl and B. Missbach).

Risk of bias assessment

Full copies of the studies were independently assessed by two authors (L. Schwingshackl and B. Missbach) for

methodological quality using the risk of bias assessment tool from the Cochrane Collaboration [13, 14]. The following sources of bias were detected: selection bias (random sequence generation and allocation concealment), detection bias (blinding of outcome assessment), blinding of participants and personnel (performance bias), attrition bias (incomplete outcome data) and reporting bias (selective reporting) (ESM Fig. 1).

Data extraction and statistical analysis

The following data were extracted from each study: the first author's last name, publication year, study duration, participant's sex, age and BMI, sample size, duration of diabetes, HbA_{1c} at baseline, drug treatment, change of treatment during the trial, treatment effects, intervention type, dose, intensity and frequency, and differences in the means of two time points or post-intervention mean values with corresponding SDs. For each outcome measure of interest, pairwise and network random effects meta-analyses were performed in order to determine the pooled relative effect of each intervention relative to every other intervention in terms of the mean differences (MDs) between the changes from baseline value scores (or post-intervention values) of the different interventions. To process the data for the meta-analysis, we imputed the data for the changes from baseline means and their SDs. When the SDs for the changes from baseline values were not available [15–20], the post-intervention values with the corresponding SDs were imputed, according the guidelines of the *Cochrane Handbook* [13].

Data were pooled if outcomes were reported by at least three studies. Heterogeneity between trial results was tested with a Cochran's Q test. A value for I^2 of >50% was considered to represent substantial heterogeneity [21]. When substantial heterogeneity was present, the random effects model was used to estimate MDs with 95% CIs. Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI. To determine the presence of publication bias, the symmetry of the funnel plots in which mean MDs were plotted against their corresponding SEs were assessed. Additionally, Begg's and Egger's regression tests were performed to detect small study effects [22, 23].

Separate pairwise meta-analyses were first used to compare all the interventions. Network meta-analysis was then used to synthesise all the available evidence [24]. Network meta-analysis methods are extensions of the standard pairwise meta-analysis model that enable a simultaneous comparison of multiple interventions while preserving the internal randomisation of individual trials. They have the advantage of adequately accounting for the correlation in relative effect estimates from three-arm trials as well as providing a single coherent summary of all the evidence. Random effects network meta-analysis models were used when substantial heterogeneity was found in any of the pairwise comparisons for that outcome. Otherwise, the choice between fixed and random effects was made by comparing the deviance information criteria for each model [24, 25]. The model with the lowest deviance information criterion was chosen (differences >3 are considered meaningful). Pooled effect sizes from the network meta-analyses are presented as posterior medians and 95% credible intervals (i.e. the Bayesian equivalent of CIs) in the appropriate units, along with the estimated between-study heterogeneity.

For pairwise meta-analyses, data were analysed using Review Manager 5.1 software, provided by the Cochrane Collaboration (http://ims.Cochrane.org/revman). Network meta-analyses were conducted using Markov chain Monte Carlo simulation implemented with the open-source software WinBUGS, version 1.4.3 [26]. The WinBUGS code used is freely available online [24, 27] (program 'TSD2-5aRE_Normal_id.odc' or 'TSD2-5aFE_Normal_id.odc').

Minimally informative normal priors were used for all treatment effect variables and a uniform prior (0, 150) was used for the between-study SD (heterogeneity) variable. Sensitivity to this prior was assessed, but there was no meaningful change in the relative effects or overall conclusions.

Three Markov chain Monte Carlo chains were used to assess convergence using Brooks–Gelman–Rubin plots and inspection of the trace plots [28]. Convergence was achieved after 20,000 iterations for all outcomes. Posterior summaries were then obtained from a further simulation of 50,000 iterations in each of the three chains (giving 150,000 in total), resulting in a small Monte Carlo error.

The potential for inconsistency was assessed by inspection of the available evidence. In case of possible inconsistency, Bayesian p values for the difference between direct and indirect evidence were calculated, and direct and indirect estimates were compared [29, 30].

Results

Overall, a total of 14 trials (16 reports) extracted from 9,477 articles met the eligibility requirements and were included for the present systematic review and meta-analysis [15–20, 31–40]. One study was excluded since it was not described as randomised [41], and two trials provided no information on whether the AET was supervised [42, 43]. The detailed steps of the article selection process for the meta-analysis are described as a flow diagram in ESM Fig. 2. The studies were published between 2003 and 2013 and had enrolled a total of 915 participants. The study duration ranged between 2 and 12 months; the patients' mean age was between 49 and 62.5 years, and their BMI between 27.1 and 43.8 kg/m^2. Fourteen trials met the objectives for meta-analysis: 10 compared RT vs AET, 9 compared CT vs AET, and 5 compared CT vs RT (ESM Fig. 3). The general and specific study

characteristics are summarised in Table 1, ESM Table 1 and ESM Table 2.

The pairwise pooled estimate of effect size for the effects of RT vs AET, CT vs AET and CT vs RT on glycaemic control, blood pressure and blood lipids are summarised in Table 2.

Pairwise meta-analysis

Primary outcome The reduction in HbA_{1c} (MD −0.20% [−2.2 mmol/mol]; 95% CI −0.32, −0.08; p=0.0007, I^2=26%, 10 trials, 515 participants) (ESM Fig. 4) was significantly more pronounced in the AET groups compared with the RT groups. When compared with AET and RT, the CT protocols resulted in a significant reduction in HbA_{1c} (MD −0.17% [−1.87 mmol/mol]; 95% CI −0.31 to −0.03; p=0.02, I^2=21%, 9 trials, 493 participants) (ESM Fig. 5) and (MD −0.62%, [−6.82 mmol/mol]; 95% CI −0.95, −0.30; p=0.0002, I^2=74%, 5 trials, 362 participants) (ESM Fig. 6).

Secondary outcomes No significant differences were observed for BW, diastolic blood pressure (DBP), SBP, TC,

Table 1 General study characteristics

Reference	Sample size, mean baseline BMI (kg/m^2)	Mean age (years), female (%)	Study duration (months)	Comparisons	Timing of post-intervention measurement since last exercise session	Findings
Bacchi et al 2012 [31]	40 29.35	56.4 30	4	RT vs AET	n.d.	RT: / AET: ↑↑ $\dot{V}O_{2max}$
Balducci et al 2010 [17]	42 30	62.5 38	12	AET vs CT	n.d.	AET: ↓ WC; ↑ $\dot{V}O_{2max}$, HDL CT: ↓ BW, WC; ↑ $\dot{V}O_{2max}$, HDL
Church et al 2010 [32]	221 34.9	55.3 62	9	RT vs AET vs CT	48-72 h after last exercise test	RT: ↓ FM AET: ↓ LBM CT: ↓ BW, FM, ↑ $\dot{V}O_{2max}$
Cuff et al 2003 [33]	19 32.9	61.4 100	4	AET vs CT	n.d.	AET: ↓↓ BW CT: ↓↓ BW
Gram et al 2010 [19]	68 32.3	60.6 46	4	AET vs CT	n.d.	AET: / CT: LDL ↓↓
Jorge et al 2011 [15] de Oliveira et al 2012 [20]	36 30.6	54.7 61	3	RT vs AET vs CT	n.d.	RT: ↓ TC, HDL, TG AET: ↓ TC, HDL, TG, ↑ $\dot{V}O_{2max}$ CT: ↓ TC, TG
Kwon et al 2011 [34] Ku et al 2010 [35]	28 27.1	55.9 100	3	RT vs AET	n.d.	RT: ↓ BW AET: ↓ BW, ↑ $\dot{V}O_{2max}$
Kadoglou et al 2013 [36]	66 32.1	57.4 27	6	RT vs AET vs CT	n.d.	AET: ↓ SBP, FG, HbA_{1c}, HOMA-IR, FI, TC, TG; ↑ $\dot{V}O_{2max}$ RT: ↓ SBP, FG, HbA_{1c}, TC, TG, HOMR-IR, FI CT: ↓ SBP, FG, HbA_{1c}, HOMA-IR, FI, TC, TG, FM ↑ $\dot{V}O_{2max}$
Lambers et al 2008 [18]	35 29.8	54 34	3	AET vs CT	After last exercise and overnight fasting	AET: / CT: ↓↓ HbA_{1c}, ↓↓ TC
Moe et al 2011 [37]	26 30	57 0	3	RT vs AET	48 h after last exercise tests	AET: ↓ HbA_{1c} ; ↑ $\dot{V}O_{2max}$ RT: ↓ WHR, HbA_{1c}
Ng et al 2010 [38]	60 27.6	58 68	2	RT vs AET	n.d.	RT: ↓↓ WC AET: ↑↑ $\dot{V}O_{2max}$
Sigal et al 2007 [16]	188 34.9	54 63	6	RT vs AET vs CT	n.d.	RT: ↓↓ HbA_{1c} AET: ↓↓ HbA_{1c}, BW, WC, FM CT: ↓↓ HbA_{1c}
Sukala et al 2012 [39]	26 43.8	49 72	4	RT vs AET	72 h after last exercise tests	RT: / AET: ↓ TG
Yavari et al 2012 [40]	60 29.5	50.2 n.d n.d	12	RT vs AET vs CT	n.d.	AET: ↓ HbA_{1c}, FG, TG ↑ $\dot{V}O_{2max}$ RT: ↓ HbA_{1c}, FG, FM, ↑ $\dot{V}O_{2max}$ CT: ↓ HbA_{1c}, FG, BMI, FM ↑ $\dot{V}O_{2max}$

/, no significant within/between-group changes; ↓↓, ↑↑ significant between-group changes (decreases and increases, respectively; including control group comparison); ↓, ↑ significant within-group changes (decreases and increases, respectively)

n.d., no data; $\dot{V}O_{2max}$, maximal oxygen uptake; WC, waist circumference; FM, fat mass; LBM, lean body mass; FI, fasting insulin

Table 2 Pooled estimates (pairwise fixed or random effect meta-analysis) of effect size (95% CIs) expressed as MD for the effects of AET vs RT, CT vs AET and CT vs RT on glycaemic control, blood lipids, blood pressure and BW

Outcomes	No. of studies	Sample size	MD[a]	95% CI	*p* values	Inconsistency I^2	Egger test
AET vs RT							
HbA_{1c} (%)	10	515	−0.20	−0.32, −0.08	0.0007	26%	0.80
HbA_{1c} (mmol/mol)			−2.20	−3.52, −0.88			
FG (mmol/l)	8	245	−0.90	−1.71, −0.09	0.03	72%	0.66
TC (mmol/l)	8	262	0.06	−0.11, 0.22	0.50	26%	0.64
LDL (mmol/l)	9	372	−0.03	−0.15, 0.09	0.62	32%	0.28
HDL (mmol/l)	9	367	0.04	−0.05, 0.13	0.35	81%	0.61
TG (mmol/l)	9	367	0.02	−0.11, 0.15	0.77	40%	0.56
DBP (mmHg)	8	342	1.03	−0.86, 2.92	0.29	38%	0.02
SBP (mmHg)	8	342	−2.97	−7.72, 1.79	0.22	60%	0.64
BW (kg)	7	410	−0.32	−0.78, 0.14	0.17	2%	0.65
CT vs AET							
HbA_{1c} (%)	9	493	−0.17	−0.31, −0.03	0.02	21%	0.17
HbA_{1c} (mmol/mol)			−1.87	−3.41, −0.33			
FG (mmol/l)	4	132	−0.59	−1.25, 0.08	0.08	49%	0.87
TC (mmol/l)	6	219	−0.15	−0.35, 0.05	0.15	5%	0.13
LDL (mmol/l)	6	291	−0.06	−0.24, 0.13	0.54	5%	0.50
HDL (mmol/l)	7	326	0.03	−0.03, 0.09	0.31	0%	0.94
TG (mmol/l)	6	281	−0.16	−0.35, 0.03	0.10	0%	0.42
DBP (mmHg)	6	291	−1.83	−4.67, 1.01	0.21	51%	0.57
SBP (mmHg)	6	291	−0.81	−4.22, 2.61	0.64	0%	0.09
BW (kg)	8	450	−0.95	−1.93, 0.02	0.05	42%	0.97
CT vs RT							
HbA_{1c} (%)	5	362	−0.62	−0.95, −0.30	0.0002	74%	0.69
HbA_{1c} (mmol/mol)			−6.82	−10.45, −3.3			
FG (mmol/l)	3	99	−1.99	−3.07, −0.90	0.0003	61%	0.45
TC (mmol/l)	3	99	−0.12	−0.90, 0.65	0.75	84%	0.72
LDL (mmol/l)	4	218	−0.14	−0.68, 0.39	0.59	83%	0.74
HDL (mmol/l)	4	218	0.10	−0.11, 0.32	0.33	91%	0.48
TG (mmol/l)	4	213	−0.28	−0.46, −0.10	0.003	0%	0.31
DBP (mmHg)	4	213	−1.13	−3.55, 1.29	0.36	0%	0.50
SBP (mmHg)	4	206	−4.42	−8.62, −0.21	0.04	41%	0.08
BW (kg)	4	317	−1.04	−2.07, −0.00	0.05	0%	0.03

[a] Fixed effect meta-analysis if $I^2 \leq 50\%$

LDL, HDL and TG between AET and RT. However, AET resulted in a significant reduction in FG (MD −0.90 mmol/l; 95% CI −1.71, −0.09; $p=0.03$, $I^2=72\%$, 8 trials, 245 participants) compared with RT (ESM Fig. 7). Compared with RT, CT resulted in a more pronounced decrease in FG (MD −1.99 mmol/l; 95% CI −3.07, −0.90; $p=0.0003$, $I^2=61\%$, 3 trials, 99 participants) (ESM Fig. 8), TG (MD −0.28 mmol/l; 95% CI −0.46, −0.10; $p=0.003$, $I^2=0\%$, 4 trials, 213 participants) (ESM Fig. 9) and SBP (MD −4.42 mmHg; 95% CI −8.62, −0.21; $p=0.04$, $I^2=41\%$, 4 trials, 206 participants) (ESM Fig. 10).

Network meta-analysis

ESM Fig. 3 shows the network of the included trials. The pooled estimates of effect size for the comparison of AET vs RT vs CT using both direct and indirect evidence on glycaemic control and cardiovascular risk outcomes are summarised in ESM Table 3 (a fixed effect network meta-analysis for BW and TG, since $I^2 \leq 50\%$). For each outcome, a common between-study heterogeneity variable was assumed to reflect the variability between studies of all the interventions (ESM Table 3). The ranking

probabilities of AET, RT and CT for each outcome are presented in ESM Table 4.

Both AET and CT were significantly more effective in reducing HbA_{1c} when compared with RT. As shown in ESM Table 4, CT turned out to be the most effective exercise intervention with respect to reducing HbA_{1c}, FG, TC, LDL, TG, DBP, SBP and BW, and increasing HDL. CT resulted in a high (>75%) probability of being best for most outcomes. There is greater uncertainty regarding which treatment is the best for LDL- and TC, although again CT yielded the highest probability of being best.

No evidence of inconsistency was found with Bayesian *p* values for the difference between direct and indirect evidence all greater than 0.90.

Risk of bias

The dropout rates ranged from 0% to 31%, with five studies reporting dropout rates <10% (ESM Table 1). Seven trials reported random sequence generation [16, 31, 32, 36–39], and only five trials reported allocation concealment [16, 31, 32, 37, 38]. None of the studies reported the blinding of volunteers towards the mode of intervention (ESM Fig. 1). Eight trials performed intention-to-treat analysis [15–17, 32, 35, 37–39], and six trials appear to have had adequate blinding of the outcome assessment [16, 17, 31, 32, 37, 38]. High risk of bias was defined as fewer than four out of a maximum yield of six low risk of bias items using the risk of bias assessment tool from the Cochrane Collaboration (ESM Fig. 1). Seven high risk of bias trials (nine reports) were identified [15, 19, 20, 33–36, 39, 40], and sensitivity analyses were performed for studies with a high vs low risk of bias.

Subgroup analysis/sensitivity analysis

Subgroup analyses were performed comparing short-term (<6 months) vs long-term (≥6 months) trials (ESM Figs 11–13), obese (BMI ≥30 kg/m^2) vs non-obese (BMI <30 kg/m^2) participants (ESM Figs 14–16) and sample size (≥50 vs <50) (ESM Fig. 17–19). Overall, pooling the long-term trials resulted in significantly greater reductions of HbA_{1c} compared with short-term trials for all comparison groups. Furthermore, including only obese patients resulted in significant reductions in HbA_{1c}. A smaller vs bigger sample size showed non-significant differences for HbA_{1c} when comparing AET vs RT. In contrast, comparisons for CT yielded significantly higher reductions in trials with a bigger sample size when compared with either AET or RT. Subgroup analysis comparing different measurement time points for HbA_{1c} provided no additional information (ESM Figs 20–22). Sensitivity analyses excluding trials with a high risk of bias changed the summary estimates and became statistically non-significant (Table 3).

Publication bias

Begg's and Egger's regression tests provided no evidence of a substantial publication bias. Funnel plots were generated only if specific outcome measures were provided by at least ten different trials. The plot with respect to change in effect size

Table 3 Low risk of bias sensitivity analysis (pairwise fixed/random effect meta-analysis) of effect size (95% CIs) expressed as weighted MD for the effects of AET vs RT, CT vs AET and CT vs RT on glycaemic control, blood lipids, blood pressure and BW

Outcomes	No. of studies	Sample size	MD	95% CI	*p* values	Inconsistency I^2
AET vs RT						
HbA_{1c} (%)	5	371	−0.07	−0.22, 0.08	0.38	0%
HbA_{1c} (mmol/mol)			−0.77	−2.42, −0.88		
FG (mmol/l)	3	101	−0.12	−0.68, 0.44	0.68	0%
TC (mmol/l)	3	121	0.11	−0.12, 0.33	0.35	0%
LDL (mmol/l)	4	226	−0.06	−0.20, 0.09	0.34	0%
HDL (mmol/l)	4	226	0.00	−0.09, 0.09	0.96	68%
TG (mmol/l)	4	226	0.08	−0.09, 0.26	0.70	0%
DBP (mmHg)	4	226	−0.86	−3.62, 1.89	0.54	0%
SBP (mmHg)	4	226	−1.18	−7.53, 5.17	0.72	60%
BW (kg)	3	310	−0.26	−0.82, 0.29	0.36	0%
CT vs AET						
HbA_{1c} (%)	4	332	−0.10	−0.32, 0.11	0.35	0%
HbA_{1c} (mmol/mol)			−1.1	−3.52, −1.21		
HDL (mmol/l)	3	184	0.07	−0.02, 0.15	0.12	34%
TG (mmol/l)	3	184	−0.28	−0.62, 0.07	0.11	19%
BW (kg)	4	332	−1.80	−7.86, 4.27	0.56	64%

for HbA_{1c} in response to AET vs RT indicates little asymmetry. Thus, publication bias cannot be completely excluded as a factor affecting the results of the present meta-analysis (ESM Fig. 23).

Discussion

According to our literature search, this is the first network meta-analysis comparing the pooled effects of AET, RT and CT on glycaemic control, blood pressure and blood lipids in patients with type 2 diabetes. The results of the present meta-analyses showed that, in patients with established diabetes, AET might be more effective in reducing HbA_{1c} and FG when compared with RT. CT was more powerful in reducing HbA_{1c} compared with AET, and more effective in reducing HbA_{1c}, FG and TG when compared with RT. However, these results could not be confirmed when only low risk of bias studies were included. Pooling both direct and indirect evidence on AET, RT and CT via network meta-analysis demonstrated that CT was the most efficacious exercise intervention regarding its impact on HbA_{1c}, FG, HDL, TG, DBP and BW (with the respective probabilities of being ranked best following Bayesian network meta-analysis of 94%, 94%, 78%, 99%, 84% and 97%).

HbA_{1c} is not unanimously regarded to be a valid predictor of cardiovascular disease, thereby limiting the relevance of the present findings with respect to their clinical implications. The interpretation of the present data is further restricted by the fact that none of the studies evaluated the impact of their interventions on clinical outcomes. Data from epidemiological studies suggest that greater physical activity is associated with a reduced risk of all-cause mortality, mortality from cardiovascular disease and risk of type 2 diabetes [44–47].

A recent meta-analysis comparing RT with AET concluded that there is no evidence that RT differs from AET in its impact on cardiovascular risk factors and safety [9]. However, for some risk factors, the ranking probabilities of the Bayesian network meta-analysis suggest that AET was the second best exercise modality. However, these probabilities should not be overinterpreted, particularly since they are not very large (not close to 80–90%). A dose–response meta-regression analysis by Umpierre et al [48] summarised the effects of CT, AET and RT on glycaemic control in patients with type 2 diabetes and concluded that the reduction in HbA_{1c} was associated with exercise frequency in supervised AET, and with the weekly volume of RT in supervised CT. Regarding the optimal dose, the authors speculated that there should be a minimal amount of AET (33 min per session) to elicit the effects of high-volume RT in CT [11].

The results of this meta-analysis are in line with data published by Chudyk et al [6] comparing CT, AET and RT with control groups. The authors concluded that RT is not significantly related to changes in HbA_{1c} levels or to changes in SBP in patients with type 2 diabetes if it is not combined with other forms of exercise. Moreover, splitting AET and RT sessions between different days might have additional benefits for glycaemic control [49]. This indicates that more elaborated training programmes might be of relevance.

According to a mechanistic model linking the combination of AET and RT with the improvement in glycaemic control in type 2 diabetes, RT enhances insulin sensitivity [50] via an increase in glucose transporter (GLUT)-4 content and an amplification of insulin signalling in muscle [51]. Similarly, AET increased GLUT-4 expression in the adipose tissue and skeletal muscle of patients with type 2 diabetes; however, the benefit of this adaption appears to be dependent on optimal beta cell function [52].

One strength of this systematic review is the application of a network meta-analysis. Direct and indirect evidence was used, taking into account the fact that AET, RT and CT were compared simultaneously in some studies. However, the multiple use of data from three-arm trials will lead to an overestimation of the corresponding data and should be avoided. The relevance of the present data is further emphasised by the small estimated between-studies heterogeneity variables as well as by the fact that there was no evidence of inconsistencies.

On the other hand, this systematic review has several limitations that should be taken into account when interpreting its findings. There is evidence that supervised exercise is more effective than unsupervised training [11], but in practice it seems unlikely that most patients would have access to supervised exercise regimens of this intensity. It is possible that either AET, RT or CT may be easier to perform effectively without supervision, thus affecting the external validity of these results since only studies with supervised training were included.

Although the network meta-analysis included all individuals for each outcome, the sample size of volunteers might be considered low when compared with drug trials. Several potential risk of bias characteristics were identified in the 14 included trials (7 trials described random sequence generation, 5 trials performed allocation concealment, 8 trials performed intention-to-treat analysis, and 6 trials had adequate blinding of outcome assessment). Taken together, more than 50% of the included trials were judged as being at high risk of bias. Therefore, the results of the present meta-analyses should be interpreted in a conservative manner.

There were some heterogeneities in study design especially with respect to the population characteristics (e.g. duration of type 2 diabetes, study length, BMI, age and ratio of male to female participants). Subgroup analyses showed that long-term trials as well as trials including obese participants with type 2 diabetes resulted in more pronounced beneficial effects

on HbA_{1c}, which might be due to carrying forward HbA_{1c} values under conditions of high dropout rates. However, no significant differences could be observed following a comparison of the dropout rates between short- and long-term studies in the present network meta-analysis. Another confounder might be the variations in the volume of exercise (min per week) prescribed. One study reported exercise duration (min per session) in the CT group to be twice as high as with their respective RT and/or AET counterparts [16]. However, a sensitivity analysis excluding this trial was able to confirm the results of the primary analysis.

With respect to the potential side effects (ESM Table 1), eight trials in the present meta-analysis reported adverse events such as hypoglycaemia, back pain, shoulder pain, musculoskeletal injury, tendonitis and other musculoskeletal discomforts following exercise, with no significant differences between the intervention groups. However, it remains possible that the number of adverse events will increase with the duration and intensity of exercise.

This systematic review and meta-analysis focused on randomised controlled trials comparing AET, RT and CT. Compared with AET or RT, CT interventions resulted in significantly more pronounced improvements in variables related to glycaemic control. With respect to single types of exercise intervention, AET was more effective in reducing HbA_{1c} and FG when compared with RT. However, the interpretation of these findings with respect to their clinical relevance is limited by the overall low to moderate quality of the studies included, the lack of information on clinically important outcomes, and the limited information on the adverse effects of exercise.

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