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SYSTEMATIC REVIEW

Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis

D. Umpierre · P. A. B. Ribeiro · B. D. Schaan · J. P. Ribeiro

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Abstract

Aims/hypothesis Supervised exercise programmes improve glycaemic control in type 2 diabetes, but training characteristics associated with reduction in HbA_{1c} remain unclear. We conducted a systematic review with meta-regression analysis of randomised clinical trials (RCTs) assessing the association between intensity and volume of exercise training (aerobic, resistance or combined) and HbA_{1c} changes in patients with type 2 diabetes.

Methods Five electronic databases were searched (1980–2012) to retrieve RCTs of at least 12 weeks' duration, consisting of supervised exercise training vs no intervention, that reported HbA_{1c} changes and exercise characteristics. Two independent reviewers conducted study selection and data extraction.

Results Twenty-six RCTs (2,253 patients) met the inclusion criteria. In multivariate analysis, baseline HbA_{1c} and exercise frequency explained nearly 58% of between-study variance. Baseline HbA_{1c} was inversely correlated with HbA_{1c} reductions after the three types of exercise training. In aerobic training, exercise volume (represented by frequency of sessions) was associated with changes in HbA_{1c} (weighted $r=-0.64$), while no variables were correlated with glycaemic control induced by resistance training. In combined training, weekly volume of resistance exercise explained heterogeneity in multivariate analysis and was associated with changes in HbA_{1c} levels (weighted $r=-0.70$).

Conclusions/interpretation Reduction in HbA_{1c} is associated with exercise frequency in supervised aerobic training, and with weekly volume of resistance exercise in supervised combined training. Therefore, exercise volume is a major determinant of glycaemic control in patients with type 2 diabetes.

Keywords Aerobic exercise · Glycosylated haemoglobin A · Resistance training · Type 2 diabetes mellitus · Systematic review

Professor J. P. Ribeiro, who supervised this research, died on 23 August 2012, before publication of this study.

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Abbreviations

1-RM	One repetition maximum
HR_{max}	Maximum heart rate
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomised clinical trial
$\dot{V}O_{2peak}$	Peak oxygen uptake
WMD	Weighted mean difference

Introduction

Different exercise interventions benefit glycaemic control in patients with type 2 diabetes [1, 2]. Systematic reviews have consistently shown that supervised exercise training is associated with absolute reduction in HbA_{1c} of approximately 0.6% [2–5]. Supervised aerobic, resistance or combined aerobic/resistance training are associated with greater decreases in HbA_{1c} than less strict strategies, such as exercise counselling alone [2, 6, 7]. Although important contributions have been made to our understanding of the impact of different types of exercise training for patients with type 2 diabetes [8, 9], investigations of the chronic impact on glycaemic control of the key characteristics of volume and intensity in structured exercise prescriptions are inconclusive.

As the manipulation of exercise training variables may optimise chronic glucose-lowering effects in different populations [10, 11], it would be useful to know which characteristics (e.g. frequency, duration of each session, total weekly duration and intensity) could be associated with greater benefits in patients with type 2 diabetes. A recent subanalysis from the multicentre Italian Diabetes Exercise Study showed that weekly exercise volume was positively related with improvements in quality of life in patients with type 2 diabetes [12], which would probably facilitate long-term adherence [13]. Supporting the importance of exercise volume, we have found that structured exercise durations of more than 150 min/week are associated with greater reductions in HbA_{1c} in type 2 diabetes [2], although previous data from aerobic training studies have indicated that exercise intensity, but not volume, is associated with reduction in HbA_{1c} levels [3]. Nonetheless, a 6 month trial has indicated that obese patients with type 2 diabetes have similar lowering of HbA_{1c} after aerobic training of either low-to-moderate or moderate-to-high intensity [14]. Furthermore, exercise volume and intensity in resistance training or combined aerobic/resistance programmes have not been studied so far.

Accordingly, this study consists of a systematic review with meta-regression analysis of randomised clinical trials (RCTs) on the associations of characteristics of supervised exercise training with changes in HbA_{1c} levels in patients with type 2 diabetes. Supervised exercise training is categorised according to whether it consists of aerobic exercise, resistance training or a combination of both.

Methods

Search strategy and eligibility criteria We conducted a structured literature search for studies published from January 1980 to June 2012. Electronic databases including MEDLINE (accessed by PubMed), Cochrane Central Register of Controlled Trials, EMBASE, SPORTdiscus and LILACS were searched. We also examined review articles and related references to identify other eligible studies. Initially, searches included terms such as 'exercise', 'diabetes mellitus' and 'physical activity'. The advanced search strategy used in the PubMed database is published elsewhere [2]. Only eligible studies published in English, Portuguese or Spanish were included (electronic supplementary material [ESM] Fig. 1). A total of eight studies were excluded by language. This systematic review and meta-analysis is reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [15].

Included RCTs were required to have at least one arm of supervised exercise training (aerobic, resistance and/or a combination of both) in participants aged over 18 and with type 2 diabetes, compared with a control group. Studies were required to have evaluated HbA_{1c} as an outcome and reported means or differences between means and statistical dispersion values of HbA_{1c}. As the present review was designed to address characteristics of exercise training, we only included trials with structured and supervised exercise programmes that were more likely to have had strict control of the variables of interest, such as intensity, session duration and frequency. We excluded studies that had non-human data, a follow-up period shorter than 12 weeks or included patients with type 1 diabetes or gestational diabetes; duplicate publications or substudies of included trials were also excluded.

Two reviewers (D. Umpierre and P. A. B. Ribeiro) independently assessed trials for inclusion in the systematic review. Disagreements were resolved by consensus or by a third reviewer (B. D. Schaan). Corresponding authors of potentially eligible studies were contacted if there was a suggestion that duplicated data were reported or data were missing.

The quality of the methods used in the included studies was evaluated by the independent reviewers, according to the PRISMA recommendation [16]. Assessment included adequate sequence generation, allocation concealment, blinding of outcomes assessors, use of intention-to-treat analysis and description of losses and exclusions. Studies without clear descriptions of an adequate sequence generation or how the allocation list was concealed were considered not to have fulfilled these criteria.

Data extraction In order to generate weighted mean differences (WMDs), absolute changes in HbA_{1c} as well as standard deviations were extracted from all studies. Whenever standard deviations or standard errors of the mean were not available, dispersion values were entered in the analysis by imputation methods.

Pertinent data regarding the details of the study methods, population characteristics, exercise training prescriptions and outcomes were extracted in standardised forms by the independent reviewers. The frequency of exercise (sessions/

week) and total time spent in exercise throughout the study, which are variables related to the training volume, were abstracted identically for the three types of supervised exercise training. In studies of aerobic training interventions, we also extracted the session duration, weekly exercise volume and relative exercise intensity (based on percentages of maximum heart rate [HR_{max}]) of each study. We used established equations to derive aerobic training intensities expressed as percentages of the peak oxygen uptake ($\dot{V}O_{2peak}$) [17]. In resistance training interventions, we extracted the number of sets and repetitions, therefore calculating their weekly correspondence with the exercise frequency in each study. Resistance exercise intensities were computed as percentages of the one-repetition maximum (1-RM). In studies that used a range of repetitions to elicit maximal efforts at each set, the percentage values of the submaximal weight loads were obtained through an appropriate equation for the conversion from repetitions-to-fatigue to 1-RM [18]. In combined training studies, the characteristics of the aerobic and resistance components were extracted separately as described above for aerobic or resistance exercise training alone.

Statistical analysis Absolute changes in HbA_{1c} were treated as differences between arithmetic means before and after interventions. Thereafter, pooled WMDs were estimated by a random-effect model with the DerSimonian–Laird method, and heterogeneity was assessed by Cochran Q and the I^2 statistic. Three comparisons were made, with each supervised exercise training group being compared with a group receiving no intervention, as follows: (1) aerobic exercise training vs control; (2) resistance exercise training vs control; and (3) combined exercise training vs control. As the present systematic review was designed to analyse the characteristics of supervised exercise programmes, we used only data from participants completing the follow-up.

In order to explore which exercise characteristics of volume and intensity would be potentially associated with larger changes in HbA_{1c} levels, we initially ran meta-regressions by using the WMD estimates of HbA_{1c} and exercise training variables such as frequency of sessions, level of intensity, minutes of aerobic exercise per week and sets of resistance exercise per week. Significant clinical and/or exercise variables in univariate models were also combined into multivariate meta-regression analyses. For each meta-regression model, the adjusted r^2 indicated the proportion of between-study variance explained by the covariates [19, 20]. In addition, we generated correlations to test the association between HbA_{1c} WMDs with variables explaining heterogeneity in meta-regression analyses as well as with key exercise variables, based on clinical judgement of their importance. All correlation analyses were weighted by the inverse of the variance of each observation, and scatter 'bubble' plots were constructed to graphically display the proportional weights of the different trials.

In trials in which multiple exercise interventions were compared with a single control group, we split this shared control group into two or more groups, with smaller sample sizes weighted in relation to each exercise group. Therefore, comparisons were reasonably independent and overcame a unit-of-analysis error for studies that could contribute to multiple and correlated comparisons [21]. All analyses were conducted using Stata 11.0 software (Stata, College Station, TX, USA).

Results

Systematic review and qualitative assessment After the exclusion of duplicate references, the search strategy resulted in 3,788 studies. Of these, 3,454 studies were excluded based on the titles and abstracts. Therefore, from 334 eligible articles that underwent full-text evaluation, 26 RCTs met the inclusion criteria and provided data on 2,253 patients. Of these, 935 patients were included in supervised aerobic exercise training, 249 in supervised resistance exercise training and 1,069 in supervised combined aerobic/resistance exercise training. The flow diagram of the search and major reasons for exclusions is shown in ESM Fig. 1.

ESM Table 1 summarises the characteristics of all the studies included [6, 8, 9, 22–44]. Trials were published from 1989 to June 2012, and the majority were small studies with sample sizes ranging from ten participants in the smallest to 563 in the largest study. The mean duration of interventions was 25 weeks (minimum–maximum: 12 to 52). The 2,253 patients had a mean age of 58 years (minimum–maximum: 53 to 69), mean baseline HbA_{1c} of 7.8% (minimum–maximum: 6.3% to 12.5%) and mean diabetes duration of 6 years (minimum–maximum: 2 to 10 years). In the quality assessment, 35% presented adequate sequence generation (nine of 26), 19% reported allocation concealment (five of 26), 23% had blinded assessment of outcomes (six of 26), 100% described losses to follow-up and exclusions (26 of 26), and 19% reported using the intention-to-treat principle for statistical analyses (five of 26) (ESM Table 2).

As shown in ESM Table 1, across 20 interventions of aerobic exercise training, [8, 9, 22–38] the mean exercise frequency was three sessions per week, mean session duration was 48 min (not including warm-up and cool down), and mean exercise intensity was 74% of the HR_{max}. In six trials (33%), exercise intensity was transformed from submaximal rates of $\dot{V}O_{2peak}$ to the corresponding percentages of HR_{max}. All of the five trials using resistance exercise training [8, 9, 26, 39, 40] had exercise frequency of three sessions per week. In these studies, the number of total sets per session ranged from 14 to 27, and repetitions in each individual set ranged from eight to 20. Regarding the weight loads used in each set, resistance exercise intensities ranged from 60% to 85% of the 1-RM. Across the ten trials of combined exercise training [6, 8, 9, 23, 26, 32, 41–44], the mean exercise frequency was three sessions per week (minimum–maximum: two to four sessions), mean session duration was 59 min (minimum–maximum: 45–90 min), mean aerobic exercise intensity was 73% of the HR_{max} (minimum–maximum: 60–85%), whereas resistance exercise intensity in each set ranged from 40% to 85% of the 1-RM. We were unable to extract or derive exercise intensity in eight interventions of aerobic training [22–29] and three interventions of combined training [23, 26, 41]. These studies were included in the systematic review, but their data were not entered in the analyses assessing exercise intensity as a covariate.

Separate meta-analyses of studies with aerobic, resistance and/or combined exercise training were initially performed in order to generate effect sizes for each type of intervention. As expected, supervised exercise training was associated with improved glycaemic control, resulting in WMDs of −0.70% (95% CI −1.02, −0.38), −0.62 (95% CI −1.14, −0.11) and −0.47 (95% CI −0.64, −0.31) for aerobic, resistance and combined exercise training, respectively.

Meta-regression analyses Data from all trials indicated that baseline HbA_{1c}, exercise frequency and weekly exercise volume partly explained the heterogeneity in the studies (Table 1). In the multivariate analysis, baseline HbA_{1c} and weekly exercise volume explained nearly 58% of the variance between studies. As shown in Fig. 1, higher baseline levels of HbA_{1c} were associated with greater HbA_{1c} reductions after the three types of exercise training (weighted $r=-0.52$, $p=0.001$).

In supervised aerobic training, univariate analysis demonstrated that exercise frequency explained nearly 32% of the between-studies variance, which was also confirmed by

Table 1 Univariate and multivariate meta-regression models

Covariates	Coefficient	95% CI	p	Adjusted R^2
Overall analysis: aerobic, resistance and combined training studies[a]				
Baseline HbA_{1c} (%), n=26	−0.30	−0.48, −0.11	0.003	44.5%
Duration of diabetes (years), n=19	−0.074	−0.16, 0.12	0.09	NS
Frequency (sessions/week), n=26	−0.30	−0.53, −0.06	0.02	31.6%
Total time spent in exercise throughout the study (h), n=26	−0.0009	−0.005, 0.002	0.6	NS
Weekly volume (min/week), n=20	−0.004	−0.007, −0.00007	0.04	15.5%
Multivariate model: baseline HbA_{1c} + exercise frequency, n=26			0.001	57.6%
Supervised aerobic training[b]				
Intensity (% HR_{max}), n=13	−0.003	−0.07, 0.058	0.9	NS
Frequency (sessions/week), n=20	−0.69	−1.03, −0.35	<0.001	62.3%
Weekly volume (min/week), n=20	−0.007	−0.014, 0.0005	0.07	NS
Multivariate model: baseline HbA_{1c} + exercise frequency, n=20			0.001	65.4%
Supervised resistance training[c]				
Intensity (% 1-RM), n=5	0.13	−0.15, 0.18	0.8	NS
Weekly volume (sets/week), n=5	0.007	−0.05, 0.06	0.72	NS
Weekly volume (repetitions/week), n=5	0.0008	−0.009 to 0.112	0.80	NS
Supervised combined training[d]				
Aerobic intensity (% HR_{max}), n=7	0.04	−0.003, 0.82	0.07	NS
Aerobic volume (min/week), n=10	−0.0005	−0.01, 0.12	0.93	NS
Resistance intensity (% 1-RM), n=10	0.007	−0.02, 0.04	0.62	NS
Resistance volume (sets/week), n=10	−0.02	−0.033, 0.001	0.06	NS
Multivariate model: baseline HbA_{1c} + resistance volume, n=10			0.04	100%

Frequency, total time spent in exercise throughout the study, and weekly volumes of each type of training were considered characteristics of volume (amount). Percentages of either HR_{max} or 1-RM were used to express intensity in aerobic and resistance exercise, respectively

n, number of studies assessed for each of the meta-regression analyses

[a] Overall unadjusted I^2 =79.8%, p for heterogeneity <0.001

[b] Unadjusted I^2 =92.6%, p for heterogeneity <0.001

[c] Unadjusted I^2 =88.7%, p for heterogeneity <0.001

[d] Unadjusted I^2 =33.8%, p for heterogeneity <0.14

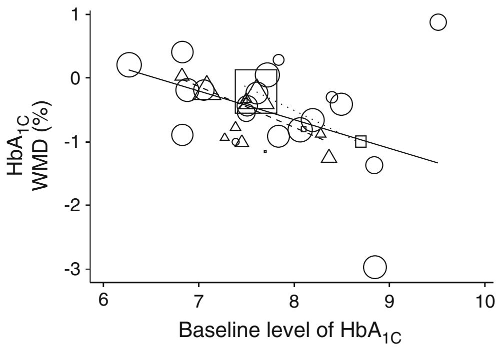

Fig. 1 Association between baseline levels of HbA_{1c} and changes in HbA_{1c} after different types of supervised exercise training. Each observation represents the WMD of HbA_{1c} between the different interventions of exercise training and control groups. The size of the symbols is proportional to the inverse variance of each study in the pooled analysis. Meta-regression lines are specific for each type of intervention: continuous line, aerobic training studies; dotted line, resistance training studies; and dashed line, combined training studies. Circles, supervised aerobic training; squares, supervised resistance training; triangles, supervised combined training. Slope for weighted regression, $y=-0.17x+0.60$. Weighted correlation, $r=-0.52$, $p=0.001$. Note that HbA_{1c} levels are shown in %. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

a multivariate model including baseline HbA_{1c} and exercise frequency (Table 1). As depicted in Fig. 2a, aerobic exercise frequency was associated with changes in HbA_{1c}, and showed a weighted regression slope of −0.39, indicating that, for each additional aerobic exercise session per week, there was a corresponding decline of 0.39% in HbA_{1c} level (weighted $r=-0.64$, $p<0.01$). Interestingly, aerobic exercise intensity did not explain between-studies variance in the univariate analysis and showed no significant association with HbA_{1c} changes ($p=0.3$, Fig. 2b).

In trials of supervised resistance training, univariate meta-regression did not show any variables that would explain the heterogeneity between studies (Table 1), therefore limiting us to enter volume or intensity variables in the multivariate analysis. Likewise, there were no correlations between weekly resistance exercise volume or resistance exercise intensity with changes in HbA_{1c} levels (Fig. 3a, b).

In trials of supervised combined training, volume and intensity were analysed in relation to aerobic and resistance components separately. As shown in Table 1 and Fig. 4, the intensity of aerobic as well as of resistance exercises was not associated with changes in HbA_{1c}. Likewise, meta-regression and correlation analyses did not indicate association between aerobic exercise volume and HbA_{1c} changes induced by combined training. However, the weekly volume of resistance exercise in this type of training trended to significance in univariate analysis, and explained the heterogeneity between studies when subsequently combined with baseline HbA_{1c} in the multivariate meta-regression (Table 1). Figure 4c shows that resistance exercise volume

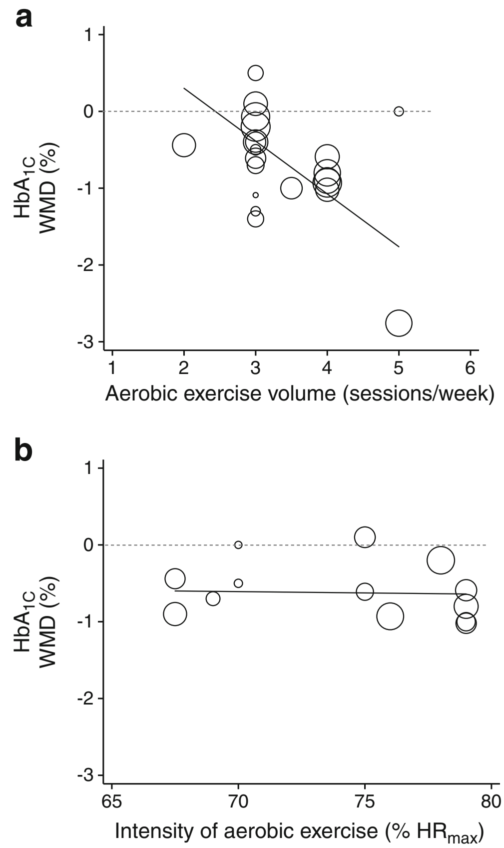

Fig. 2 Association between exercise volume (**a**) and intensity (**b**) with HbA_{1c} changes in studies of supervised aerobic training. Exercise volume is expressed as the frequency of sessions within a week and intensity is expressed as submaximal percentages of the HR_{max}. Each observation represents the WMD of HbA_{1c} between the aerobic training and control groups. The size of the circles is proportional to the inverse variance of each study in the pooled analysis. Slopes for weighted regressions, $y=-0.39x+0.65$ and $y=-0.03+2.03$, for aerobic volume and intensity, respectively. Weighted correlations, $r=-0.64$, $p=0.002$ and $r=-0.32$, $p=0.3$ for aerobic volume and intensity, respectively

was inversely correlated with WMD in HbA_{1c} levels (weighted $r=-0.70$, $p=0.04$), showing a weighted regression slope of −0.02, indicating that, for each additional resistance exercise set per week, there was a corresponding decrease of 0.02% in HbA_{1c} level after combined training interventions.

Discussion

The present systematic review provides an updated synthesis of the factors associated with improvements in glycaemic control induced by different types of supervised exercise training in type 2 diabetes. Overall, higher baseline HbA_{1c} levels were associated with greater reductions in HbA_{1c} levels after exercise interventions, supporting previous

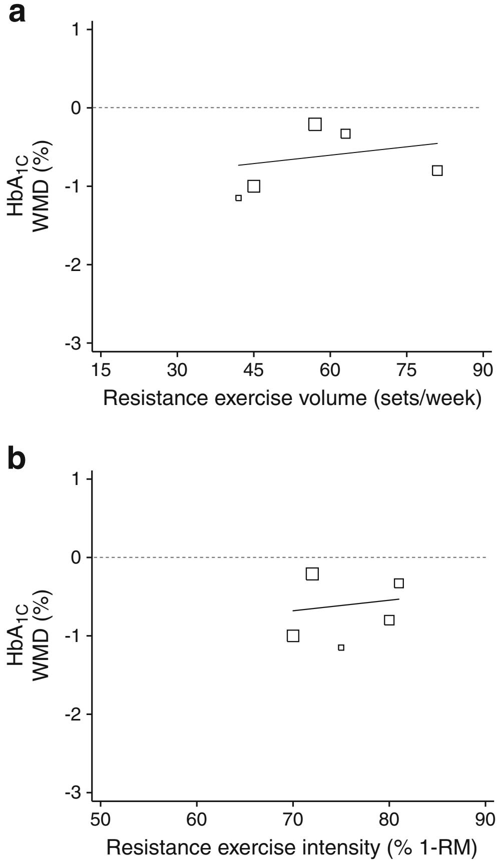

Fig. 3 Association between exercise volume (**a**) and intensity (**b**) with HbA_{1c} changes in studies of supervised resistance training. Exercise volume is expressed as the number of sets within a week and intensity is expressed as submaximal percentages of the 1-RM. Each observation represents the WMD of HbA_{1c} between the resistance training and control groups. The size of the squares is proportional to the inverse variance of each study in the pooled analysis. Slopes for weighted regressions, $y=-0.01x-1.30$ and $y=-0.02-2.12$ for resistance volume and intensity, respectively. Weighted correlations, $r=0.26$, $p=0.7$ and $r=0.18$, $p=0.8$ for resistance volume and intensity, respectively

observations [2, 8, 9]. Although no exercise variables were found to be possible candidates to explain the effects of resistance training, the volume of exercise was associated with HbA_{1c} reductions in supervised aerobic training as well as in combined aerobic/resistance training studies. More specifically, we found that each aerobic exercise session added within a week may produce an additional reduction of 0.39% in HbA_{1c} level. Interestingly, as we explored the aerobic and resistance components of combined training studies separately, we found that volume of resistance exercise was the characteristic associated with change in HbA_{1c} level in this training modality.

In a sensitivity analysis published recently, we found that durations of weekly exercise longer than 150 min were associated with absolute reductions in HbA_{1c} of 0.89% in patients with type 2 diabetes [2]. Although this estimate was derived from a pooled analysis of studies with aerobic, resistance and combined exercise training, it highlighted an important role of the exercise volume in the exercise-induced glycaemic improvements. In this context, the present study demonstrates that the frequency of exercise is the specific factor more likely to underlie the beneficial effects of aerobic training, meaning that the repetition of exercise sessions may be more important than longer or more intense sessions.

To our knowledge, only one previous systematic review with meta-analysis was designed to address quantitatively the characteristics of exercise training in type 2 diabetes [3]. In contrast with our findings on supervised aerobic training, that previous study [3] showed that weekly volume was not associated with glycaemic control, whereas exercise intensity was inversely correlated with HbA_{1c} levels after aerobic training interventions. We would attribute such conflicting results to fundamental differences in most of the studies included, which reflect distinct eligibility criteria regarding the minimal duration of exercise training interventions, training group assignments (as in the aerobic arm of the analysis, we entered groups performing aerobic exercise alone) and the number of studies analysed (an inherent limitation when comparing systematic reviews over time). Interestingly, a study has shown that 6 months of continuous aerobic training at low-to-moderate intensity or interval training at moderate-to-high intensities, matched for energy cost, induced similar HbA_{1c} reductions in patients with type 2 diabetes [14]. While an RCT [11] has indicated the importance of exercise volume for improvements in insulin sensitivity in non-diabetic individuals, other studies [45–47] have yielded controversial results on the role of intensity in aerobic programmes. In accordance with the findings of the present analysis, we have recently shown that lower- ($55\pm 2\%$ of HR_{max}) and higher-intensity ($79\pm3\%$ of HR_{max}) aerobic training resulted in similar reductions in HbA_{1c} in patients with type 2 diabetes or metabolic syndrome [48]. However, aerobic training at a higher intensity resulted in a larger improvement in endothelial function, indicating that more clinical trials should be conducted to better define the best training intensity for different outcomes [48]. Considering the inverse relationship between exercise volume and intensity, it is reasonable to think that the exercise intensity does not limit additional improvements in glycaemic control but, instead, the lower volume required to perform exercise at this level of effort. In this regard, a 10 week exercise training trial combining moderate cycling with episodes of very intense exercise resulted in important HbA_{1c} reductions in patients with type 2 diabetes [49].

In resistance training programmes, meta-regression models as well as weighted correlations did not show a relationship between intensities and changes in HbA_{1c}. Although gains in lean body mass may have a positive association

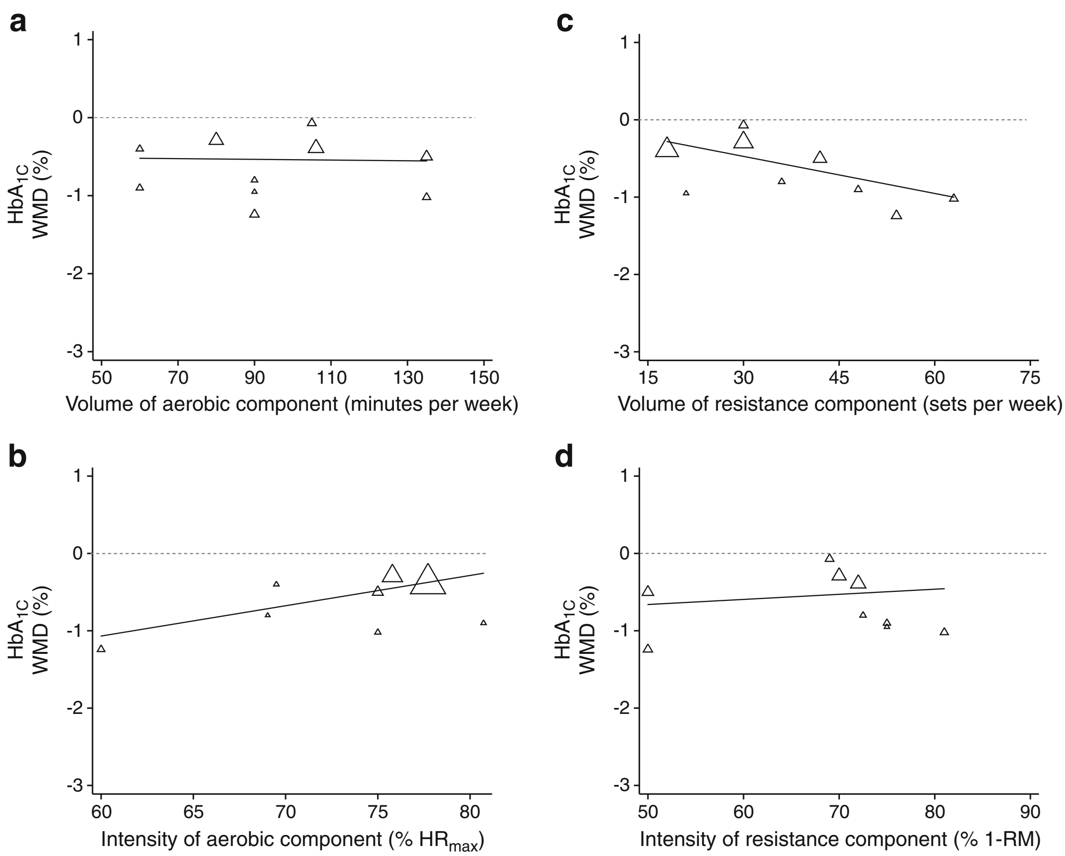

Fig. 4 Association between exercise volume and intensity with HbA_{1c} changes in studies of supervised combined training showing the aerobic and resistance components separately. Scatterplots show both aerobic (**a**, **b**) and resistance (**c**, **d**) components. Exercise volume is expressed as minutes of aerobic exercise per week for the aerobic component or number of sets per week for the resistance component. Likewise, intensity is expressed as percentages of HR_{max} or 1-RM for aerobic and resistance components, respectively. Each observation represents the WMD of HbA_{1c} between the combined training group and control group. The size of the triangles is proportional to the inverse variance of each study in the pooled analysis. Slopes for weighted regressions and weighted correlations were, respectively: $y=10^{-5}-05x-0.65$ and $r=-0.08$, $p=0.8$ for the volume of aerobic component, and $y=0.02x-2.5$ and $r=0.67$, $p=0.07$ for the intensity of aerobic component. For the resistance components, slopes for weighted regressions and weighted correlations were, respectively: $y=-0.02-0.10$ and $r=-0.70$, $p=0.04$ for the volume of the resistance component, and $y=0.001x-0.76$ and $r=0.27$, $p=0.5$ for the intensity of the resistance component

with enhanced insulin action in different populations [50–52], resistance training seems to improve insulin sensitivity and reduce HbA_{1c} even without increases in muscle mass [53], through increases in GLUT4 content and insulin signalling [54]. Therefore, exercise intensity would not necessarily need to induce muscle hypertrophy to improve glucose control. We point out that the exercise frequency was the same (three sessions/week) in all resistance training studies, therefore limiting our analysis to the association between HbA_{1c} and volume of resistance exercise. However, we did not observe significant associations between the number of sets or repetitions with changes in HbA_{1c}, suggesting that training volume plays a minor role in glycaemic control for isolated resistance training.

Regarding the combined training studies, the novel finding of our study is that the volume of resistance exercises seems to be the differential characteristic related to glycaemic control, as reflected by the inverse association between the number of sets per week and HbA_{1c} levels. Given that the mean duration of the aerobic component in combined interventions was 33 min per session, we would expect larger HbA_{1c} reductions when more sets of resistance exercises are added to that amount of aerobic exercise. Supporting this notion, results from an RCT comparing aerobic, resistance and combined training also suggest the importance of exercise volume in lowering HbA_{1c} after combined training programmes [9]. Although our analysis of the distinct aerobic and resistance components indicates that resistance exercise volume most importantly underlies the benefits of combined training, it is still a matter of discussion whether this type of training could induce additional HbA_{1c} reductions when exercise volume is comparable with that of aerobic or resistance training alone [8, 9, 55, 56]. Considering the results shown, we speculate that there should be a minimal amount of aerobic exercise

(~33 min) so that the effects of high-volume resistance exercise could be elicited in combined exercise programmes. Moreover, although the findings may seem counterintuitive, the resistance exercise in combined training is not comparable with the high intensity of aerobic exercise. This result suggests that, once the volume is appropriate, the use of additional resistive exercises will also induce larger reductions in HbA_{1c} levels.

One strength of this study is that we performed a systematic review to quantitatively assess weighted estimates for the characteristics related to the effects of supervised exercise training. It indicates reductions of approximately 0.6% in level of HbA_{1c}, which is numerically comparable with the effect of adding non-insulin glucose-lowering drugs to metformin therapy [57]. Further, it extends the knowledge for designing exercise prescriptions aiming to optimise glycaemic control in type 2 diabetes. By assessing several variables in aerobic training studies, we identified the importance of frequency of sessions. Furthermore, we conducted separate analyses of combined training studies and added insight on the likely role of resistance exercise as part of combined aerobic/resistance training. Therefore, the present study demonstrates objective training factors that may be further investigated in RCTs as well as suggesting the need to address differences in exercise training in future guidelines.

As increased exercise intensity might reduce the compliance with supervised exercise programmes [58], our findings underscore the importance of recommending more frequent exercise sessions for patients with type 2 diabetes [1].

There are some limitations to our analysis. First, as a systematic review of published literature, we extracted information that was sometimes dynamic throughout the studies, such as progressive exercise durations and/or intensities. Therefore, our results have a potential bias due to the use of averages generated in secondary data analysis. To minimise this effect, we contacted authors either to clarify issues around the methods used or to obtain additional data. When the information was considerably imprecise (e.g. exercise intensity in some studies), data were not entered in qualitative analyses. Second, we analysed only supervised exercise interventions, which may not be feasible for all patients with type 2 diabetes. Thus, our findings are relevant to centre-based exercise prescriptions, but cannot be generalised to all exercise programmes in type 2 diabetes. We point out that, despite well-known health benefits, physical activity recommendations alone have not been shown to be effective in improving glycaemic control [2, 6, 7], highlighting the need for improved strategies to deliver these interventions. Finally, the present study suggests the need for a large multi-arm trial comparing different regimens of exercise training focusing on either intensity or volume for patients with type 2 diabetes. Reduction in HbA_{1c} is associated with exercise frequency in supervised aerobic training, and with weekly volume of resistance exercise in supervised combined training. Therefore, exercise volume is a major determinant of glycaemic control in patients with type 2 diabetes following structured exercise programmes.

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