Effects of Long-Term Exercise Interventions on Glycaemic Control in Type 1 and Type 2 Diabetes: a Systematic Review

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Effects of Long-Term Exercise Interventions on Glycaemic Control in Type 1 and Type 2 Diabetes: a Systematic Review

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Key words
- resistance training
- endurance training
- combined training
- glycemic control
- systematic review

Abstract

Aim: Physical activity is one of the cornerstones in the prevention and management of diabetes mellitus, but the effects of different training forms on metabolic control still remain unclear. The aims of this review are to summarize the recommendations of 5 selected diabetes associations and to systematically review the effects of long-term supervised exercise interventions without calorie-restriction on glycemic control in people with type 1 and 2 diabetes focusing on resistance, endurance and combined training consisting of both endurance and resistance training.

Methods: Literature searches were performed using MEDLINE for articles published between January 1, 2000 and March 17, 2015. Of 76 articles retrieved, 15 randomized and controlled studies met the inclusion criteria and allowed for examining the effect of exercise training in type 1 and 2 diabetes.

Results: Diabetes associations recommend volume-focused exercise in their guidelines. In our analysis, all 3 training forms have the potential to improve the glycemic control, as assessed by HbA_{1c} (absolute changes in HbA_{1c} ranging from −0.1% to −1.1% (−1.1 to −12 mmol/mol) in resistance training, from −0.2% to −1.6% (−2.2 to −17.5 mmol/mol) in endurance training and from +0.1% to −1.5% (+1.1 to −16.4 mmol/mol) in combined training, respectively).

Conclusions: There is evidence that combined exercise training may improve glycemic control to a greater extent than single forms of exercise, especially under moderate-intensive training conditions with equal training durations. In addition, intensity of training appears to be an important determinant of the degree of metabolic improvement. Nonetheless, it is still unknown to what extent exercise effects glycemic homeostasis.

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Introduction

Besides a genetic predisposition and a hypercaloric diet, physical inactivity is an important risk factor for the development of type 2 diabetes, which affects more than 90% of the people with diabetes [1]. Therefore, exercise training is a cornerstone in the prevention and treatment of type 2 diabetes [2,3]. But also in people with type 1 diabetes, current treatment strategies comprise regular exercise training [4,5]. However, the effects of different training modalities and general physical activity, especially in a long-term approach [6], on the metabolic control are not completely understood. Few studies analyzed the isolated effects of resistance training (RT), endurance training (ET) or a combined training (CT) on metabolic risk factors, glycaemic control and blood lipids in type 2 diabetes showing preferable outcomes for CT [7–9], whereas hardly any data are available for type 1 diabetes.

Currently, there are also no overarching standard recommendations of the leading diabetes associations with regard to physical activity in diabetes [10–13]. Recently published meta-analyses investigated the impact of exercise interventions on glycemic control and indicated considerable heterogeneity between studies with respect to study design and outcomes [14–18]. Furthermore, some of these studies combined training interventions with calorie-restrictive diets which makes it difficult to disentangle the relative contributions of these interventions to improvements in glycated hemoglobin A (HbA_{1c}) [14,15]. Another gap in the current study literature concerns the effect of training intensity on glycemic control, which can be expressed as physical effort by heart frequency or number of repetitions [14–18].

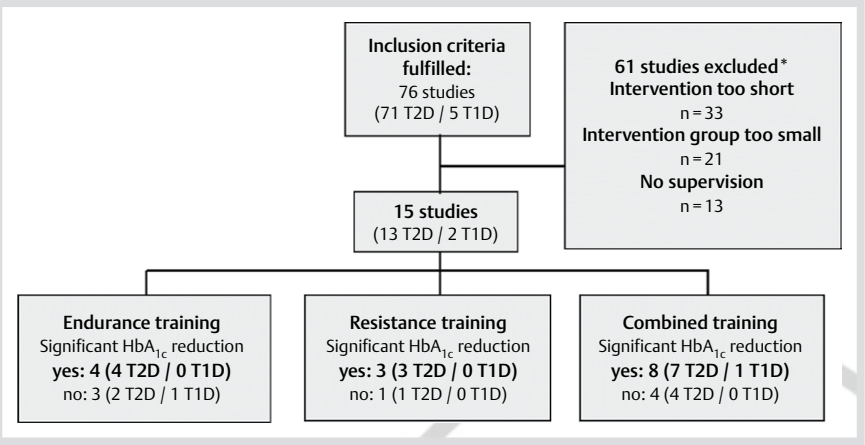

Fig. 1 Flowchart summarizing the process of literature search and identified studies. * Multiple exclusion criteria possible. T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 1 Exercise recommendations of the American Diabetes Association (ADA), Canadian Diabetes Association (CDA), European Association for the Study of Diabetes (EASD), Diabetes UK (UK) and German Diabetes Association (DDG) for patients with type 1 diabetes.

	ADA	CDA	EASD	UK	DDG
Frequency (per week)	≥3	≥5	n.r.	n.r.	n.r.
Training type	ET	ET *, RT *, CT *	ET, RT, CT	n.r.	n.r.
Duration (min per week)	≥150	≥150	≥150	n.r.	n.r.
Intensity	mod	mod to mod-int	mod to mod-int	n.r.	n.r.

* Supervised training sessions; mod, moderate intensity of 50–69% of maximum heart rate (HR_{max}) or 50–74% one repetition maximum (1RM); mod-int, moderate-intensive of 70–85% of maximum heart rate (HR_{max}) or 75–85% one repetition maximum (1RM); n.r., no recommendation; CT, combined training; ET, endurance training; RT, resistance training

It is therefore the purpose of this review to summarize systematically effects of endurance, resistance, and combined training on glycemic control in long-term and supervised training interventions without calorie restriction in type 1 and type 2 diabetes.

Methods

Search strategy

Literature searches were performed using MEDLINE between January 1, 2000 and March 17, 2015. Search terms used were: (diabetes OR type 1 diabetes OR type 2 diabetes) AND (exercise OR combined training OR aerobic training OR endurance training OR resistance training OR strength training OR physical activity) AND (HbA_{1c} OR glycosylated hemoglobin A OR A_{1c} OR blood glucose) in article title and abstract. Reference lists of review articles and all included articles identified by the search were also examined for other potentially eligible studies. Clinical practice guidelines were extracted from the official homepages of the selected diabetes associations. Search results are shown in **Fig. 1** and **Table 1,2**.

Eligibility criteria

Studies that met the following criteria were included in this review: (i) published in English, (ii) randomized and controlled intervention study that did not include a calorie-restrictive diet, (iii) resistance, endurance or combined training intervention, (iv) people with type 1 or type 2 diabetes and (v) measurements of changes in HbA_{1c} available. Non-supervised exercise intervention studies were excluded along with studies that did not include at least a number of 17 participants in their exercise group. This criterion is based on a sample size calculation of Kadoglou et al. to detect an absolute reduction of at least 0.5% (5.5 mmol/mol) in HbA_{1c} [19]. Interventions that did not last for at least 12 weeks to investigate the chronic and long-term effects of exercise on metabolic control were also excluded.

Data analysis

Due to the methodological differences in terms of frequency, training intensity, intervention duration and length of the exercises, we could not conduct a meta-analysis and thus only summarize the means and standard deviations of previously reported intervention effects from each included study (**Fig. 2a–c**). A clinically relevant improvement of metabolic control was defined as an absolute reduction of 0.6% (6.6 mmol/mol) in HbA_{1c} [20].

Quality assessment

The existence of publication bias in this investigation is estimated graphically by funnel plots (**Fig. 3a–c**). A reverse funnel shape of the effect size distribution of the included exercise interventions represents an unbiased distribution.

Results

Training recommendations of diabetes associations

The training recommendations of 5 selected diabetes associations, i.e., (i) the American Diabetes Association (ADA), (ii) the Canadian Diabetes Association (CDA), (iii) the European Association for the Study of Diabetes (EASD), (iv) Diabetes UK and (v) the German Diabetes Association (DDG), for people with type 1 and type 2 diabetes are summarized in **Table 1,2**, respectively. As shown in **Table 1** there is no standard recommendation for physical activity in type 1 diabetes by these 5 diabetes associations. The guidelines of the German Diabetes Association and Diabetes UK do not contain any detailed information about training conditions and recommend physical activity only in general terms for people with type 1 diabetes. The ADA guideline focuses in particular on moderate aerobic exercise with a weekly duration of at least 150 min split over 3 days. The Canadian and European diabetes associations recommend primarily combined training with an intensity ranging from moderate up to moderate-intensive with a weekly duration of at least 150 min

Table 2 Exercise recommendations of the American Diabetes Association (ADA), Canadian Diabetes Association (CDA), European Association for the Study of Diabetes (EASD), Diabetes UK (UK) and German Diabetes Association (DDG) for patients with type 2 diabetes.

	ADA	CDA	EASD	UK	DDG
Frequency (per week)	≥5	≥5	n.r.	3–5	6–7
Training type	ET, RT, CT	ET*, RT*, CT*	ET, RT, CT	ET	ET, RT, CT
Duration (min per week)	≥150	≥150	≥150	15–60 min per session	≥180
Intensity	mod	mod – mod-int	mod – mod-int	mod	mod

* Supervised training sessions; mod, moderate intensity of 50–69 % of maximum heart rate (HR_{max}) or 30–65 % one repetition maximum (1RM); mod-int, moderate-intensive of 70–85 % of maximum heart rate (HR_{max}) or 65–80 % one repetition maximum (1RM); n.r., no recommendation; CT, combined training; ET, endurance training; RT, resistance training

as well. With respect to type 2 diabetes, the recommendations of the leading diabetes associations on physical activity are less divergent as shown in **Table 2**. All 5 associations recommend a volume-focused training with a moderate up to moderate-intensive intensity. In particular, a supervised and combined training is recommended [10–13].

Systematic review of the effects of training intervention studies on HbA_{1c} in people with diabetes

The following analysis will give insights into the effects of supervised long-term resistance, endurance and combined training on glycemic control (assessed by measurements of HbA_{1c}). Of 76 identified articles, 15 randomized and controlled studies met our inclusion criteria and examined the effect of physical exercise on the metabolic control in type 1 and 2 diabetes. **Table 3** provides an overview of the studies and study samples included in this review stratified by type of intervention, whereas **Table 4** shows the characteristics and outcomes of the study separately.

Endurance training

Endurance training can result in meaningful improvements of glycemic control in people with diabetes [4,14]. For a better comparability of the included aerobic exercise studies, we evaluated the intensity of the workouts and categorized them into 3 intensity groups. A training intensity between 50–69 % of the maximum heart rate (HR_{max}) (55–69 % of the maximum oxygen consumption (VO_2max)) was considered to be of moderate intensity, 70–85 % of HR_{max} (70–89 % of VO_2max), also known as vigorous, was considered as moderate-intensive training and equal to and greater than 85 % of the HR_{max} (>89 % of VO_2max) was considered to be intensive exercise [21]. For type 1 diabetes, only one exercise intervention was identified through an electronic search meeting our inclusion criteria. Laaksonen et al. investigated the effect of moderate endurance training on the glycemic control in people with type 1 diabetes and found a decrease in HbA_{1c} of 0.2 % (2.2 mmol/mol) (absolute) and 2 % (relative), respectively [22]. For type 2 diabetes, 6 long-term endurance training intervention studies were found [19,23–27] with a significant reduction of HbA_{1c} in 4 studies. Of these 4 studies, 3 exercise interventions showed a clinically relevant absolute reduction of HbA_{1c} ranging from 0.7 % to 1.6 % (7.7 to 17.5 mmol/mol) [19,25,26]. In the study by Balducci et al., HbA_{1c} decreased on average by 1.0 % (10.9 mmol/mol) (absolute) and 13 % (relative) through intensive and short exercise sessions ($p<0.01$) [25]. In contrast, Sridhar et al. found an improvement in HbA_{1c} by 1.6 % (17.5 mmol/mol) and 19 % in absolute and relative levels, respectively ($p<0.05$) by a volume-focused exercise [26]. Kadoglou et al. showed a decrease of 0.7 % (7.7 mmol/mol) in HbA_{1c} through a moderate-intensive endurance exercise intervention [19]. Altogether, endurance training trials in type 1 and 2 diabetes showed an absolute and relative mean reduction in HbA_{1c} ranging from −0.2 % to −1.6 % (−2.2 to −17.5 mmol/mol) and from −2 % to −19 %, respectively. Focusing on training intensity, moderate aerobic exercise only has a small impact on glycemic control. In 2 of 3 training interventions with a heart rate between 50–69 % of HR_{max}, HbA_{1c} reached an absolute and relative reduction of only −0.2 % (−2.2 mmol/mol) and 2 %, respectively.

Resistance training

Resistance training is usually recommended only in combination with endurance training, because the effects of resistance exercise on the metabolic control are not fully understood and so far no clear relationship between dose and response has been established [28]. However, resistance training has the potential to improve glycemic control being a safe exercise form for individuals with diabetes [29]. For a better comparability of the included resistance exercise studies, we evaluated the intensity of the workouts and categorized them into 3 intensity groups. A training intensity between 50–74 % of the one-repetition maximum (1RM) (8–15 repetitions per set) was considered to be of moderate intensity, 75–85 % of 1RM (5–8 repetitions per set) was considered as a moderate-intensive training load, also known as vigorous, and equal to and greater than 85 % of the 1RM (1–5 repetitions per set) was considered to be intensive exercise [21]. Our electronic literature search did not identify any strength or resistance exercise intervention in people with type 1 diabetes that fulfilled our inclusion criteria. For type 2 diabetes, 4 studies were found [19,23,27,30]. 3 of the 4 studies showed a significant reduction of HbA_{1c}. Only one of these 3 exercise interventions showed a clinically relevant reduction of HbA_{1c}. Castaneda et al. found in a moderate-intensive resistance intervention an absolute reduction of HbA_{1c} by 1.1 % (12 mmol/mol) corresponding to a relative reduction of 13 % ($p<0.05$) [30]. On average, resistance training trials showed an absolute and relative mean reduction in HbA_{1c} ranging from −0.1 % to −1.1 % (−1.1 to −12 mmol/mol) and from −1 % to −13 %, respectively.

Combined training

Combined exercise consists of an endurance and a resistance training component which are usually performed in equal proportions during training. Regarding the training intensity and the intensity categorizes, combined training and its components were assessed in the same way as the isolated forms of resistance and endurance training before [21]. For type 1 diabetes, only one exercise intervention was identified through a systematic database search. Salem et al. investigated the effect of moderate-intensive combined training on HbA_{1c} and found an absolute and relative decrease of 1.1 % (12 mmol/mol) and 12 %

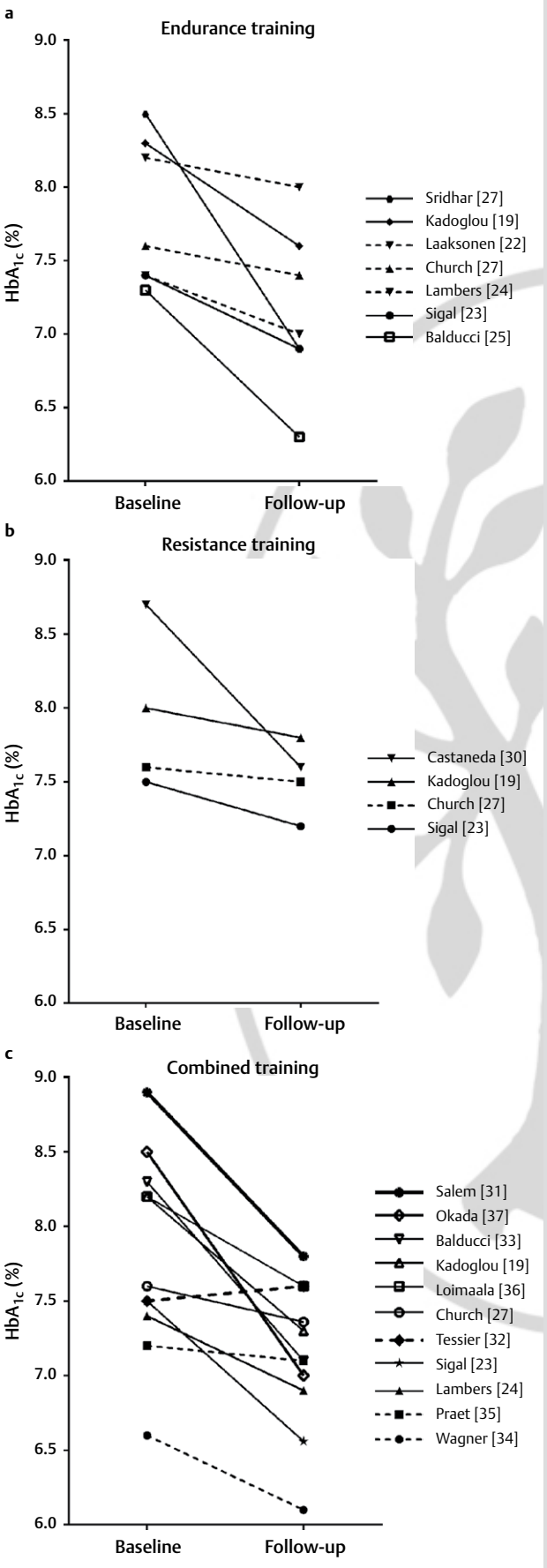

Fig. 2 Absolute changes of HbA1c in endurance **a**, resistance **b** and combined exercise **c** interventions. The dotted lines represent non-significant changes in HbA1c and solid lines describe significant changes in HbA1c.

($p<0.05$), respectively [31]. For type 2 diabetes, 10 studies [19,23,24,27,32–37] were found, fulfilling the inclusion criteria. In these exercise studies, absolute and relative change of HbA_{1c} ranged from +0.1 to −1.5% (+1.1 to −16.4 mmol/mol) and from +1% to −17%, respectively. In 7 of these 10 studies, HbA_{1c} was significantly reduced ($p<0.05$). 5 [19,23,33,36,37] of these 7 combined training studies showed a clinically relevant

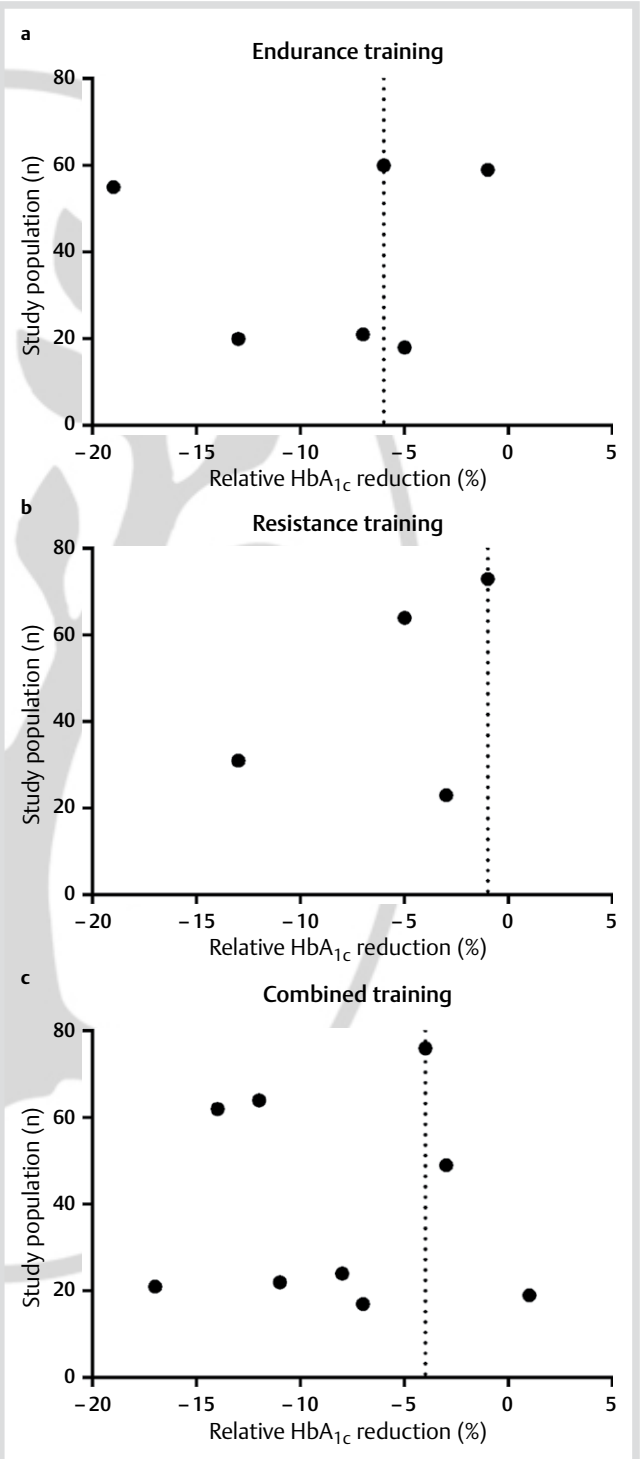

Fig. 3 Relative changes of HbA1c in endurance **a**, resistance **b** and combined exercise **c** interventions shown in funnel plots for estimating publication bias in studies in type 2 diabetes. In the absence of a summary estimate from a meta-analysis, the grid lines represent the relative change in HbA1c from the studies with the largest sample size in each training modality.

Table 3 Participants' characteristics of the included studies with different training forms.

		T1D	T2D
ET	Number of studies, n	1	6
	Study population, n	20	222
	Study size, n	20	20–59
	Age, yrs	32	52–64
	BMI, kg/m^2	24.4	27.5–35.5
	Baseline HbA_{1c}, % (mmol/mol)	8.2 (66)	7.3–8.5 (56–69)
	Diabetes duration, yrs	14	5–9
	Diabetes treatment, diet/OAD/insulin *	0/0/20	12/187/23
RT	Number of studies, n	n.a.	4
	Study population, n	n.a.	182
	Study size, n	n.a.	23–73
	Age, yrs	n.a.	54–66
	BMI, kg/m^2	n.a.	29.0–36.0
	Baseline HbA_{1c}, % (mmol/mol)	n.a.	7.5–8.7 (58–72)
	Diabetes duration, yrs	n.a.	6–8
	Diabetes treatment, diet/OAD/insulin *	n.a.	11/157/14
CT	Number of studies, n	1	11
	Study population, n	73	330
	Study size, n	73	17–76
	Age, yrs	14	54–69
	BMI, kg/m^2	n.r.	28.5–34.5
	Baseline HbA_{1c}, % (mmol/mol)	8.9 (74)	6.6–8.5 (49–69)
	Diabetes duration, yrs	5	4–10
	Diabetes treatment, diet/OAD/insulin *	0/0/73	45/276/32

Data are given as total number (n) or range of mean values in the respective studies; * Diabetes treatment at study begin; CT, combined training; ET, endurance training; RT, resistance training; n.a., not applicable; n.r., not reported

absolute reduction of HbA_{1c} ranging from 0.6% to 1.5% (6.6 to 16.4 mmol/mol). In type 2 diabetes, all exercise interventions with a training intensity of at least moderate-intensive induced an absolute and relative reduction in HbA_{1c} ranging from −0.4% to −1.2% (−4.4 to −13.1 mmol/mol) and from −7% to −14%, respectively [19,23,24,33,36]. In 4 of 5 training interventions with moderate intensity HbA_{1c} was not lowered to a clinically relevant degree with changes ranging from +0.1% to −0.5% (+1.1 to −5.5 mmol/mol) in absolute and from +1% to −7% in relative levels [27,32,34,35].

Conclusions

In the present review on supervised long-term training studies without parallel caloric restriction, we found that all 3 training forms (endurance, resistance and combined training) can significantly reduce HbA_{1c} in type 2 diabetes. In type 1 diabetes, only one study with combined training reduced HbA_{1c} to a clinically relevant extent [31].

The trials that met our inclusion criteria indicate that the largest effects of resistance, endurance and combined training are evident in a combination of at least 3 training sessions per week under moderate-intensive conditions with a duration of at least 45 min per training in type 2 diabetes [23,30,33]. In line with this, the leading diabetes associations recommend a weekly training duration of at least 150 min split over 3 days. However, an increase in training intensity can markedly reduce the time of training over the week, especially in type 2 diabetes, as shown for example in the study from Balducci et al. [25]. This intensive training intervention reduced the HbA_{1c} to a clinically relevant extent with only 2 training sessions per week with a duration of 60 min each. The importance of intensity regarding glycemic control was also shown by other groups [16,18,38]. Umpierre et al. investigated the association between different training factors and their influence on glycemic control and found that only length in minutes and frequency in units per week of training sessions influenced metabolic control [14,15]. In contrast, other forms of physical activity like Tai Chi or Yoga with a mild to moderate intensity and a training duration up to 250 min per week had no significant impact on HbA_{1c}, as reported in recent meta-analyses [16,18]. These results are in line with our review showing that interventions are more likely to improve glycemic control if the training intensity is at least moderate-intensive [11,16,17,19,25,30,33]. In line with this, Mann et al. reported recently that intensive training in resistance as well as endurance exercise can lead to better improvements of diabetes-related parameters like insulin sensitivity or glycemic control than milder training intensity [38]. As shown by recent studies in comparable diabetes populations, high intensity interval training (HIIT) could be a time-efficient alternative for intense exercise interventions [39–43]. However, none of these studies met our inclusion criteria and were, therefore, not considered further in our review [44,45].

For type 1 diabetes, only 2 studies met the inclusion criteria [22,31]. Our data do not allow, therefore, a comprehensive analysis regarding type 1 diabetes. In general, little has been published on the relationship between physical exercise and type 1 diabetes so far. This is most probably the reason for the limited recommendations of the leading diabetes associations [10–13].

Isolated endurance and resistance training or combined training achieved in more than 50% of the examined studies a significant reduction of HbA_{1c} in type 1 and type 2 diabetes. But combined endurance and resistance training improved glycemic control to a greater extent than either aerobic or resistance interventions alone as shown in **Fig. 2a–c**. Long-term exercise intervention studies showed that combined training reduced HbA_{1c} more strongly than the isolated training forms endurance and resistance training alone [19,23,27], even when the duration of the training session was equal [19,27].

The reason for this may lie in additive effects resulting from stimulation of different molecular pathways by resistance and endurance training. The endurance component improves primarily insulin sensitivity and mitochondrial biogenesis at the cellular level. Acute exercise-stimulated glucose uptake in skeletal muscle is initiated by muscular contraction resulting in an activation of AMP-activated protein kinase (AMPK) dependent activation of downstream signaling cascades. These signaling pathways lead to a translocation of the glucose transporter-4 (GLUT4) to the membrane of the cell and thereby enable insulin-independent glucose transport. Furthermore, chronic endurance exercise improves insulin-dependent GLUT4 translocation, for example, due to an increased activity of hexokinase II (HKII) and consequently of the tricarboxylic acid cycle (TCA cycle) [46]. While the effect of acute resistance training on glucose metabolism is less clear, chronic resistance training induces an increased muscle mass due to an enhanced protein synthesis following activation of the mechanistic target of rapamycin (mTOR)/serine

Table 4 Exercise interventions and related glycated hemoglobin A (HbA_{1c}) changes.

Reference	Study population, n	Age, years	Baseline HbA_{1c}, % (mmol/mol)	Known diabetes duration, years	Training intervention	Training frequency (min per week)	Study duration, weeks	Intensity	Relative change of HbA_{1c} in %
Laaksonen et al. [22]	20m T1D	32±6	8.2±1.1 (66±12)	14±9	ET	3–5×30–60 min	16	mod	−2%
Sigal et al. [23]	39m/21f T2D	54±7	7.4±1.5 (57±16)	5±4	ET	3×45 min	26	mod-int	−6%*
Lambers et al. [24]	16m/2f T2D	52±8	7.4±1.7 (57±19)	n. a.	ET	3×40 min	12	mod-int	−5%
Balducci et al. [25]	12m/8f T2D	64±8	7.3±1.4 (56±15)	9±6	ET	2×60 min	52	mod-int	−13%**
Sridhar et al. [26]	30m/25f T2D	62±3	8.5±0.6 (69±7)	9±1	ET	5×45 min	52	mod	−19%*
Church et al. [27]	20m /39f T2D	54±9	7.6±1.0 (60±11)	7±6	ET	3×50 min	39	mod	−1%
Kadoglou et al. [19]	6m/15f T2D	58±5	8.3±1.1 (67±12)	8±2	ET	4×60 min	26	mod-int	−7%*
Castaneda et al. [30]	10m/21f T2D	66±8	8.7±0.3 (72±3)	8±1	RT	3×45 min	16	mod-int	−13%*
Sigal et al. [23]	40m/24f T2D	54±7	7.5±1.5 (58±16)	6±5	RT	3×45 min	26	mod-int	−5%*
Church et al. [27]	38m/35f T2D	57±9	7.6±0.9 (60±10)	7±6	RT	3×50 min	50	mod	−1%
Kadoglou et al. [19]	7m/16f T2D	56±2	8.0±0.7 (64±8)	7±3	RT	4×60 min	26	mod-int	−3%*
Tessier et al. [32]	12m/7f T2D	69±4	7.5±1.2 (58±13)	4±4	CT	3×60 min	16	mod (ET) & mod (RT)	+1%
Balducci et al. [33]	30m/32f T2D	60±9	8.3±1.7 (67±19)	10±7	CT	3×80 min	52	mod-int (ET) & mod (RT)	−14%**
Wagner et al. [34]	14m/3f T2D	54±4	6.6±0.3 (49±3)	4±2	CT	3×50 min	12	mod (ET) & mod (RT)	−7%
Sigal et al. [23]	40m/24f T2D	54±7	7.5±1.5 (58±16)	5±5	CT	3×50–90 min	22	mod-int (ET) & mod-int (RT)	−12%**
Praet et al. [35]	27m/22f T2D	59±9	7.2±1.4 (55±15)	5±5	CT	3×30–75 min	52	mod (ET) & mod (RT)	−3%
Lambers et al. [24]	7m/10f T2D	56±10	7.4±1.5 (57±16)	n. a.	CT	3×40–60 min	12	mod-int (ET) & mod-int (RT)	−7%*
Loimaala et al. [36]	24m T2D	54±6	8.2±2.1 (66±23)	n. a.	CT	4×30–75 min	104	mod (ET) & mod-int (RT)	−8%**
Church et al. [27]	27m/49f T2D	55±8	7.6±1.0 (60±11)	7±5	CT	3×50 min	50	mod (ET) & mod (RT)	−4%*
Salem et al. [31]	73 T1D (sex n. a.)	14±2	8.9±1.6 (74±18)	5±2	CT	3×65 min	26	mod-int (ET) & mod-int (RT)	−12%*
Okada et al. [37]	10m/11f T2D	62±9	8.5±1.8 (69±20)	10±8	CT	3–5×75 min	12	mod (ET) & mod (RT)	−17%**
Kadoglou et al. [19]	5m/17f T2D	58±7	8.2±1.0 (66±11)	5±2	CT	4×60 min	26	mod (ET) & mod-int (RT)	−11%**

Data are given as mean ±SD for age, HbA1c and diabetes duration; *$p<0.05$; **$p<0.01$; n. a., not available; m, male; f, female; mod, moderate; mod-int, moderate-intensive; CT, combined training; ET, endurance training; RT, resistance training; T1D, type 1 diabetes; T2D, type 2 diabetes

kinase 6 (S6K) pathway. In parallel to the increased muscle mass, the number of insulin signaling molecules, such as insulin receptor substrate-1 (IRS-1), increases and facilitates insulin-dependent glucose uptake [47]. The activation of diverse signaling pathways by endurance and resistance training appears to be the underlying cause of enhanced improvement of metabolic control after combined training compared to the isolated training forms [47,48].

Another important mechanism which mediates the beneficial aspects of exercise is the modulation of inflammatory processes as downstream event of the aforementioned signaling cascades. Skeletal muscle releases multiple proteins which have also been termed "myokines" [49] and which act in autocrine, paracrine and endocrine fashion. Several of the proteins (e.g., interleukin-1 receptor antagonist, interleukin-10) have anti-inflammatory properties and are involved in the cross-talk between skeletal muscle and tissues throughout the body which benefit from exercise. Marked decreases in pro-inflammatory cytokines as a result of increased physical activity or participation in a long-term exercise intervention have been described and may explain some of the health benefits of these interventions. These anti-inflammatory effects are related to exercise modality and activity intensity preferring intense and/or combined training [50].

Our study has several limitations. First, the number of the included studies, especially for type 1 diabetes, is low. Focusing on subgroups in regard to different training types, our ability to clarify the impact of exercise on glycemic control is therefore limited. Second, some studies adjusted glucose-lowering medication in response to metabolic improvements due to the exercise intervention so that the impact of exercise on HbA_{1c} as our primary outcome may have been underestimated. Finally, the heterogeneity of the included exercise interventions with respect to design and study sample precluded a meaningful meta-analysis, so that the calculation of a summary estimate for exercise effects on HbA_{1c} was not possible. Strengths of our study included the systematic approach in the retrieval of relevant studies and the clear focus on HbA_{1c} as outcome because it represents the most common parameter to monitor disease progression in people with diabetes. The methodological quality of each study was independently rated by 2 investigators. Because of the strict inclusion criteria with regard to the characterization of the included studies, study population and the main outcome (HbA1c), quality assessment was not used as exclusion criterion. Publication bias can be estimated using funnel plots as shown by the **Fig. 3a–c**. There is a slight left shift in all of the 3 funnel plots towards higher reductions of glycemic control. Therefore, we cannot exclude that the distribution of changes in HbA_{1c} is distorted (with studies missing that yielded smaller effects), which may have led to an overestimation of training effects on glycemic control in this systematic review.

In summary, physical activity is an important component of diabetes treatment. Our review revealed that in particular moderate-intensive training conditions can improve glycemic control. Ideally, a combination of endurance and resistance training should be performed, but also isolated training forms can cause a significant reduction in HbA_{1c}. Despite the evident benefits of physical exercise for individuals with diabetes, further research is required to determine the minimum effective dose for frequency, intensity and the duration of chronic physical exercise and should be addressed in future studies to improve the understanding of the impact of physical exercise on metabolic control. Especially type 1 diabetes exercise interventions studies are missing, necessitating research in this field.

Contribution Statement

MaR, MiR, TS, CH and KM designed the study. MaR and KM performed the literature search. MaR wrote the manuscript; CH, TS, MiR and KM contributed to discussion and critically reviewed/edited the manuscript. All authors approved of the final version of the manuscript.

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