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SYSTEMATIC REVIEW

In Search of the Ideal Resistance Training Program to Improve Glycemic Control and its Indication for Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Background Resistance training (RT) is effective for glycemic control in type 2 diabetes mellitus (T2DM) patients. However, the characteristics of an RT program that will maximize its effect and those of patients that will especially benefit from RT are unknown.

Objective The objectives of this systematic review were to identify via a comprehensive meta-analysis the characteristics of an RT program for patients with T2DM that might increase the patients' improvement in glycemic control and the characteristics of patients that will benefit from RT.

Data Sources Electronic-based literature searches of MEDLINE and EMBASE entries from 1 January 1966 to 25 August 2014 were conducted to identify clinical trials examining the effect of RT on glycemic control among patients with T2DM. Study keywords were text words and thesaurus terms related to RT and T2DM.

Study Selection Studies were included if they (1) were clinical trials consisting of two groups with and without RT exercise intervention; (2) had an intervention period of at least 5 weeks; (3) clarified that all patients had T2DM; and (4) reported or made it possible to estimate the effect size [i.e., change in glycosylated hemoglobin (HbA_{1c}) in the RT group minus that in the control group] and its corresponding standard error.

Study Appraisal and Synthesis Methods The effect size in each study was pooled with a random-effects model. Analyses were stratified by several key characteristics of the patients and RT exercise programs; meta-regression analysis was then used to detect a difference in the effect size among strata within each factor. Linear regression analyses were added by entering each of the following profiles: patients' baseline characteristics [mean baseline age, body mass index (BMI), and HbA_{1c} levels] and exercise characteristics (total sets per week, total sets per bout of exercise, frequency, and intensity).

Results There were 23 eligible studies comprising 954 patients with T2DM. The pooled effect size (95 % confidence interval) was −0.34 % (−0.53 to −0.16). A program with multiple sets (≥21 vs. <21) per one RT bout was associated with a large effect size ($P = 0.03$); however, the linear correlation between the number of sets and effect size was not significant ($P = 0.56$). A larger effect size was observed in studies with participants with diabetes of a relatively short duration (<6 vs. ≥6 years; $P = 0.04$) or a high baseline HbA_{1c} [≥7.5 % (58 mmol/mol) vs. <7.5 %;

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$P = 0.01$] while a smaller effect size was observed in studies with a particularly high mean baseline BMI value ($\geq$32 vs. <32 kg/m^2; $P = 0.03$). Linear regression analyses predicted that each increment of 1 % in the baseline HbA_{1c} would enlarge the effect size by 0.036 %, while each increment of 1 kg/m^2 in the baseline BMI decreased it by 0.070 % in the range between 22.3 and 38.8 kg/m^2.

Conclusion In terms of glycemic control, RT could be recommended in the early stage of T2DM, especially for patients with relatively poor glycemic control. More benefit would be elicited in less obese patients within a limited range of the BMI. A substantial amount of exercise might be required to stimulate post-exercise glucose uptake, although the dose-dependency was not specifically clarified.

Key Points

This meta-analysis detected a larger effect on glycosylated hemoglobin (HbA_{1c}) reduction in type 2 diabetes mellitus patients in studies where the resistance training (RT) program consisted of a relatively high number of sets per bout of exercise ($\geq$21 sets) or where the patients had a relatively (1) short duration of diabetes (<6 years), or (2) high baseline HbA_{1c} level ($\geq$7.5 %), while the effect was limited in studies of patients with a particularly high baseline body mass index (BMI) ($\geq$32 kg/m^2).

In addition, the results of the linear regression analysis suggest that each 1 % increment in baseline HbA_{1c} would enlarge the HbA_{1c} reduction by 0.036 % while each 1 kg/m^2 increment in baseline BMI would decrease it by 0.070 %.

Our current analyses have significant implications for establishing an ideal exercise protocol for RT and for prescribing tailor-made exercise programs for patients with diabetes.

1 Introduction

1.1 Rationale

Improving glycemic control is essential for preventing various long-term diabetes-related complications (e.g., blindness, amputation, dialysis, cardiovascular disease) that affect quality of life. For monitoring blood glucose, physicians usually monitor glycosylated hemoglobin (HbA_{1c}), which is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose.

While aerobic training (AT) is a traditionally established form of exercise therapy for improving metabolic profiles, including HbA_{1c}, in patients with type 2 diabetes mellitus (T2DM) [1], resistance training (RT) has been recently noted to improve glycemic control as well as providing other advantages such as maintaining bone mineral density, increasing muscle strength, and preventing osteoporosis [2]. Indeed, although a previous meta-analysis provided evidence that RT reduces HbA_{1c} levels [3], several further studies regarding this topic have been published. Although AT has been found to be slightly superior to RT in reducing HbA_{1c} levels [1], its benefit in reducing glucose levels has been reported to depend on a patient's ability to get a sufficient amount of exercise [4]. Some patients are unable or unwilling to engage in a sufficient amount of aerobic exercise to maximize health benefits. Therefore, RT may be the first choice for patients with diabetes who are unable or unwilling to elicit substantial energy expenditure from AT.

A previous meta-analysis suggested that the ability of RT to reduce HbA_{1c} was found to be heterogeneous [3]. However, the study did not clarify whether or not this heterogeneity was attributed to the characteristics of the RT programs or the patients. If the characteristics of the RT programs that would reduce HbA_{1c} were identified and the characteristics of patients who receive the most benefit from RT were determined, this information would be helpful from a practical viewpoint to healthcare professionals such as physicians who recommend exercise for patients with T2DM.

1.2 Objectives

The aims of this meta-analysis were therefore to update information on the effect of RT on HbA_{1c} levels among patients with T2DM and to suggest the characteristics of an RT program that would maximize its effect and those of patients that would especially benefit from RT through comprehensive sensitivity analyses.

2 Methods

2.1 Data Sources and Search Strategy

We fundamentally conducted this meta-analysis according to the PRISMA checklist [5]. Electronic-based literature searches of MEDLINE and EMBASE entries from 1 January 1966 to 25 August 2014 were conducted to identify clinical trials that examined the effect of RT on glycemic control among patients with T2DM. Study keywords were

text words and thesaurus terms related to RT and diabetes [Electronic Supplementary Material (ESM), Online Resource 1]. Studies were included if they (1) were clinical trials consisting of two groups with and without an RT exercise intervention; (2) had an intervention period of at least 5 weeks, because this period was more than 4 weeks within the period in which HbA_{1c} reaches a new steady state after a change in glucose concentration [6]; (3) clarified that all patients had T2DM; and (4) reported or made it possible to estimate the effect size (i.e., change in HbA_{1c} in the RT group minus that in the control group) and its corresponding standard error (SE).

In order to focus on the effects of RT alone, studies were excluded if they included other non-RT interventions in the control and/or intervention groups (e.g., AT or supplements, due to the possibility of synergetic effects of RT) or if these interventions could not be ruled out. Stretching was not regarded as an intervention because there is no evidence that stretching affects glucose homeostasis.

2.2 Data Extraction and Quality Assessment

We extracted data on the following study characteristics: first author; publication year; country; number of patients; patients' baseline characteristics [mean age, sex, diabetes duration, HbA_{1c}, body mass index (BMI), total cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, and diastolic blood pressure (ESM Online Resource 2)]; exercise protocols [intervention period, number of RT items, and details of these items (number of repetitions and sets per exercise item, frequency per week, intensity, and interval minutes); ESM Online Resource 3]; and HbA_{1c} levels before and after the intervention.

Exercise intensity was expressed as the intensity relative to 1 repetition maximum (1 RM). 1 RM is defined as the greatest resistance that can be moved through the full range of motion in a controlled manner with good posture. In studies wherein the intensity was expressed as the number of repetitions to reach fatigue, relative intensity was estimated using Brzycki's formula [7] (Eq. 1):

$$1\ \mathrm{RM} = \frac{W}{\left(\frac{102.78 - 2.78 \times R}{100}\right)} \tag{1}$$

where W is the weight used and R is the maximal number of repetitions performed. This equation was the most accurate among six possible prediction equations [8]. The correlation coefficient (r) between the 1 RM test and the Brzycki equation was 0.99 [9].

Study quality was evaluated by the following criteria (ESM Online Resource 4):

1. Was the study question well-defined in the introduction or methods section of the article?
2. Was the outcome that was investigated appropriate?
3. Were the selection criteria for the patients adequately described?
4. Were methods for randomization described?
5. Was the recording of dropouts clear?
6. If dropouts were excluded from the study, were the reasons for their exclusion given? Otherwise, was an intention-to-treat analysis conducted?
7. Were the baseline characteristics of the patients reported?
8. Were these baseline characteristics compared between the RT and control groups?
9. Were the rules for stopping the intervention in patients described?
10. Did the study confirm the effectiveness of its RT program by performing a strength test after the intervention?
11. Did the study change the individual workload over time during the RT program?

The total number of criteria that each of the studies met was used as the study quality score.

2.3 Data Synthesis, Sensitivity Analyses, Statistical Analyses

The effect size in each study was pooled with a random-effects model [10]. The corresponding SE was calculated using a P value for the effect size. Otherwise, the SE was estimated from the standard deviation (SD) of the change in HbA_{1c} from before to after the intervention for each RT and control group. If the SD was not presented, we estimated it using the formula advocated by Follmann et al. [11] (Eq. 2):

$$\mathrm{SE} = \sqrt{(\mathrm{SE}_{\mathrm{baseline}})^2 + (\mathrm{SE}_{\mathrm{final}})^2 - 2 \times 0.5 \times (\mathrm{SE}_{\mathrm{baseline}}) \times (\mathrm{SE}_{\mathrm{final}})},$$
$$\mathrm{SD} = \frac{\mathrm{SE}}{\sqrt{n}} \tag{2}$$

where it was assumed that the correlation coefficient between pre- and post-intervention values was 0.5. Between-study heterogeneity was assessed using I^2 [12].

Analyses were stratified by several key characteristics of the patients and RT exercise programs; meta-regression analysis was then used to detect a difference in the effect size among strata within each factor. Linear regression analyses were added by entering each of the following profiles that had fewer than three missing data as an explanatory variable: patients' baseline characteristics (mean baseline age, BMI, and HbA_{1c} levels) and exercise characteristics (total sets per week, total sets per bout of exercise, frequency, and intensity).

Publication bias was assessed by two formal methods: Begg's rank correlation test [13] and Egger's asymmetry test [14]. If publication bias was suggested statistically, we tried to adjust the pooled estimates for publication bias using the trim and fill method [15]. This method involves the assumption that the funnel plot is symmetrical if there is no publication bias, detection of the hypothetically unpublished data that causes the funnel plot to be asymmetrical, and recalculation of the pooled risk estimates after including these data as though they had actually existed. A P value of ≤ 0.05 was considered statistically significant. All analyses were performed with STATA® software version 10 (STATA Corporation, College Station, TX, USA).

3 Results

3.1 Literature Searches

Figure 1 shows the results of the selection process. Of 2899 articles retrieved from the electronic literature searches and references of included articles, 2786 articles were excluded on the basis of title and abstract and 113 articles underwent full-paper review. Of 25 studies meeting the initial inclusion criteria in the full-paper review, two pairs of studies [16–19] used the same study populations. Among these two pairs, we selected de Oliveira et al. [17] because it provided more detailed data than the other study [16] and Dunstan et al. [19] because it was an original version of another article [18]. Ultimately, 23 studies consisting of 954 patients [17, 19–40] with T2DM were included in the present meta-analysis.

3.2 Study Characteristics

ESM Online Resource 2 summarizes the characteristics of the 23 eligible studies. The studies were published between 1997 and 2013. Eight trials were conducted in European and American countries [Canada, Finland, Germany, Greece ($n = 2$), UK, USA (n = 2)], and 15 trials were performed in others [Australia ($n = 6$), Brazil, India ($n = 3$), Iran, Japan, Korea ($n = 2$), New Zealand]. Except for two studies [28, 40] that included only female patients and one study [34] that included only male patients, 20 studies included both males and females. However, no study investigated sex differences in the effect size. Among the total study population, the ranges of mean HbA_{1c}, BMI, and duration of diabetes were 6.7–9.2 % (50–77 mmol/mol), 22.3–38.8 kg/m^2, and 4.8–9.5 years, respectively. In the RT program (ESM Online Resource 3), the ranges of the intervention period, number of RT items, frequency, and relative intensity were 5–48 weeks, 5–10 items, 2–5 sessions/week, and 45–81 % of 1 RM, respectively. The study quality score ranged from 5 to 11 (ESM Online Resource 4). Although in most of the included studies (19 studies) the individual workload was changed over time during the RT program, only six studies confirmed the

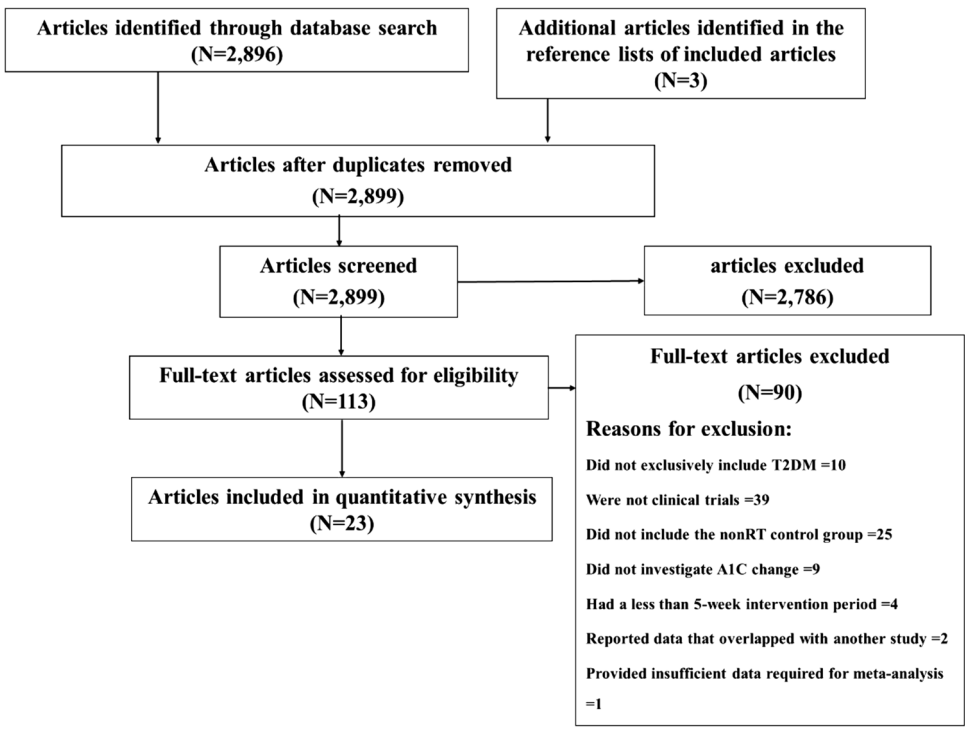

Fig. 1 Flow chart showing the results of the selection process. *HbA_{1c}* glycosylated hemoglobin, *RT* resistance training, *T2DM* type 2 diabetes mellitus

effectiveness of the RT program by performing a strength test after the interventions.

3.3 Overall Effect Size of Resistance Training (RT)

Figure 2 shows the forest plot overall and for each of the included studies. Overall, RT changed the HbA_{1c} levels by −0.34 % [$P < 0.001$, 95 % confidence interval (CI), −0.53 to −0.16 %]. However, the magnitude of the effect size was highly heterogeneous among studies (I^2, 78.3 %; $P < 0.001$). Publication bias was statistically suggested not by Begg's test ($P = 0.56$) but by Egger's test ($P = 0.03$). In addition, publication bias was visually suggested by an unsymmetrical funnel plot (ESM Online Resource 5). Nevertheless, adjustment for publication bias via the trim and fill method did not change the study result because this method could detect no hypothetical results to correct the asymmetry.

3.4 Influence of RT Characteristics on the Effect Size

Linear regression analyses indicated that there was no relationship between the total amount of exercise, expressed as the total number of sets per week, and effect size ($P = 0.91$). None of the other elements constituting one bout of the RT program was associated with a larger effect size [$P = 0.20$ for number of items; $P = 0.56$ for total number of sets per session; $P = 0.38$ for exercise frequency (sessions/week); $P = 0.18$ for exercise intensity].

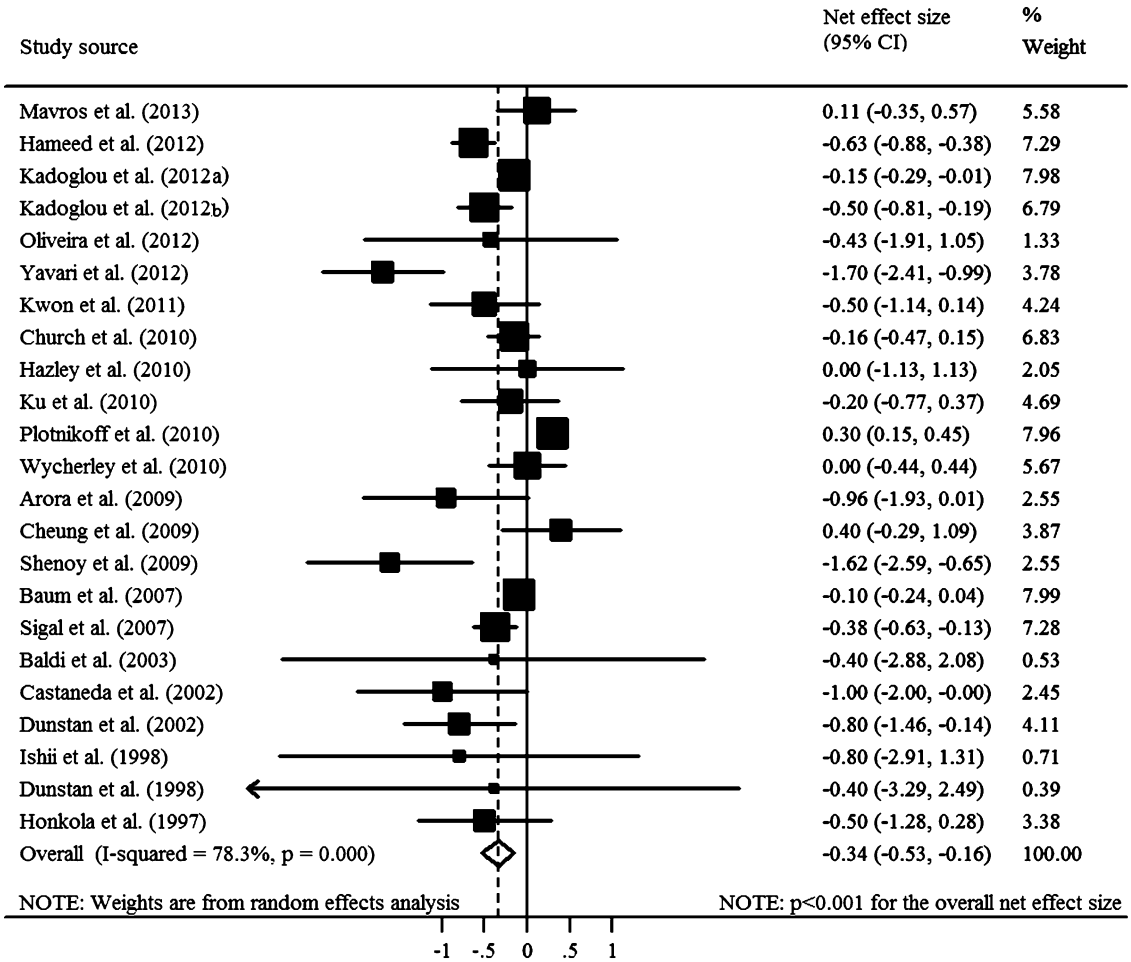

Fig. 2 Box plot of the effect size (i.e., change in glycosylated hemoglobin in the resistance training group minus that in the control group) with 95 % confidence intervals overall and for each study. The effect size in each study and overall are indicated by *squares* and *diamonds*, respectively. *Horizontal lines* indicate the range of the 95 % confidence interval. The *areas of the squares* are proportional to the study weight, expressed as the inverse of the square of standard error based on a random-effects model [17, 19–40]. *CI* confidence interval

The results of the stratified analysis (Table 1) were consistent with these regression analyses. However, an RT program with 21 or more sets per session had a larger effect size than one with fewer than 21 sets per session ($P = 0.03$).

3.5 Influence of Patients' Characteristics on the Effect Size

To conduct stratified analyses, we a priori specified 6 years, 32 kg/m^2, and 7.5 % as cut-off values for the mean duration of diabetes, mean baseline BMI, and mean baseline HbA_{1c}, respectively, because these values were close to the median values in the included studies (6.1 years for duration of diabetes; 31.2 kg/m^2 for baseline BMI; 7.6 % for baseline HbA_{1c}).While a significantly larger effect size was observed in studies of patients with a short duration of diabetes (<6 vs. ≥6 years; $P = 0.01$) or a high HbA_{1c} value at baseline [≥7.5 % (77 mmol/mol) vs. <7.5 % (77 mmol/mol); $P = 0.01$), a smaller effect size was observed in studies with a particularly high value for the mean baseline BMI (≥32 vs. <32 kg/m^2; $P = 0.03$). A significant difference among strata was not detected for age, proportion of men, or any metabolic profile related to blood pressure and lipids (Table 2).

We added a linear regression analysis using the mean HbA_{1c} and BMI as continuous variables. There was a positive association between the mean baseline HbA_{1c} level and the extent of the effect size ($R^2 = 0.33$, $P = 0.004$), and a negative association between the mean baseline BMI and the extent of the effect size ($R^2 = 0.33$, $P = 0.004$) (Fig. 3). It was predicted that each increment of 1 % in the baseline HbA_{1c} would enlarge the effect size by 0.036 %, while each increment of 1 kg/m^2 in the baseline BMI would decrease it by 0.070 %. The influence of mean age on the extent of HbA_{1c} reduction was not significant ($P = 0.49$).

3.6 Influence of the Other Characteristics on the Effect Size

When the publication year of each study was entered as a categorical variable, no categories significantly influenced the results (P value ranged from 0.42 to 1.00). The stratified analysis indicated no statistical difference ($P = 0.35$) in the HbA_{1c} reduction (95 % CI) between studies that were published up to and including 2009 [−0.46 % (−0.76

Table 1 Analysis of the effect size (i.e., change in glycosylated hemoglobin in the resistance training group minus that in the control group) stratified by characteristics of the resistance training program

Characteristic	No. of data	Effect size (95 % CI) [%]	I^2	P value (heterogeneity)	P value (difference between strata)
Intervention period					
≥12 weeks	12	−0.33 (−0.60 to −0.06)	84.9	<0.001	
<12 weeks	11	−0.39 (−0.62 to −0.17)	46.5	0.04	0.72
Frequency					
≥3/week	17	−0.25 (−0.44 to −0.06)	77.8	<0.001	
<3/week	6	−0.66 (−0.88 to −0.44)	11.7	0.34	0.09
No. of items					
≥9 items	10	−0.54 (−0.90 to −0.19)	49.7	0.04	
<9 items	13	−0.25 (−0.47 to −0.04)	84.1	<0.001	0.24
Intensity					
≥75 % of 1 RM	10	−0.41 (−0.72 to −0.09)	86.8	<0.001	
<75 % of 1 RM	10	−0.30 (−0.51 to −0.09)	53.3	0.02	0.60
Interval					
≥1.5 min	8	−0.47 (−0.88 to −0.06)	91.3	<0.001	
<1.5 min	5	−0.38 (−0.97 to −0.21)	0.0	0.95	0.85
Total sets per bout of exercise					
≥21 sets	10	−0.65 (−0.97 to −0.32)	62.7	0.004	
<21 sets	13	−0.16 (−0.38 to 0.05)	79.8	<0.001	0.03
Total sets per week					
≥60 sets	14	−0.32 (−0.58 to −0.06)	80.9	<0.001	
<60 sets	9	−0.40 (−0.70 to −0.09)	72.6	<0.001	0.09

1 RM 1 repetition maximum, *CI* confidence interval

Table 2 Analysis of the effect size (i.e., change in glycosylated hemoglobin in the resistance training group minus that in the control group) stratified by the characteristics of patients with type 2 diabetes mellitus

Characteristic	No. of data	Effect size (95 % CI) [%]	I^2	*P* value (heterogeneity)	*P* value (difference between strata)
Geographic region					
European and American countries	8	−0.19 (−0.28 to −0.11)	37.2	0.13	
Others	15	−0.45 (−0.81 to −0.08)	83.8	<0.001	0.46
HbA_{1c}					
≥7.5 % (77 mmol/mol)	13	−0.68 (−0.98 to −0.37)	69.7	<0.001	
≤7.5 % (77 mmol/mol)	10	−0.10 (−0.32 to 0.12)	77.8	<0.001	0.01
Age					
≥55 years	12	−0.16 (−0.25 to −0.08)	38.4	0.09	
<55 years	11	−0.63 (−1.10 to −0.16)	87.9	<0.001	0.16
% of men					
≥50 %	10	−0.49 (−0.77 to −0.21)	70.8	<0.001	
<50 %	10	−0.28 (−0.57 to 0.10)	84.5	<0.001	0.32
BMI					
≥32 kg/m^2	8	−0.10 (−0.35 to 0.14)	82.6	<0.001	
<32 kg/m^2	15	−0.58 (−0.86 to −0.29)	70.1	<0.001	0.03
Duration of diabetes					
≥6 years	7	−0.18 (−0.30 to −0.06)	29.5	0.20	
<6 years	7	−0.47 (−0.64 to −0.29)	22.5	0.26	0.04
SBP					
≥130 mmHg	11	−0.34 (−0.51 to −0.17)	60.6	0.005	
<130 mmHg	7	−0.61 (−1.18 to −0.04)	88.5	<0.001	0.59
DBP					
≥80 mmHg	9	−0.25 (−0.43 to −0.08)	50.4	0.04	
<80 mmHg	9	−0.52 (−0.95 to −0.09)	89.9	<0.001	0.63
TC					
≥5.2 mmol/L	7	−0.44 (−0.69 to −0.18)	60.6	0.02	
<5.2 mmol/L	7	−0.65 (−1.14 to −0.15)	68.0	0.005	0.55
TG					
≥1.7 mmol/L	14	−0.45 (−0.76 to −0.14)	84.7	<0.001	
<1.7 mmol/L	3	−0.17 (−0.29 to −0.04)	26.5	0.27	0.64
LDL					
≥2.6 mmol/L	7	−0.42 (−0.63 to −0.21)	61.2	0.02	
<2.6 mmol/L	8	−0.37 (−0.78 to 0.04)	84.2	<0.001	0.67

BMI body mass index, *CI* confidence interval, *DBP* diastolic blood pressure, *HbA_{1c}* glycosylated hemoglobin, *LDL* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglycerides

to −0.17)] and after 2009 [−0.28 % (−0.54 to −0.02)]. A significant difference in the effect size could not be detected according to characteristics especially associated with study quality such as whether the effectiveness of RT was confirmed using strength tests [effect size (95 % CI) −0.56 % (−1.23 to 0.11) and −0.32 % (−0.48 to −0.15) for confirmed and not-confirmed, respectively; *P* for difference = 0.67) or whether the patients' workload was changed over time [effect size (95 % CI) −0.30 % (−0.52 to −0.08) and −0.55 % (−1.02 to −0.08) for changed and not changed, respectively; *P* for difference = 0.39).

4 Discussion

Strong evidence for the effectiveness of RT in reducing the HbA_{1c} level among patients with T2DM was indicated by the highly significant effect size ($P < 0.001$), although the large heterogeneity in the magnitude of the effect size and the statistically suspected publication bias might lower the grade of the strength of evidence [41]. It is of note that the net HbA_{1c} change by RT (−0.34 % overall) was relatively modest in comparison with that brought about by anti-hyperglycemic agents such as metformin (−0.97 %), which is

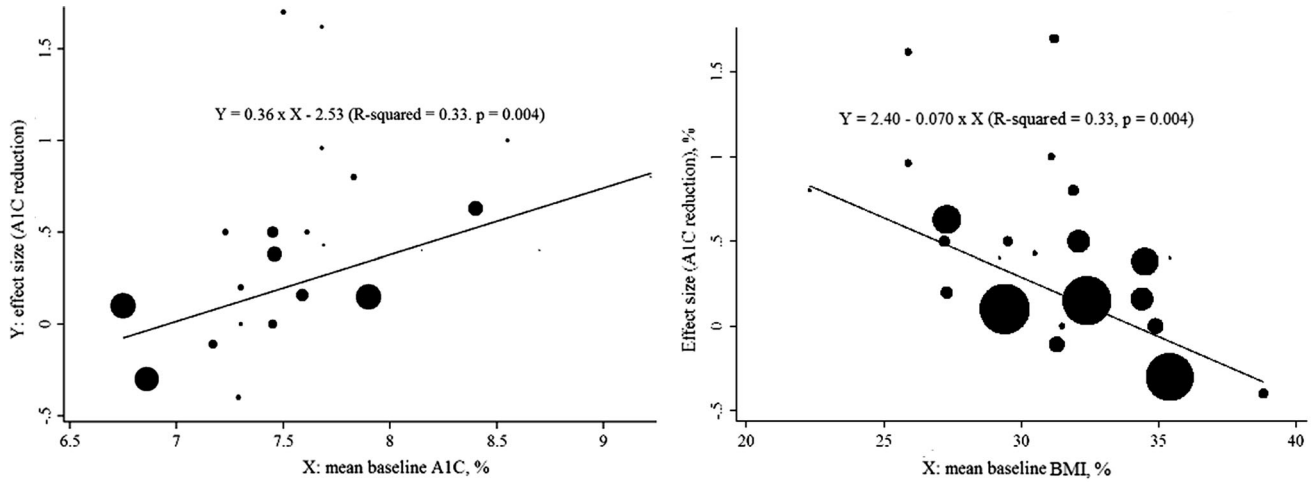

Fig. 3 The effect size (i.e., change in glycosylated hemoglobin in the resistance training group minus that in the control group) due to resistance training, regressed on mean baseline glycosylated hemoglobin (*left*) and body mass index (*right*). Each *circle* indicates an individual study. The *areas of the circles* are proportional to the study weight, expressed as the inverse of the square of standard error. *BMI* body mass index, *HbA_{1c}* glycosylated hemoglobin

the most widespread first-line agent [42], and acarbose (−0.77 %) [43], although the large between-study heterogeneity in the magnitude of HbA_{1c} reduction in these trials indicated that the results should be interpreted with caution. In addition, from the result of the stratified analysis showing that the effect size was not significant in studies with participants having a mean HbA_{1c} level <7.5 % (77 mmol/mol) [effect size (95 % CI) −0.10 % (−0.32 to 0.12)], RT exercise only might present difficulties in achieving strict glycemic control.

Generally, the increase in muscle mass that may result from RT can contribute to increasing glucose uptake [44]. However, the RT exercise prescribed to patients with diabetes may be insufficient to elicit these effects. Another mechanism is that RT promotes glucose utilization by the enhancement of insulin action in skeletal muscle, which is reflected by increased protein content of glucose transporter-4 (GLUT-4), insulin receptor, protein kinase B-α/β, glycogen synthase (GS), and GS total activity. Moreover, this effect was likely to be independent of increases in muscle mass [45].

It was speculated that the increase in glucose uptake via insulin action played a substantial role in the improvement of glycemic control based on the results of current sensitivity analyses indicating that patients with a high baseline BMI or a long duration of diabetes were low responders to RT in terms of glycemic control. Protein kinase B, the downstream kinase of the insulin receptor substrate-1 (IRS-1)–phosphatidylinositol 3 (PI 3)-kinase pathway, is considered to stimulate the translocation of GLUT-4 [46]. However, among patients with T2DM, glucose uptake due to an impairment in insulin signaling might be lower in obese individuals than in non-obese individuals even if the intracellular GLUT-4 concentration had increased. Exercise training did not enhance the ability to stimulate IRS-1-associated PI 3-kinase activity in overweight subjects [47]. Similarly, the enhancement of insulin-stimulated glucose uptake might be small among patients with a long duration of diabetes because, in general, β cell function decreases with the duration of diabetes [48]. Among patients with T2DM, enhancement of insulin action could be restricted in those with impaired basal insulin secretion due to a long duration of diabetes or with severe insulin resistance due to obesity.

The current sensitivity analyses indicated that the characteristics of the RT program had little influence on the magnitude of HbA_{1c} reduction. In particular, high-frequency exercise would not lead to a greater HbA_{1c} reduction as seen from the result that there was no difference in the effect size between ≥3 and<3 sessions/week. Actually, two to three times per week is the standard frequency of RT, although RT is recommended to be combined with AT [44]. However, we note that there was no evidence that fewer than 2 sessions/week of RT might improve glycemic control because the lowest frequency in the included studies was 2 sessions/week. Similarly, no relationship was indicated between RT intensity and HbA_{1c} reduction. However, the estimated intensity was within the range of 60–80 % of 1 RM in most of the studies included, and the effect of an intensity beyond this range should not be concluded from the current meta-analysis. Exceptionally, it might be of note that a significant difference in the effect size was found when the meta-analysis studies were stratified by whether the RT program included 21 or more

sets/session, although no linear relationship was indicated between the amount of exercise and the effect size. The amount of exercise might have less emphasis in RT than in aerobic exercise. However, a substantial amount of exercise might be required to cause a reduction in the HbA_{1c} level.

Several limitations should be addressed. First, this meta-analysis indirectly identified the characteristics of patients with T2DM who would elicit a greater effect from RT by several sensitivity analyses across studies. An analysis across patients would be essential in the future to more directly elucidate the suggestions made from the sensitivity analyses. Also, in the future it should be investigated whether the HbA_{1c} reduction differs by exercise protocols such as intensity, frequency, and the number of sets to clarify the optimal characteristics of an RT program. Second, most of the studies did not confirm the effectiveness of their RT program by performing a strength test after the intervention although most changed the individual workload over time during the RT program. Fortunately, the failure to confirm the effectiveness of the RT program or to change the patients' workload did not significantly influence the results of the current meta-analysis. Nevertheless, the potential influence on the actual effectiveness could not be ruled out. Third, no change in medication during the intervention period was described in most of the publications examined. If the control group had received a more intense drug regimen than the intervention group, as is often the case with a co-intervention with medication, the effect of RT on glycemic control would have been underestimated. Fourth, the current meta-analysis suggested that RT could reduce HbA_{1c} levels, especially in non-obese patients with T2DM. However, the cut-off value of the mean baseline BMI used in the stratified analysis was 32 kg/m^2, which should be defined as obesity. Studies must target exclusively non-obese patients (BMI <25 kg/m^2) to provide evidence to support this suggestion. Fifth, potential publication bias was visually and statistically suggested to enlarge the effect of RT. However, adjustment for bias using the trim and fill method did not change the general conclusion. Nevertheless, the impact of this bias on the results is unlikely to be perfectly estimated using this method.

We need to address one important issue. A more direct study outcome would be diabetes-specific complications rather than the HbA_{1c} level, considering the major aim of diabetes care. However, no exercise intervention studies have investigated whether an exercise intervention lowers the risk of such complications, unlike studies on antidiabetic agents. For example, the UK Prospective Diabetes Study indicated that intensive glycemic control through pharmacological treatments lowered the incidence of myocardial infarction by 16 % and that of microvascular diseases by 25 % for a 0.9 % reduction in HbA_{1c} [49]. Evidence for a positive association between the improvement in glycemic control through an exercise intervention and the future risk reduction of such complications would be essential to clarify the effectiveness of implementing exercise training in clinical practice.

5 Conclusions

RT caused a modest but statistically significant reduction in HbA_{1c} in patients with T2DM. RT could be recommended in the early stage of T2DM, especially for patients with relatively poor glycemic control. More benefit would be elicited in less obese patients within a limited range of BMI (from 22.3 to 38.8 kg/m^2). A substantial amount of exercise might be required to stimulate post-exercise glucose uptake, although the dose dependency was not clarified. To elucidate these suggestions from the current meta-analysis, future studies are needed to analyze the characteristics of patients who experience a large reduction in HbA_{1c} from RT or investigate whether the HbA_{1c} reduction differed according to the RT program such as frequency, intensity, or number of sets.

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All study members contributed substantially to the following: (1) conception and design of the study or acquisition of data, or analysis and interpretation of data; (2) drafting the article or reviewing it; and (3) providing final approval of the version to be published. In addition, all of the authors certify that they have participated sufficiently in the work to believe in its overall validity and to take public responsibility for appropriate portions of its context. HI, SK, and HS played leading roles in the conception and design of the study, all processes of the study methods, and drafting all sections of the manuscript. KF and ASH selected studies that met the inclusion criteria and acquired the full-paper version of studies that underwent further review. RH and YY gave various opinions in interpretation of the study results and helped to draft the manuscript. NO and HS designed the study's analytic strategy and provided technical support in carrying out the statistical analyses. OH supervised the study and revised the draft critically for important intellectual content. HI, SK, and HS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with Ethical Standards

Conflict of interest Hajime Ishiguro, Satoru Kodama, Chika Horikawa, Kazuya Fujihara, Ayumi Sugawara Hirose, Reiko Hirasawa, Yoko Yachi, Nobumasa Ohara, Hitoshi Shimano, Osamu Hanyu, and Hirohito Sone declare that they have no conflict of interest.

Ethical standards This manuscript does not include clinical studies or patient data.

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