The relationship between the level of exercise and hemoglobin A1c in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

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Introduction

According to the International Diabetes Federation (IDF), an estimated 4.6 hundred million people around the world have diabetes, and approximately 90% of them have type 2 diabetes mellitus (T2DM) [1]. T2DM contributes to cardiovascular disease, cancer, dementia, and worse morbidity and mortality [2–7]. As an example, a meta-analysis of cohort studies reported that a 1% increase in hemoglobin A1c (HbA1c) in T2DM patients increased the risk of cardiovascular disease by 1.13-fold and stroke by 1.26-fold [7].

The risk of T2DM depends greatly on lifestyle [8], and decreased physical activity is a major factor in the development of T2DM [9]. A meta-analysis of epidemiological studies indicated that a sedentary lifestyle over a prolonged period increased the incidence of T2DM [10]. In order to alleviate T2DM, the American Diabetes Association (ADA) guidelines...
recommend engaging in exercise at moderate or greater intensity (i.e., ≥3.0 metabolic equivalents [METs]; 3.0 METs is equivalent to walking 4.0 km/h on a firm surface [11]) for ≥2.5 h per week [12]. Epidemiological studies reported a relationship between the incidence of cardiovascular disease and the exercise level in T2DM patients [13–18]. For example, a cohort study that followed Japanese T2DM patients for 8 years reported that the risk of stroke decreased if the exercise level per week was ≥15.4 METs × hour [13]. In addition, several systematic reviews and meta-analyses involving randomized controlled trials (RCTs) reported that exercise improved HbA1c in T2DM patients [19–31], although there was heterogeneity in the improvement among the studies [19, 20, 22, 23, 25–27, 29, 30]. One of those meta-analyses reported that decreased HbA1c was associated with high exercise levels [19]; thus, differences in exercise levels might be the reason for the heterogeneity. However, this meta-analysis was limited to RCTs involving only supervised aerobic exercise [19]. Types of exercise have become more varied [11], and systematic reviews and meta-analyses have evaluated the effects of various forms of exercise, including resistance exercise [22, 23], interval exercise [24], tai chi [27, 29, 30], yoga [28–30], and aquatic exercise [31], on HbA1c in T2DM patients. No systematic review and meta-analysis have evaluated all types of exercise. We hypothesized that, in line with epidemiological studies [15–18], a meta-analysis of RCTs would indicate that HbA1c improvement depends on the exercise level. In addition, previous systematic reviews [19–31] did not assess the quality of individual RCTs or evidence overall and did not adequately discuss a form of exercise to improve HbA1c and evidence for it.

Thus, the aim of the current systematic review and meta-analysis was to evaluate the relationship between changes in HbA1c and the exercise level when performing various types of exercise in T2DM patients and assess the quality of individual RCTs and evidence overall.

Methods

The current paper reported all 27 items that should be disclosed in a systematic review and meta-analysis as described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [32] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020181566) [33].

Data sources, study selection, and data extraction

The current systematic review searched six database search engines (MEDLINE via PubMed, Embase, Scopus, SPORTDiscus, CINAHL, and Cochrane library [CENTRAL]) with a combination of search terms related to diabetes mellitus, HbA1c, physical activity, exercise, and sports (Supplementary Material 1). In addition, a search of other sources was conducted by referring to articles cited in the current study and previous systematic reviews that reviewed the effect of exercise in T2DM patients. These searches were performed prior to August 31, 2020.

The inclusion criteria for RCTs were as follows: studies involving subjects with T2DM and a mean age of ≥18 years; increased exercise performed by intervention group; no increase in exercise performed by control group; neither group received another intervention (e.g., diet and/or lifestyle change); the study reported specifics of exercise (e.g., type, intensity, time [total exercise time per session], frequency [number of exercise sessions per week], and overall duration of intervention); the study reported the mean HbA1c and standard deviation (SD) or standard error of mean (SEM) at baseline and post-intervention for the intervention and control groups, and the overall duration of intervention was ≥12 weeks (since HbA1c indicates blood glucose levels over approximately that last 12 weeks [34]). The identified articles were first screened by title and abstract, and the full text was obtained if the study included subjects with T2DM, intervention involving exercise, and reported HbA1c. The first and second authors determined whether the identified studies should be included in this systematic review. If they disagreed, the third author made the final decision regarding inclusion.

The current study was in accordance with the Cochrane data collection form for intervention review (RCTs only) [35]. The first and second authors independently extracted data (number of subjects, mean age, mean duration of diabetes, mean HbA1c, mean body mass index [BMI], and respective SDs or SEMs for the intervention and control groups) from each study in order to perform the meta-analysis. In addition, the type, intensity, time (min/session), frequency (sessions/week), and overall duration (weeks) of exercise were extracted as specifics of the intervention. METs in each study were estimated as the intensity of exercise. If studies indicated the percentage of maximal oxygen consumption (% VO2max), percentage of heart rate reserve (% HRR), percentage of maximal heart rate (% HRmax), or Borg rating of perceived exertion (RPE), these values were converted to METs based on the characteristics and modalities of exercise [36]. If studies did not indicate the intensity, METs were estimated based on activity codes and the MET intensities defined by the American College of Sports Medicine (ACSM) [11].

Risk of bias

The first and second authors used the version 2 of the Cochrane Collaboration tool to assess the risk of bias in
each study [37]. This tool consists of six domains (bias arising from the randomization process generation, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall bias). Each domain is ranked in one of three categories (low risk, some concerns, or high risk).

Data synthesis

The baseline and form of the exercise (intensity, time, frequency, and overall duration) data were expressed as the mean and SD, weighted by the number of subjects in each study.

The mean difference (mean value at post-intervention in the exercise group – mean value at baseline in the exercise group) was used as the effect size [38] and the mean difference in HbA1c and BMI were calculated for each study. The weighted mean difference (WMD) was defined as the mean difference weighted by the inverse of the squared SEM of differences from baseline to post-intervention for each study; the current study pooled all WMDs as overall effects. The meta-analysis followed a random-effects model in accordance with $\gamma = \theta + \varepsilon + \mu$ (Eq. 1), where $\gamma$ represents the effect size in each study, $\theta$ represents the true value, $\varepsilon$ represents the sampling error, and $\mu$ represents the between-study variance [39]. The pooled WMD was calculated using restricted maximum likelihood (REML) [40]. This approach is a random-effects model that takes into account within-study and between-study variances as opposed to the fixed-effect model, which ignores between-study variance and which readily yields positive results. In comparison to the DerSimonian–Laird approach, which is typically used for random-effects models, this method avoids underestimation errors [41].

In order to evaluate the relationship between the exercise level and changes in the HbA1c and BMI, we performed a multivariate meta-regression analysis, in which $\theta$ was replaced with $\beta_0x_0 + \beta_1x_1$ (where $\beta$ represents the meta-regression coefficient and $x$ represents the explanatory variable) in Eq. 1. Intensity (METs), time (min/session), frequency (sessions/week), and overall duration (weeks) of exercise were selected as $x_0$ for the analysis. Furthermore, since a previous systematic review and meta-analysis reported that the baseline HbA1c was inversely associated with changes in HbA1c as a result of exercise [25], $x_1$ was adjusted with the mean baseline HbA1c in the current meta-regression analysis. The meta-regression equations were calculated, then $R^2$ (the proportion of between-study variance explained by covariates) was calculated [42].

Sensitivity analyses were used to evaluate the influence of study characteristics and quality, and eight categories (mean age ≥40 years, mean baseline HbA1c ≥6.5%, mean duration of T2DM ≥5.0 years, mean baseline BMI ≥30 kg/m², calculation of the WMD in BMI, the performance of aerobic exercise alone, rate of subject drop-out ≤10%, and no inclusion of a high risk of bias [37]) were defined. Once studies were limited to those falling into a given category, the pooled WMD in HbA1c was calculated and meta-regression analyses were performed.

The mean difference, pooled WMD, and meta-regression coefficient were expressed with 95% confidence interval (CI). The heterogeneity of the pooled WMD as a result of variations among studies was assessed using Cochran’s $Q$ statistic and $I^2$ statistic. The $Q$ statistic was tested using the chi-squared test. $P$ values of <0.05 were considered to indicate significant heterogeneity. In addition, the degree of heterogeneity was assessed in low ($I^2 < 25\%$), moderate ($I^2: 25–75\%$), and high ($I^2 > 75\%$) risk studies [43].

Publication bias was assessed using funnel plots consisting of the mean difference in the HbA1c or BMI ($x$-axis) and the inverse of the SEM ($y$-axis). First, Egger’s regression test was performed to evaluate the asymmetry of funnel plots [44], and $P$ values of <0.05 were considered to indicate a significant publication bias. Second, the trim and fill method of Duval and Tweedie was applied to estimate the number of missing studies and coordinates when they were located on a funnel plot [45]. If the results suggested that studies were missing, then the pooled WMDs in HbA1c and BMI were adjusted by the addition of coordinates. The result was expressed as the WMD in light of the effect of these studies and the 95% CI.

The current meta-analyses were performed using the JASp software program (Version 0.14.1; University of Amsterdam, Netherlands).

The certainty of evidence

The overall evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [46]. The five domains (study limitations [risk of bias], inconsistency, indirectness, imprecision, and risk of publication bias) were ranked as one of the following: downgraded 2 levels (if very serious), downgraded 1 level (if serious), or not downgraded (if not serious); publication bias was downgraded 2 levels (if very likely), downgraded 1 level (if likely), or not downgraded (if not likely). The body of evidence was assessed as a high level of evidence (if not downgraded in any domain), a moderate level of evidence (if downgraded a total of 1 level), a low level of evidence (if downgraded 1 level in two domains, i.e., downgraded a total of 2 levels), or a very low level of evidence (if the aforementioned criteria were no met).
Results

Study characteristics and risk of bias

The literature search yielded 304 studies. These studies involved subjects with T2DM, intervention in the form of exercise, and reported HbA1c data. Among these, 256 studies did not meet the selection criteria and were excluded. Finally, 48 studies were analyzed (Fig. 1 and Supplementary Material 2). Table 1 shows a general description of the studies. The studies involved 2395 subjects (1514 subjects in exercise groups and 881 subjects in control groups). Table 2 shows the baseline and form of exercise data. Supplementary Material 3 shows the assessed risk of bias. Six studies [Raz, et al., Dela, et al., Murrock, et al., de Oliveira, et al., Karstoft, et al, and Park, et al.] had a high risk of bias in overall bias.

Data synthesis

Figure 2 shows the baseline results and the forest plot of the mean difference from each study and the pooled WMD in HbA1c. The pooled WMD was significantly decreased but contained significant heterogeneity (moderate risk). The pooled WMD in BMI was calculated and evaluated with 35 studies reporting the mean BMI and its SD or SEM at baseline and post-intervention; the result decreased significantly (−0.55 kg/m²; 95% CI, −0.58 to −0.51) and did not contain heterogeneity (Q = 25.8, P = 0.99; I² = 0.0%; low risk). Table 3 shows the results of the sensitivity analyses of HbA1c. When studies were limited to those in a given category, there was a significant decrease in all pooled WMDs in HbA1c and the WMDs contained significant heterogeneity (moderate risk); that is, there was no change in the results.

Tables 4 and 5 show the results of a meta-regression analysis of the relationship between exercise level and WMD in HbA1c; here, the WMD in HbA1c was adjusted by the mean baseline HbA1c. All meta-regression coefficients of the mean baseline HbA1c were <0.00, and the meta-regression coefficient was significantly associated with the WMD in HbA1c. The intensity of exercise was not significantly associated with the WMD in HbA1c, and that result did not contain significant heterogeneity. The time and frequency of exercise were not significantly associated with the WMD in HbA1c; these results did not contain significant heterogeneity. However, the overall duration of exercise was significantly associated with the WMD in HbA1c, and those results did not contain significant heterogeneity. Sensitivity analyses indicated no change in that relationship in any.

Supplementary Material 4 shows the results of a meta-regression analysis of the relationship between the exercise level and WMD in BMI; here, the WMD in BMI was adjusted by the mean baseline HbA1c. The intensity, time, frequency, and overall duration of exercise were not significantly associated with the WMD in BMI.

Supplementary Materials 5 and 6 show funnel plots for publication bias with regard to HbA1c and BMI, respectively. Egger’s regression test showed no significant asymmetry in HbA1c and BMI (P = 0.31 and P = 0.35, respectively). Duval and Tweedie’s trim and fill method suggested that four studies were missing HbA1c data and eight studies were missing BMI data. After adjusting for the effects of these missing studies, the pooled WMD in HbA1c was estimated to
### Table 1 Characteristics of the studies

| Study name (year; country) | Subjects | Intervention of exercise | Description (type, intensity, time, and frequency) | Estimated intensity of exercise, METs | Overall duration, weeks |
|---------------------------|----------|--------------------------|--------------------------------------------------|-------------------------------------|------------------------|
| Romnemaa, et al. (1986; Finland) | 25 20.0 52.5 (NR) 7.1 (NR) 92.0 | Walking, jogging or skiing, 70% VO2max, 45 min/session, and 5–7 sessions/week | 7.0 17 |
| Verity, et al. (1993; United States) | 10 100 59.2 (7.9) NR 0.0 | Walking, 65–80% HRR, 60–90 min/week, and 3 sessions/week | 7.6 17 |
| Raz, et al. (1994; Israel) | 38 63.2 56.6 (7.1) NR 100 | Ergometry bicycle, treadmill, and rowing machine, 65% VO2max, 45 min/session, and 3 sessions/week | 5.7 12 |
| Tessier, et al. (2000; Canada) | 39 41.0 69.4 (7.0) 6.5 (5.8) 74.4 | Aerobic exercise: walking, 35–79% HRmax, 20 min/session; aerobic/ resistance exercise: major muscle group, 20 repetitions/set, 2 sets, 20 min/session, and 3 sessions/week | 5.5 16 |
| Tsujuchi, et al. (2002; Japan) | 26 NR 62.9 (7.3) NR NR | Qi-gong relaxation exercise, and 120 min/week | 3.0 17 |
| Cuff, et al. (2003a; Canada) | 15 100 62.3 (6.7) 4.0 (3.1) 73.3 | Aerobic exercise: treadmills, stationary bicycles, recumbent steppers, elliptical trainers, and rowing machines, 60–75% HRR; resistance exercise: five exercises (leg press, leg curl, hip extension, chest press, and latissimus pull-down), 12 repetitions/set, 2 sets; total 75 min/session, and 3 sessions/week | 5.3 16 |
| Cuff, et al. (2003b; Canada) | 14 100 59.6 (7.0) 3.7 (2.6) 71.4 | Treadmills, stationary bicycles, recumbent steppers, elliptical trainers, and rowing machines, 60–75% HRR, 75 min/session, and 3 sessions/week | 7.0 16 |
| Loomaala, et al. (2003; Finland) | 49 0.0 53.8 (6.3) NR 73.5 | Aerobic exercise: jogging or walking, 65–75% VO2max, 30 min/session; resistance exercise: eight exercises for large muscle groups from the trunk and upper and lower extremities, 70–80% maximum voluntary contraction, 10–12 repetitions/set, 3 sets, and 2 sessions/week | 5.1 52 |
| Dela, et al. (2004a; Denmark) | 8 NR 50.1 (4.3) 4.4 (2.7) NR | Ergometer cycle, 40–75% VO2max, 30–40 min/session, and 5 sessions/week or more | 6.9 12 |
| Dela, et al. (2004b; Denmark) | 16 NR 53.6 (8.5) 6.0 (3.9) NR | Ergometer cycle, 40–75% VO2max, 30–40 min/session, and 5 sessions/week or more | 6.9 12 |
| Bjørgaas, et al. (2005; Norway) | 23 0.0 57.4 (7.5) 2.0 (NR) 91.3 | Aerobic exercise: light jogging, co-ordination exercises, knee bends and stretching, 50–85% HRmax, 45 min/session; resistance exercise: no reported type of exercise, 15 min/session, and 2 sessions/week | 5.6 12 |
| Brooks, et al. (2006; United States) | 62 35.5 66.0 (7.0) 9.5 (5.6) 93.5 | Five exercises using pneumatic machines (upper back, chest press, leg press, knee extension, and flexion), 60–80% 1RM, 8 repetitions/set, 3 sets, 35 min/session, and 3 sessions/week | 4.4 16 |
| Gordon, et al. (2006; United States) | 30 50.0 67.0 (8.0) 10.5 (9.9) 93.3 | Five exercises (knee extension, chest press, leg curl, upper back, and leg press), 60–80% of 1 RM, 8 repetitions/set, 3 sets, 45–60 min/session, and 3 sessions/week | 5.0 16 |
| Middlebrook, et al. (2006; United Kingdom) | 55 53.8 63.4 (8.0) 4.4 (4.3) 55.8 | Aerobic exercise (no reported type of exercise), 80% HRmax, 30 min/session, and 3 sessions/week | 5.5 26 |
| Kadoglu, et al. (2007; Greece) | 56 58.9 61.5 (7.4) 6.8 (4.1) 90.0 | Walking or running on the treadmill, cycling, and calisthenics involving the upper and lower limbs, 50–75% VO2max, 30–40 min/session, and 4 sessions/week | 6.2 26 |
| Lam, et al. (2008; Australia) | 44 54.5 62.1 (9.8) NR NR | Tai chi (yang and sun style 20-form), 60 min/session, and 1–2 sessions/week | 3.0 26 |
| Lambers, et al. (2008a; Belgium) | 23 54.3 56.2 (5.9) NR 97.7 | Circuit exercise (walking or jogging, elbow flexion and extension, cycling, knee flexion and extension, and stepping), 60–85% HRR, and 60–85% 1RM, 50 min/session, and 3 sessions/week | 5.6 13 |
| Lambers, et al. (2008b; Belgium) | 24 18.8 53.5 (5.8) NR 97.6 | Walking (or jogging), cycling, stepping, 60–85% HRR, 50 min/session, and 3 sessions/week | 8.0 13 |
| Ribeiro, et al. (2008; Brazil) | 21 66.7 55.2 (8.5) 8.6 (8.0) 85.7 | Cycle-ergometer, AT level and respiratory compensation point, 40 min/session, and 3 sessions/week | 7.0 17 |
| Murrock, et al. (2009; United States) | 38 100 62.6 (7.8) 10.3 (NR) 78.9 | Dance, own pace, 45 min/session, and 2 sessions/week | 4.0 12 |
| Shenoy, et al. (2009a; India) | 14 57.1 52.7 (4.7) 5.3 (2.1) 92.9 | Seven exercises (biceps curls, triceps curls, front lateral pull-down, back lateral pull-down, knee extension exercises, hamstring curls, and abdominal curls), 60–100% 1RM, 10 repetitions/set, 3 sets, and 2 sessions/week | 4.7 16 |
| Shenoy, et al. (2009b; India) | 15 40.0 54.3 (4.5) 4.9 (2.2) 73.3 | Walking, 70% HRmax, 30 min/session, and 3 sessions/week | 6.0 16 |
| Church, et al. (2010a; United States) | 87 60.1 57.2 (4.5) 7.2 (5.5) 100 | Nine exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 10–12 repetitions/set, 2–3 sets, and 2 sessions/week (141 min/week) | 3.5 39 |
| Church, et al. (2010b; United States) | 86 63.1 54.5 (4.5) 7.4 (5.9) 93.5 | Aerobic exercise (no reported type of exercise), 12 kcal/kg/week, and 150 min/week | 6.4 39 |
| Church, et al. (2010c; United States) | 90 64.8 55.9 (4.4) 6.8 (5.4) 97.8 | Aerobic exercise: no reported type of exercise, 10 kcal/kg/week, 150 min/week; resistance exercise: 9 exercises (bench press, seated
| Study name (year; country) | Subjects | Intervention of exercise | Description (type, intensity, time, and frequency) | Estimated intensity of exercise, METs | Overall duration, weeks |
|---------------------------|----------|--------------------------|--------------------------------------------------|-----------------------------------|-------------------------|
| Hosaka, et al. (2010; Japan) | 24 58.3 | 59.0 (8.4) NR NR NR | Aquatic exercise (no reported type of exercise), 70% HRmax, 45 min; resistance exercise: 8 exercises on weight machines (no reported type of exercise), 8 RM, 8 repetitions, 2–3 sets, and 3 sessions/week | 4.0 | 13 |
| Plotnikoff, et al. (2010; Canada) | 48 66.7 | 54.6 (9.3) NR NR NR | Total of 8 exercises, 4 of core exercises (squats, seated row, chest press, shoulder press), and 4 of 9 assistance exercises (lungs, lateral pull-down, standing triceps extension, standing pulley abdominal twists, biceps curl, triceps press, reverse rhomboid flies, lateral pulley defl... | 5.0 | 16 |
| Reid, et al. (2010a; Canada) | 74 34.2 | 53.7 (4.9) 5.2 (4.7) NR | Aerobic exercise: treadmills and/or bicycle ergometers, 60–75% HRmax, 45 min; resistance exercise: 8 exercises on weight machines (no reported type of exercise), 8 RM, 8 repetitions, 2–3 sets, and 3 sessions/week | 5.1 | 26 |
| Reid, et al. (2010b; Canada) | 68 35.1 | 54.8 (4.8) 5.9 (4.7) NR | Eight exercises on weight machines (no reported type of exercise), 8 RM, 8 repetitions, 2–3 sets, and 3 sessions/week | 3.5 | 26 |
| Reid, et al. (2010c; Canada) | 75 35.7 | 54.2 (5.1) 5.1 (3.8) NR | Total of 8 exercises, 4 of core exercises (squats, seated row, chest press, shoulder press), and 4 of 9 assistance exercises (lungs, lateral pull-down, standing triceps extension, standing pulley abdominal twists, biceps curl, triceps press, reverse rhomboid flies, lateral pulley defl... | 3.5 | 12 |
| Sun, et al. (2010a; United States) | 16 NR | 56.3 (8.1) NR 100 | Progressive resistance exercise (no reported type of exercise), 30–60 min/session, and 3 sessions/week | 3.5 | 12 |
| Sun, et al. (2010b; United States) | 16 NR | 56.3 (8.1) NR 100 | Progressive resistance exercise (no reported type of exercise), 30–60 min/session, and 3 sessions/week | 3.5 | 12 |
| Yavari, et al. (2010; Iran) | 60 53.3 | 49.8 (6.7) 4.5 (2.5) 100 | Treadmill, bicycle, elliptical, and/or ergometers, 50–75% HRmax, 50–60 min/session, and 3 sessions/week | 5.2 | 16 |
| Belli, et al. (2011; Brazil) | 19 100 | 54.7 (7.4) 4.1 (3.2) 78.9 | Walking, VT intensity, 20–60 min/session, and 3 sessions/week | 7.5 | 12 |
| Kuran, et al. (2011; Turkey) | 60 51.7 | 53.7 (7.0) 6.4 (4.9) 100 | Walking, moderate-intensity, 50 min/session, and 3 sessions/week | 4.0 | 13 |
| Kwon, et al. (2011a; Republic of Korea) | 21 100 | 56.8 (5.9) 6.0 (6.0) 100 | Brisk walking using an accelerometer, moderate-intensity (3.6–6.0 METs), 60 min/session, and 5 sessions/week | 3.1 | 12 |
| Kwon, et al. (2011b; Republic of Korea) | 20 100 | 57.3 (6.0) 4.7 (3.6) 100 | Ten exercises using bands (bicep curls, tricep extensions, upright row, shoulder chest press, seated rows, trunk side bends, leg press, hip flexions, leg flexions, and leg extensions), 1.2–3.2 kg of resistance, 3 sets, 40 min/session, and 3 sessions/week | 4.8 | 12 |
| de Oliveira, et al. (2012a; Brazil) | 15 58.0 | 52.4 (6.3) 5.4 (4.0) 100 | Cycle-ergometer, LT intensity, 20–50 min/session, and 3 sessions/week | 6.7 | 12 |
| de Oliveira, et al. (2012b; Brazil) | 14 62.1 | 53.9 (6.5) 7.0 (3.8) 100 | Circuit of 7 exercises (leg press, bench press, lateral pulley deltoid raise, or pulley abdominal curls), 50% 1RM, 10 repetitions/set, 1–4 sets, and 3 sessions/week | 4.9 | 12 |
| de Oliveira, et al. (2012c; Brazil) | 14 62.1 | 56.6 (6.5) 6.7 (4.6) 100 | Aerobic exercise: cycle-ergometer, LT intensity, 10–25 min/ session; resistance exercise: circuit of 7 exercises (leg press, bench press, lat pull down, seated rowing, shoulder press, abdominal curls, and knees curls), 50% 1RM or 8–12 RM, 15 repetitions/set, 1–4 sets; half the volume of aerobic and resistance exercise, and 3 sessions/week | 4.0 | 12 |
| Nuttamonwarakul, et al. (2012; Thailand) | 40 60.0 | NR NR NR | Aquatic exercise (no reported type of exercise), 70% HRmax, 30 min/session, and 3 sessions/week | 4.5 | 12 |
| Swift, et al. (2012a; United States) | 62 62.4 | 56.3 (5.1) 7.5 (5.7) 94.7 | Aerobic exercise (no reported type of exercise), 50–80% VO2max, and 122 min/week (average) | 8.0 | 39 |
| Swift, et al. (2012b; United States) | 70 58.1 | 58.7 (4.8) 7.6 (5.6) 99.6 | Nine exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 2–3 sets, 10–12 repetitions, and 3 sessions/week | 3.5 | 39 |
| Swift, et al. (2012c; United States) | 71 63.0 | 57.0 (4.7) 6.8 (5.5) 98.2 | Aerobic exercise: no reported type of exercise, 50–80% VO2max; resistance exercise: 9 exercises (bench press, seated row, shoulder press, pull down, leg press, extension, flexion, abdominal crunches, and back extensions), 10–12 repetitions/set, 2–3 sets and 106 min/week (average) | 5.8 | 39 |
| Tan, et al. (2012; China) | 25 64.0 | 65.5 (6.7) 16.2 (6.9) 100 | Aerobic exercise: walking/running, 55–70% HRmax, 30 min; resistance exercise: 5 leg exercise (knee flexion, knee extension, hip abduction, hip adduction, and standing calf raise), 50–70% IRM, 10–12 repetitions/set, 2 set, 10 min, and 3 sessions/week | 4.8 | 26 |
| Fritz, et al. (2013; Sweden) | 47 34.0 | 61.2 (7.2) 5.1 (3.7) 64.0 | Nordic walking, a pace with slight shortness of breath and perspiration, and 3.9 hours/week | 3.5 | 17 |
| Karstoft, et al. (2013a; Denmark) | 16 34.4 | 59.9 (5.7) 5.8 (5.0) 59.4 | Continuous-walking, 55% of the peak energy-expenditure, 60 min/session, and 5 sessions/week | 5.5 | 17 |
| Karstoft, et al. (2013b; Denmark) | 16 40.6 | 57.4 (5.7) 3.8 (3.0) 59.4 | Continuous-walking, 55% of the peak energy-expenditure, 60 min/session, and 5 sessions/week | 5.5 | 17 |
| Study name (year; country) | Intervention of exercise                                                                 | Subjects | n | Male, % | Mean age, years (SD) | T2DM, duration, years (SD) | 2%ME, % | Estimated intensity of exercise, METs | Overall duration, weeks |
|---------------------------|-----------------------------------------------------------------------------------------|----------|---|---------|---------------------|--------------------------|--------|-------------------------------------|------------------------|
| Sparks, et al. (2013a; Netherlands) | Interval-walking, consisting of 3 min fast walking and 3 min slow walking above or below the target of 70% of the peak energy-expenditure, 60 min/session, and 5 sessions/week | 15 | 58.0 | 55.5 (5.0) | 6.6 (6.0) | NR | 8.0 | 39 |
| Sparks, et al. (2013b; Netherlands) | Aerobic exercise (no reported type of exercise), 50–80% VO2peak, and 150 min/week | 21 | 55.7 | 55.4 (5.0) | 8.8 (6.4) | NR | 3.5 | 39 |
| Sparks, et al. (2013c; Netherlands) | Aerobic exercise: 9 exercises (bench press, seated row, shoulder press, lat pull down, leg press, leg extension, leg flexion, abdominal crunches, and back extensions), 10–12 repetitions/set, 2–3 sets, 45–50 min/session, and 3 sessions/week | 15 | 58.0 | 60.5 (4.2) | 6.1 (4.0) | NR | 7.9 | 38 |
| Youngwanichsetha, et al. (2013; Thailand) | Tai chi qigong exercise, 50 min/session, and 3 sessions/week | 64 | 100 | 35.6 (5.3) | 2.6 (1.2) | 0.0 | 3.0 | 12 |
| Mitravan, et al. (2014a; Thailand) | Continuous aerobic exercise, 50–65% VO2peak, 30 min/session, and 3 sessions/week | 22 | 63.6 | 61.4 (7.3) | 20.9 (1.7) | 100 | 5.1 | 12 |
| Mitravan, et al. (2014b; Thailand) | Interval aerobic exercise (no reported type of exercise), 50–85% VO2peak, 30 min/session, and 3 sessions/week | 22 | 63.6 | 61.1 (7.3) | 20.3 (1.7) | 100 | 5.5 | 12 |
| Yan, et al. (2014; United States) | No reported type of exercise, 50–75% VO2peak, 45 min/session, and 3–5 sessions/week | 41 | 0.0 | 53.5 (5.9) | NR | 90.2 | 5.7 | 12 |
| Dede, et al. (2015; Turkey) | Treadmill, 60–75% HRmax, 45 min/session, and 3 sessions/week | 60 | 51.7 | 54.0 (7.9) | 6.4 (4.9) | 100 | 6.5 | 12 |
| Lee, et al. (2015; Taiwan) | Brisk walking, jogging, or riding an exercise bike, 60–80% HRmax, 30 min/session, and 5 sessions/week | 80 | 51.3 | 56.1 (8.5) | 7.4 (5.7) | NR | 5.8 | 12 |
| Park, et al. (2015; Republic of Korea) | Aerobic exercise: stationary bicycle and cross-walker, 9–14 RPE, 3–5/set, 1–3 sets; circuit exercise: strengthening exercise, 6 exercises (leg extension, leg curl, seated row, standing chest press, and back extensions), 30 min/session, and 3 sessions/week | 37 | 54.1 | 70.7 (5.4) | NR | 97.3 | 4.0 | 12 |
| Xiao, et al. (2015; China) | Tai chi ball, 60–120 min/session, and 3 sessions/week | 32 | NR | 65.5 (NR) | NR | NR | 3.0 | 13 |
| Cassidy, et al. (2016; United Kingdom) | High-intensity intermittent exercise: cycle ergometry, RPE 9–17, 4–5 min/set, 3 sets; resistance exercise: 4 exercises using bands (face pull, horizontal push, horizontal pull, and 30° pull), 1 min/set, 4 set, and 3 sessions/week | 23 | 21.7 | 60.0 (8.2) | 4.5 (2.6) | 100 | 4.8 | 12 |
| Keshavarz, et al. (2016; Iran) | Rhythmic movements, 60% HRmax, 20–45 min/session, and 3 sessions/week | 20 | 100 | 49.4 (6.2) | 7.6 (4.3) | 100 | 3.8 | 12 |
| Tomas-Carus, et al. (2016; Portugal) | Aerobic exercise: no reported type of exercise, 60–65% HRmax, 25 min/session; resistance exercise: lower and upper limbs (using subject’s own weight as resistance, lightweight loads, or soft rubber bands), 15 min/session, and 3 sessions/week | 30 | 43.3 | 59.4 (6.3) | 10.4 (7.0) | NR | 4.0 | 12 |
| Annibalini, et al. (2017; Italy) | Aerobic exercise: walking, 40–65% HRmax, 60 min/session, and 12–20 repetitions/set, 2–4 sets, and 4–6 sessions/week | 16 | 0.0 | 58.5 (7.3) | 9.0 (6.3) | 100 | 5.7 | 16 |
| Bottone, et al. (2018; Brazil) | Functional exercises (squat and steps up and down), additional load or step if <6 on OMNI scale, 10–15 repetitions/set, 2–3 sets; traditional exercises: 9 exercises (leg press, leg extension, leg curl, hip abduction, inclined bench press, low row, biceps curl, triceps, and crank), 12–15 RM, 10–12 repetitions/set, 2–3 sets, and 3 sessions/week | 26 | 42.3 | 69.6 (7.7) | 11.0 (7.7) | 100 | 3.0 | 12 |
| Hsieh, et al. (2018; Taiwan) | Eight exercises (chest press, shoulder press, biceps curl, hip abduction, standing hip flexion, leg press, standing calf raise, and abdominal crunch), 40–75% 1RM (or Borg scale 12–16), 8–12 repetitions/set, 3 sets, and 3 sessions/week | 30 | 63.3 | 71.2 (6.8) | 12.5 (7.3) | NR | 8.0 | 12 |
| Stubbs, et al. (2019a; United States) | Treadmill walking, 71–90% VO2peak, 30–45 min/session, and 3 sessions/week | 15 | 6.7 | 61.7 (5.4) | 11.4 (6.7) | 100 | 6.8 | 12 |
| Stubbs, et al. (2019b; United States) | Leg extensions, 10 repetitions/set, 3–6 sets, and 3 sessions/week | 15 | 0.0 | 63.3 (5.4) | 10.8 (8.1) | 100 | 2.8 | 12 |
| Stubbs, et al. (2019c; United States) | Aerobic exercise: treadmill walking, 71–90% VO2peak, 30–45 min/session, and 3 sessions/week | 15 | 6.7 | 62.5 (5.4) | 9.9 (7.9) | 100 | 6.4 | 12 |

*AT* anaerobic threshold, *HR*$_{max}$ maximum heart rate, *HRR* heart rate reserve, *LT* lactate threshold, *MED* subjects taking medication, *METs* metabolic equivalents, *n* number of subjects; *NR* not reported, *RM* repetition maximum; SD standard deviation, *T2DM* type 2 diabetes mellitus, *VO2peak* peak oxygen uptake, *VO2max* maximal oxygen uptake, *VT* ventilation threshold
Table 2 Baseline and form of exercise data

| Characteristic                              | n (%)       |
|---------------------------------------------|-------------|
| Female                                      | 1192 (52.4) |
| Age, years [mean (SD)]                      | 55.2 (6.4)  |
| BMI, kg/m² [mean (SD)]                      | 31.4 (5.0)  |
| Duration of T2DM, years [mean (SD)]        | 7.2 (5.1)   |
| Subjects with medication, % [mean (SD)]    | 88.1 (21.9) |
| Intensity of exercise, METs [mean (SD)]    | 5.1 (1.4)   |
| Time of exercise, min/session [mean (SD)]  | 54 (17)     |
| Frequency of exercise, sessions/week [mean (SD)] | 3.2 (0.9) |
| Overall duration of exercise, weeks [mean (SD)] | 21.5 (11.3) |

BMI body mass index, METs metabolic equivalents, n number of subjects, SD standard deviation, T2DM type 2 diabetes mellitus

be −0.5% (95% CI, −0.6 to −0.4; Q = 119.0, P < 0.05 for heterogeneity, I² = 39.5%), and the pooled WMD in BMI was estimated to be −0.55 kg/m² (95% CI, −0.59 to −0.51; Q = 32.7, P > 0.05 for heterogeneity, I² = 0.0%).

The certainty of evidence

The study limitations (risk of bias) domain was ranked as serious, but there were no serious concerns in other domains (the inconsistency, indirectness, imprecision, and publication of bias). Thus, there was a moderate level of evidence for a decrease in HbA₁c as a result of exercise.

Discussion

This systematic review and meta-analysis were conducted to evaluate the effect of exercise on HbA₁c in T2DM patients. The results indicated a decrease in HbA₁c; however, the effect contained heterogeneity. In addition, results of meta-regression analyses indicated that changes in HbA₁c were associated with the overall duration of exercise (weeks) but not the intensity (METs), time (min/session), or frequency (sessions/week) of exercise.

Comparison with other studies

Several previous meta-analyses reported a decrease in HbA₁c as a result of exercise [19–31]. However, the meta-analyses involved aerobic exercise or resistance exercise alone and the observed effects contained heterogeneity [19, 20, 22, 23, 30], indicating that the effect on HbA₁c differed among RCTs even if those RCTs were limited to studies involving the same type of exercise. The current study assumed that the effect on HbA₁c was affected by the exercise level. Results of analyses indicated that the intensity, time, and frequency of exercise were not associated with changes in HbA₁c, and those results were similar to the results of an analysis limited to RCTs involving aerobic exercise. Thus, differences due to the type of exercise presumably have no effect on the improvement of HbA₁c. Notably, a meta-analysis that evaluated the percentage of T2DM patients who dropped out from an exercise intervention reported that a protocol involving vigorous exercise resulted in a higher percentage of drop-outs in comparison to moderate-intensity exercise [47]. Given that a difference in intensity of exercise did not affect the improvement in HbA₁c, T2DM patients should probably perform an exercise at low to moderate intensity. In fact, meta-analyses of studies involving low to moderate-intensity exercises, such as walking [20, 30], yoga [30], or tai chi [27], reported that these types of exercise were associated with HbA₁c improvement.

Since the current study indicated that changes in HbA₁c were associated with the overall duration of exercise and that heterogeneity in the changes improved, the overall duration of exercise may depend on changes in HbA₁c, and it may be a cause of that heterogeneity. However, these results indicated that exercise for an extended duration was associated with an increase in HbA₁c. Therefore, the current results may mean that improvement in HbA₁c becomes evident early on in T2DM patients (at approximately 12 weeks). A previous systematic review and meta-analysis involving adults without exercise habits reported that fasting blood glucose, fasting insulin, and HOMA-IR did not decrease significantly as a result of resistance exercise for 24 weeks or longer but did decrease significantly as a result of that form of exercise for 7–23 weeks, and the decrease was greater than that as a result of exercise for 24 weeks or longer [48]. Subjects of this previous systematic review and meta-analysis were not limited to T2DM patients, and HbA₁c was not evaluated [48]. However, the results of that review and meta-analysis did agree with the current results in one regard: neither found that prolonged exercise had a beneficial effect on indices of glucose metabolism. One reason for this is that all of the RCTs analyzed in this meta-analysis involved an exercise intervention alone (without diet, medication, or lifestyle modifications). Although in the minority, a previous meta-analysis reported that HbA₁c decreased as a result of a combination of diet and exercise recommendations but was not by the recommendation of exercise alone [26]. In addition, a recent meta-analysis on nutrition reported that HbA₁c and BMI improved in the short term following intervention in the form of a low-carbohydrate diet alone; however, these effects were not sustained over the long term [49]. Thus, previous studies and the current study only indicated the effect of intervention in the form of nutrition or exercise alone, instead of evaluating the effects of multiple interventions. A meta-analysis of RCTs involving subjects without T2DM reported that exercise and diet significantly decreased the incidence of T2DM while exercise alone or diet alone did not [50]. Thus, intervention combining exercise and diet may be essential to alleviate T2DM. A recent meta-analysis of cohort
### Baseline mean HbA1c and forest plot for the WMD in the HbA1c. Each study is presented by black squares (WMD) and width (95% CI). The pooled WMD is represented by black rhombuses and widths (95% CI). HbA1c, hemoglobin A1c, WMD weighted mean difference
Table 3 Results of sensitivity analyses of study on HbA1c

| Category                        | N (n) | Baseline (SD) | Pooled WMD (95% CI) | Q   | I² (%) |
|---------------------------------|-------|---------------|---------------------|-----|--------|
| Mean age ≥40 years              | 47 (2331) | 7.6 (1.3)    | −0.5 (−0.6 to −0.4) | 103.1⁺ | 37.0   |
| Mean baseline HbA1c ≥6.5%       | 47 (2370) | 7.6 (1.3)    | −0.5 (−0.6 to −0.4) | 103.7⁺ | 37.4   |
| Mean duration of T2DM ≥5.0 years| 28 (1598) | 7.5 (1.1)    | −0.5 (−0.6 to −0.4) | 73.2⁺   | 42.0   |
| Mean baseline BMI ≥30 kg/m²      | 29 (1701) | 7.6 (1.2)    | −0.4 (−0.5 to −0.3) | 73.8⁺   | 39.9   |
| Calculation of the WMD in BMI   | 35 (1730) | 7.6 (1.3)    | −0.4 (−0.5 to −0.3) | 79.7⁺   | 38.3   |
| Aerobic exercise alone          | 28 (1046) | 7.7 (1.4)    | −0.5 (−0.7 to −0.3) | 45.7⁺   | 39.6   |
| Rate of subject drop-out ≤10%   | 27 (1286) | 7.6 (1.2)    | −0.5 (−0.6 to −0.4) | 43.0⁺   | 37.4   |
| Did not include a high risk of bias | 42 (2183) | 7.5 (1.2)    | −0.5 (−0.6 to −0.4) | 98.6⁺   | 42.3   |

BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; N, number of studies; n, number of subjects; SD, standard deviation; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

⁺Significant heterogeneity (P < 0.05)

Table 4 The relationship between the WMD in HbA1c and the intensity or time of exercise according to a meta-regression analysis and sensitivity analysis

| Category                        | Intensity of exercise [METs] | Time of exercise [min/session] |
|---------------------------------|------------------------------|--------------------------------|
|                                | MRC (95% CI) | R², % | Q | I², % | MRC (95% CI) | R², % | Q | I², % |
| Studies not limited             | 0.01 (−0.05 to 0.07) | 41.5 | 81.7 | 24.4 | 0.01 (−0.34 to 0.36) | 47.2 | 71.7 | 21.4 |
| Mean age ≥40 years              | 0.01 (−0.06 to 0.07) | 42.6 | 81.5 | 25.0 | 0.01 (−0.34 to 0.36) | 44.4 | 71.6 | 22.2 |
| Mean baseline HbA1c ≥6.5%       | 0.01 (−0.05 to 0.07) | 47.3 | 79.6 | 23.5 | 0.02 (−0.33 to 0.36) | 50.9 | 69.9 | 20.5 |
| Mean duration of T2DM ≥5.0 years| 0.02 (−0.05 to 0.10) | 30.2 | 56.9 | 32.6 | −0.22 (−0.76 to 0.33) | 34.0 | 48.5⁺ | 29.1 |
| Mean baseline BMI ≥30 kg/m²      | −0.02 (−0.09 to 0.05) | 54.0 | 51.6 | 22.4 | 0.13 (−0.27 to 0.54) | 54.0 | 46.1 | 21.0 |
| Calculation of the WMD in BMI   | 0.02 (−0.05 to 0.08) | 42.9 | 58.9 | 25.5 | 0.08 (−0.34 to 0.49) | 44.9 | 51.9 | 22.6 |
| Aerobic exercise alone          | 0.08 (−0.01 to 0.17) | 62.9 | 30.7 | 18.3 | −0.06 (−0.67 to 0.54) | 33.9 | 32.9 | 26.5 |
| Rate of subject drop-out ≤10%   | −0.02 (−0.10 to 0.07) | 27.0 | 32.6 | 28.3 | −0.17 (−0.81 to 0.47) | 35.1 | 26.9 | 24.2 |
| Did not include a high risk of bias | 0.01 (−0.05 to 0.08) | 42.6 | 77.3⁺ | 29.0 | 0.00 (−0.36 to 0.36) | 44.3 | 67.3 | 26.3 |

BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; METs, metabolic equivalents; MRC, meta-regression coefficient; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

⁺Significant heterogeneity (P < 0.05)

Table 5 The relationship between the WMD in HbA1c and the frequency or overall duration of exercise according to a meta-regression analysis and sensitivity analysis

| Category                        | Frequency of exercise [sessions/week] | Overall duration of exercise [weeks] |
|---------------------------------|--------------------------------------|-------------------------------------|
|                                | MRC (95% CI) | R², % | Q | I², % | MRC (95% CI) | R², % | Q | I², % |
| Studies not limited             | −0.04 (−0.16 to 0.08) | 54.7 | 70.7 | 18.7 | 0.01 (0.002−0.016) | 70.0 | 72.3 | 14.7 |
| Mean age ≥40 years              | −0.04 (−0.16 to 0.08) | 53.7 | 70.5 | 19.5 | 0.01 (0.002−0.016) | 68.5 | 72.3 | 15.4 |
| Mean baseline HbA1c ≥6.5%       | −0.05 (−0.17 to 0.07) | 60.0 | 68.6 | 17.5 | 0.01 (0.002−0.017) | 74.5 | 69.8 | 13.1 |
| Mean duration of T2DM ≥5.0 years| 0.03 (−0.15 to 0.20) | 32.1 | 49.8⁺ | 29.0 | 0.01 (0.002−0.018) | 67.9 | 48.1 | 18.5 |
| Mean baseline BMI ≥30 kg/m²      | −0.21 (−0.46 to 0.04) | 62.0 | 51.3 | 17.4 | 0.01 (0.003−0.018) | 72.0 | 47.2 | 17.0 |
| Calculation of the WMD in BMI   | −0.12 (−0.29 to 0.05) | 63.3 | 48.7 | 16.3 | 0.01 (0.002−0.017) | 69.4 | 51.4 | 15.2 |
| Aerobic exercise alone          | 0.28 (−0.15 to 0.20) | 35.5 | 33.0 | 26.6 | 0.01 (0.003−0.024) | 99.9 | 27.3 | 0.0 |
| Rate of subject drop-out ≤10%   | −0.03 (−0.23 to 0.17) | 43.2 | 25.6 | 21.1 | 0.01 (0.002−0.018) | 59.3 | 28.5 | 20.6 |
| Did not include a high risk of bias | −0.03 (−0.17 to 0.11) | 50.8 | 66.7 | 24.0 | 0.01 (0.002−0.017) | 70.5 | 67.2 | 17.0 |

BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; MRC, meta-regression coefficient; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference. *Significant heterogeneity (P < 0.05)
studies found that the combination of exercise and diet should be emphasized for T2DM patients [18]. RCTs and/or meta-analyses of multiple interventions should be conducted in the future.

Mechanisms

The mechanisms responsible for the alleviation of T2DM by exercise have been attributed to several physiological processes [51]. Several epidemiological studies reported that BMI was associated with insulin resistance [52, 53]; the current study indicated that BMI was significantly decreased as a result of exercise but that the effect did not contain significant heterogeneity; changes in BMI were not significantly associated with the exercise level. Thus, a decrease in HbA1c may differ from changes in BMI. In addition, adipocytokines dramatically affect the action of insulin. A previous meta-analysis of RCTs involving T2DM patients examined the effects of exercise on adipocytokines; the results indicated improvements in leptin and interleukin-6 but no change in adiponectin [54]. Interleukin-6 is considered to a factor associated with enhanced insulin secretion [55]; thus improvement in interleukin-6 as a result of exercise may cause a decrease in HbA1c. However, few studies have evaluated adipocytokines [Bjørgaas, et al., Gordon, et al., Kadoglou, et al., Lam, et al., and Dede, et al.; Supplementary Material 2], a fact that became apparent from the RCTs analyzed in the current study. Furthermore, the mechanisms underlying the lack of decrease in HbA1c after continued exercise, a finding from the current study, are unclear. Although a stand-alone finding, a systematic review suggested that continued exercise inhibited the gastrointestinal function and depressed the immune system in healthy individuals [56]. Excessive exercise may have some effect on the immune system and/or glucose metabolism. The underlying mechanisms should be investigated in the future.

Strengths and limitations

One strength of the current meta-analysis is that it attempted to account for the effects of confounding factors in order to indicate the relationship between the exercise level and HbA1c. Subject characteristics (age, state of blood glucose levels at baseline, duration of T2DM, and overweight), rate of subject drop-out, and the form of exercise (aerobic exercise alone) were considered in sensitivity analyses, and the results did not change even when analyses were limited to certain RCTs. Furthermore, the change in HbA1c was adjusted based on the mean baseline level in the current meta-regression analyses; thus, the influence of the aforementioned factors was presumably minimized. In addition, previous studies [19–31] did not assess the quality of each RCT using the version 2 of the risk of bias tool [37] and/or evidence overall using the GRADE approach [46], so evidence of the effects of exercise on HbA1c in T2DM patients may have been insufficient. The use of these assessments in the current study is presumably another one of its strengths. Nevertheless, approximately 10% of the RCTs analyzed in the current study included a high risk of bias and in particular, had issues in terms of the random allocation process and/or missing outcome data, so this study had limitations. The influence of this bias contributed to a moderate level of evidence overall according to the GRADE approach. When studies were limited to those not including a high risk of bias in sensitivity analyses, heterogeneity did not change as a result of exercise. However, these issues with the intervention need to be considered and addressed in the future.

Another limitation of this study is that the findings did not provide sufficient evidence of the effect of exercise over a prolonged period. All RCTs analyzed in this systematic review and meta-analysis involved an intervention for ≤1 year; thus, a systematic review and meta-analysis of RCTs involving an exercise intervention for ≥1 year should be conducted.

Conclusions

In conclusion, the current results indicated that HbA1c decreased as a result of the intervention of exercise in T2DM patients; however, exercise for an extended duration was associated with an increase in HbA1c. Therefore, the effects of exercise may be evident early on, but exercise for a prolonged period alone may increase HbA1c.

Data availability

All data are available in submitted paper or as electronic supplementary material.

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