

Delayed effect of different exercise modalities on glycaemic control in type 1 diabetes mellitus: a systematic review and meta-analysis

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Author Contributions

GV and RDN designed the review and meta-analysis. GV was the principal investigator and guarantor. GV and RDN were the main coordinators of the review. GV, DM and GT conducted the review. RDN and GT performed statistical analyses. GV wrote the

studies with the support of DM, GT and RDN. All authors revised and approved the final version of the manuscript.

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Abstract

Aims: Exercise is known to prevent the onset of comorbidities and complications in type 1 diabetes mellitus (T1DM). Despite these benefits, people living with T1DM are often insufficiently physically active and this is mainly due to the fear of hypoglycaemia. Research using continuous glucose monitoring devices has shown that exercise affects glycaemic control in T1DM for over 24 hours. The aim of this systematic review and meta-analysis is therefore to investigate the delayed effects of different exercise modalities on glycaemic control in adults with T1DM.

Data Synthesis: The literature search of experimental studies was conducted on PubMed, SPORTDiscus and EMBASE from January 2009 to September 2019. Twelve studies were included in the review. Compared to endurance, intermittent exercise increased the time spent in hypoglycaemia (0.62, 0.07 to 1.18; standardised effect size, 95% CI) and reduced the mean interstitial glucose concentration (-0.88, -1.45 to -0.33). No clear differences emerged in the time spent in hyperglycaemia (-0.07, -0.58 to 0.45) or in the proportion of exercisers experiencing hypoglycaemic events (0.82, 0.45 to 1.49; proportion ratio, 95% CI) between conditions. The systematic review also found a reduced risk of hypoglycaemia if exercise is performed in the morning rather than in the afternoon, and with a 50% rapid-acting insulin reduction.

Conclusions: For the first time, we systematically investigated the delayed effect of exercise in adults with T1DM, highlighting undetected effects and providing advice to future investigators to obtain more comparable results and improve exercise prescription in T1DM.

Keywords: Exercise, Type 1 diabetes, Glycaemic control, Hypoglycaemia.

Highlights:

- Exercise modalities influence the glycaemic response late after exercise
- The glycaemic response to exercise is different in the early and late recovery
- Aerobic exercise is recommended for glycaemic control late after exercise
- Rapid-acting insulin reduction and diurnal variations affect glycaemic control
- Criteria to standardise future research in this area are provided

1. Introduction

Type 1 diabetes mellitus (T1DM) is a chronic disease characterised by the progressive and irreversible destruction of the pancreatic β-cells due to an autoimmune reaction against these cells responsible for producing insulin [1]. T1DM affects 425 million people worldwide [2], and data from extensive epidemiologic studies indicate that the incidence of T1DM has been increasing by 2–5% in ten years [3].

The progressive damage of the pancreatic β-cells results in a reduction of insulin production up to its complete absence, and this requires individuals living with T1DM to monitor the blood glucose level and to normalise it by insulin supplementation [1]. Multiple external factors, such as dietary intake [4] and physical activity [5], can modify glycaemic levels and require people living with T1DM to modify the quantity and frequency of insulin injections as needed [6].

Despite the exogenous insulin use, in prolonged exposure to the condition, T1DM increases the risk of developing comorbidities and complications [7] compared to subjects without diabetes. These comorbidities, of which the most common are in charge of the microvascular (retinopathy, neuropathy and nephropathy) and macrovascular system (coronary heart disease, cerebrovascular disease and peripheral vascular disease), can drastically reduce the quality of life [8] and will eventually lead to an increased mortality of adults with T1DM [9].

Exercise is a powerful prevention tool against the development of these comorbidities [10, 11], and its ability to improve health and reduce mortality in the general population is maintained for T1DM. In fact, increasing evidence shows how physical activity in T1DM is inversely associated with cardiovascular risk factors (e.g., obesity, dyslipidemia and hypertension) and ketoacidosis; and how long-term complications, such as peripheral neuropathy and retinopathy, are reduced in more physically active people [12, 13]. Furthermore, exercise is associated with a lower risk of premature all-cause and cardiovascular mortality in individuals living with T1DM [14]. A final consideration of the possible health benefits of exercise in this population is due. The ability of exercise to reduce glycated haemoglobin (HbA1c) in T1DM has been investigated for a long time,

but always struggled between contradictory results [15, 16]. However, a recent extensive study identified an inverse relationship between both [12], adding further good reasons for the practice of exercise.

In spite of all the benefits that exercise can have for this population, children with T1DM engage in less physical activity than their peers without diabetes. This trend is carried into adulthood, as adults with T1DM are less active than their healthy counterpart [17]. This low compliance to exercise prevents people with T1DM from obtaining benefits from physical activity and indirectly exposes them to higher risks and premature mortality [18].

To increase the level of physical activity in people living with T1DM, however, it is not enough to act as in the general population, but specific disease-related barriers must be considered. The highest barrier to regular physical activity is the fear of hypoglycaemia, followed by work schedule, loss of control over diabetes, and low levels of fitness. Otherwise, perceived well-being, knowledge of insulin pharmacokinetics, social support, and the knowledge of strategies to reduce the exercise-induced hypoglycaemia, are associated with fewer barriers [19, 20]. In light of this, it is essential to know exactly how exercise can modify glycaemia and which is the best strategy to decrease or avoid the occurrence of exercise-induced hypoglycaemia. Furthermore, this knowledge should be known by doctors and coaches and shared with persons with diabetes in order to increase their understanding and decrease the fear of exercise.

Despite the importance and significance of the aforementioned, exercise prescription for T1DM is based on limited and conflicting evidence [21]. Upon examination of these studies, it is clear how, only recently, researchers focused their attention on the delayed effect that exercise can have on glycaemic control. This delayed effect is often masqueraded by proactive behaviours but during the night, the inability of patients to monitor glycaemia can expose them to severe hypoglycaemic events that could be harmful or life-threatening [22].

Based on the necessity of people living with T1DM to exercise and have a clear understanding of the impact that exercise can have on their long-term glycaemic control, the main

aim of this systematic review and meta-analysis is to investigate the effect of different exercise modalities on glycaemic control in adults with T1DM; with particular focus on the delayed responses and differences between exercise types. In-depth review of the studies will then be oriented in the investigation of the impact that exercise parameters, diurnal variations and rapid-acting insulin reduction (RAIR) can have on glycaemic control.

We addressed particular attention on exercise types, exercise parameters, diurnal variations and RAIR because these parameters can profoundly affect glycaemic control . At the same time, these parameter can be easily modified by a physician or exercise physiologist who prescribes and monitors exercise in order to obtain the best possible outcome.

2. Methods

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [23] and follows the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [24]. The review protocol was written following the PRISMA-P recommendation [25].

2.1 Identification of Studies

A structured electronic literature search was conducted following the PRISMA statement. Three electronic databases (PubMed, SPORTDiscus and EMBASE) were searched from January 2009 to September 2019 included.

The following search strings were used on PubMed: (Type 1 diabetes OR Ketosis-Prone Diabetes Mellitus OR Autoimmune Diabetes OR Insulin-Dependent Diabetes OR IDDM) AND (exercise* OR High-Intensity Interval OR HIIT OR Motor activit* OR Sport* OR Gymnastic* OR Physical Activit*) AND (blood glucose OR blood sugar* OR Glucose fluctuation* OR Glucose variability OR Hyperglycemi* OR Hypoglycemi* OR Glycemic Control OR TIR OR time in range).

78 The search strings were modified for SPORTDiscus and EMBASE adding "NOT type 2
79 diabetes" after the addition of research filters. Studies were filtered by "year" and "clinical trials"
80 on PubMed and EMBASE, by "year" and "academic journals" on SPORTDiscus. Three more
81 studies were found screening the reference lists in sector-specific reviews [5, 21, 26]. After
82 duplicates were removed, studies were initially assessed by screening titles and abstracts. If
83 suitability could not be determined during this process, full-text studies were accessed and
84 compared against inclusion criteria.

85 *2.2 Selection Criteria*

86 Two authors (GV and DM) independently assessed the eligibility of studies for inclusion
87 using the criteria below, and they consulted with the other two authors (RDN and GT) in case of
88 disagreement. The independent assessment was carried out using Rayyan QCRI [27], thereby
89 blinding the individual work. Studies within a specific ten-year timeframe, from January 2009 to
90 September 2019, were considered for the review. The decision of limiting the review in this manner
91 was based on the growth and widespread use of continuous glucose monitoring (CGM) devices
92 during this period, which is known to have significantly increased the reliability of glycaemic
93 detection [28, 29]. By default, studies monitoring glycaemia without CGM systems were excluded.
94 Only studies involving adults were considered and whilst studies involving both males and females
95 were preferred, studies with only gender profile were also included. The following additional
96 inclusion criteria were applied during the selection of the studies:

97 1. The follow-up period must be longer than 6h in order to evaluate the delayed effects of
98 exercise.
99 2. Studies need to assess at least one aspect of glycaemic control (e.g., the frequency of hypo-
100 or hyperglycaemic events, their intensity, or any other measure of glycaemic control and/or
101 variability).
102 3. The exercising population must be free of any complication, disease, pregnancy and any
103 health impairment different from T1DM.

4. Studies with other interventions (e.g., minor nutritional interventions) can be included in the study but must be reported in the table summarizing the outcomes and weighted during the analyses. Furthermore, any other intervention different from exercise must not cause a major risk of bias.
5. Results must be reported with numerical values, studies with only qualitative results such as "improved" or "worsened" cannot be included in the review.
6. Studies must be peer-reviewed and the full text should be available in the English language.
7. Studies different from randomised controlled trials (RCT) can be included if their results can strengthen the review, however, their quality must be assessed carefully together with their risk of bias.

All the authors agreed on the systematic review protocol before the data extraction and analyses, and then strictly followed it in order to avoid any interference in the objective evaluation of the literature.

2.3 Critical Appraisal

The critical appraisal and the risk of bias assessment were conducted in agreement with the Cochrane guidelines [30]. Six items were evaluated to assess the quality of the outcomes (study design, risk of bias, inconsistency, indirectness, imprecision, publication bias) and all the results were provided after the individual assessment of each study reporting the specific outcome. Quality of the evidence is reported in the result section (Table 2) and affected the discussion of findings. For the evaluation of each outcome was followed the same protocol [30]:

1. Identify whether the evidence for that outcome comes from RCTs (where the rating starts at HIGH quality) or non-RCTs (where the rating starts at LOW quality).
2. Systematically work through each of the GRADE criteria, deciding whether to downgrade and/or upgrade the quality of the evidence and by how much.
3. Keep a comprehensive and transparent record of the reasons for all the decisions about rating the quality of the evidence.

4. Come to an agreement about the overall quality of the evidence for that outcome.

Data extraction and quality assessment were independently performed by two reviewers (GV and DM), and inconsistencies solved by consensus.

2.4 Meta-Analyses

A number of metrics were used to assess the four different outcomes. Differences in the number of exercisers experiencing hypoglycaemic events was evaluated as a risk ratio – i.e., as the difference in the proportions of individuals in the intermittent (INT) and endurance (END) exercising conditions experiencing hypoglycaemic events. The following scale was used to interpret the magnitude of this difference in proportions: >0.9, trivial; 0.7-0.9, small; 0.5-0.7, moderate; <0.5, large [31]. Differences in post-exercise interstitial glucose concentration and differences in time spent in hypoglycaemia and hyperglycaemia between exercise conditions were evaluated as standardised effects: i.e. as the difference in the mean values (for interstitial glucose concentration and in time spent in hypoglycaemia and hyperglycaemia) between groups divided by their respective between-groups standard deviation. Given the small sample sizes within studies, as well as the small total number of studies included in these latter two meta-analyses, we opted for Hedges' g with J-correction as our measurement of standardised effect size [32]. The following scale of magnitudes was used to evaluate the size of these standardised effects: <0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; >1.2, large [31]. For each of the three meta-analyses, the point estimate and their respective 95% confidence intervals indicate the pooled effect. Between-study heterogeneity was assessed using the chi-squared-based Cochrane Q statistic, which represents the sum of the squared deviations of individual study effects from the pooled effect, the I2 statistic, which represents the proportion of variance in study effect sizes that is not attributable to sampling variation, and the Tau2 or T2, which represents the extent of variability in the pooled effects between studies [33-35]. Given the limited number of studies included in the individual meta-analyses, no further exploratory subgroup analyses were conducted. Data were meta-analysed in R Studio using the meta package. The metacont and metabin functions were used for continuous

(interstitial glucose concentration and in time spent in hypoglycaemia and hyperglycaemia) and categorical (number of exercisers experiencing a hypoglycaemic event) outcomes, respectively [36].

3. Results

3.1 Overview of Studies

In total, 355 records were identified through database searching and twelve studies met the inclusion criteria. Figure 1 provides an overview of how studies were identified and screened for inclusion. Six studies compared INT and END [37-42], two resistance (RES) and END [43, 44], one END with different percentages of RAIR [45], one END performed in the morning or in the afternoon [46], one combined (COMB) performing END before or after RES [47], and one investigated the effect of END with 50% RAIR [48]. We classified as INT exercise all exercise protocols alternating continuous moderate-intensity periods with other periods of different intensity. All the characteristics of the included studies are shown in Table 1.

Studies were conducted across eight different nations. The number of participants enrolled in each trial varied from six to twelve with only one study recruiting 32 patients and for a total of 145 exercisers. Study participants were adults with T1DM, but without complications or other diseases. Seven out of twelve studies included both males and females. Furthermore, all the participants were physically active (except for one study where it is not reported) and in good glycaemic control.

Eleven studies were RCTs and one is a non-RCT. Each of the studies monitored post-exercise glycaemic control with a continuous glucose monitoring (CGM) for at least 10 hour and all of the studies clearly reported how insulin and nutrition were standardised. Six studies adopted a strategy of RAIR from 20 to 75% of the usual dose. Four studies also included a control session while others compared the outcomes between different treatments or pre and post-exercise.

The threshold at which hypoglycaemia was defined was different between studies and varied in a range from 3.3 to 4 mmol/L. Five studies defined hypoglycaemia as blood glucose equal to or

lower than 3.9 mmol/L, four equal or lower than 3.5, two below 3.3 and one below 4 (Electronic Supplementary Material Table S1).

[INSERT FIGURE 1 AND TABLE 1 ABOUT HERE]

3.2 Quality of the Outcomes

The average quality of the outcomes was moderate to low and the most common reason to downgrade quality was the risk of bias (Table 2). The quality assessment is reported separately for the meta-analysed or systematically reviewed outcomes.

[INSERT TABLE 2 ABOUT HERE]

3.3 Outcomes

An extended presentation of the extracted data can be found in the Electronic Supplementary Material Table S1. The type of data that authors investigated and reported is varied and few outcomes are comparable between studies. Except for Moser et al. [38], each of the other studies reported the occurrence of hypoglycaemia during the post-exercise period. Of these studies, Reddy et al. [44] also reported patients experiencing severe hypoglycaemia. The majority of studies reported the number of patients experiencing hypoglycaemia, the number of hypoglycaemic events, or both. The third most commonly reported outcome is the mean interstitial glucose level found in five studies. All the other outcomes were found in no more than three studies.

3.4 Meta-Analysis of patients who experienced hypoglycaemia

Of the 12 studies included in the systematic review, two were eligible for the meta-analysis to assess the difference in the proportions of individuals experiencing hypoglycaemic events in the INT and END exercise conditions. Figure 2A provides a summary of the proportions included in the

meta-analysis alongside the individual study and pooled risk ratios. The forest plot shows that there was a small and non-statistically significant difference between the proportions of participants experiencing hypoglycaemic events across conditions (0.82, 0.45 to 1.49; risk ratio, 95% confidence interval) (p = .512). In other words, fewer participants in the INT exercising condition experienced post-exercise hypoglycaemic events. Moreover, the forest plot shows that there was a limited between-study heterogeneity (*Tau* = 0.17, I^2 = 0%). However, given the limited number of studies included in the meta-analysis, and given the resulting width of the confidence interval, the relative effect of INT and END exercising on an individuals' risk of experiencing hypoglycaemic events ought to be interpreted as unclear.

3.5 Meta-Analysis of mean interstitial glucose level

A further three studies were eligible for the meta-analysis to assess the difference in post-exercise interstitial glucose concentration between subjects completing INT and END. Figure 2B provides a summary of the descriptive statistics included in the meta-analysis (left) alongside their respective standardised effects (right). The forest plot shows a moderate-sized difference in post-exercise interstitial glucose between INT and END (-0.88, -1.45 to -0.33; standardised effect size, 95% confidence interval) (p = .003). In other words, post-exercise interstitial glucose was substantially lower (i.e., ~0.9 units of a standard deviation lower) for the INT exercising condition. The accompanying Cochrane's Q statistic provides no compelling evidence of between-study heterogeneity in the overall direction of the effect. The *Tau* also reflects the limited effect of magnitude of between-study heterogeneity. Finally, the I^2 suggests that a trivial proportion (i.e. <25%) of the variability in study effects were due to sampling variation

3.6 Meta-Analysis of time spent in hypoglycaemia and hyperglycaemia

A final three studies were eligible for the meta-analyses regarding the difference in the total study time spent by subjects in hypoglycaemia and hyperglycaemia (again, comparing the INT and

END conditions). Figures 2C and 2D provide descriptive statistics (left) and standardised effects (right) for time spent in hypoglycaemia and hyperglycaemia, respectively. The forest plot in Figure 2C shows a moderate and statistically significant difference in the time spent in hypoglycaemia between exercise conditions (0.62, 0.07 to 1.18; standardised effect size, 95% confidence interval) (p = .028. However, the accompanying data reveal that there was a substantial between-study heterogeneity (*Tau* = 0.947, I^2 = 79%), likely due to the contrasting findings of Zaharieva et al [41]. On average, across studies, exercisers in the INT condition spent longer in hypoglycaemia.

The forest plot in Figure 2D shows a non-statistically significant difference in the time spent in hyperglycaemia between exerciser conditions (-0.07, -0.58 to 0.45; standardised effect size, 95% confidence interval) (p = .794). Furthermore, the *Q, Tau,* and I^2 show a trivial between-study heterogeneity in relation to the time spent in hyperglycaemia by subjects in the INT and END groups.

[INSERT FIGURE 2 ABOUT HERE]

4. Discussion

This systematic review and meta-analysis provided a comprehensive overview of the delayed effects that different exercise modalities have on glycaemic control in people living with T1DM. Considering the increasing awareness of risks and benefits of exercise in this population, there was a particular need to gather and systematically investigate current knowledge on this topic to inform both real life exercise prescription and future research studies.

With the primary purpose of meta-analysing the information regarding glycaemic control during late recovery, we immediately identified the scarcity and variability of the reported data as a major limitation. Notwithstanding restrictive inclusion criteria and the homogeneous study design of the included studies, the selective reporting of the outcomes have limited the possible comparisons. Furthermore, due to different exercise protocols, intervention strategies and different

comparisons within studies, the majority of outcomes could not be included in the meta-analysis. Of the different types of exercise, END is the most commonly investigated both to compare different treatments or in comparison to other protocols. Therefore, we used INT as a reference condition during the meta-analyses.

Early investigations of the short-term effect of END on T1DM glycaemic control [49, 50] found a reduction in the post-exercise glucose levels and an increased risk of experiencing hypoglycaemia. Hereafter, other research appeared to focus attention towards establishing exercise protocols to prevent hypoglycaemia and identified INT as the best approach [51-53]. Since then, the comparison between END and INT became predominantly and neglected other exercise protocols like RES and COMB limiting our knowledge. This trend is reflected in the available literature and in fact, it was only possible to meta-analyse the comparison between END and INT.

The invasive glycaemic monitoring techniques used in these pioneering studies (e.g., venous catheter) often limited the follow-up period [54] to a few hours post-exercise. Due to the ease of use and affordability of CGM devices in the last 10 years [55], it has been possible to monitor the glycaemic response up to 24 hour or more after exercise and, as identified by this systematic review and meta-analysis, the effects obtained are very different from those that may be expected.

We found that, after INT, T1DM participants spent significantly more time in hypoglycaemia (Figure 2C) and presented lower mean interstitial glucose levels (Figure 2B) compared to END, while time spent in hyperglycaemia (Figure 2D) or the risk of experiencing it (Figure 2A) did not differ between the two interventions. Therefore, we can suggest that T1DM participants are more prone to experience lower glucose levels late after INT exercise and, in case of hypoglycaemia, it may last longer. However, INT neither increased the risk of hypoglycaemia nor accentuated glycaemic fluctuations (i.e., no differences in time spent in hyperglycaemia).

One consideration is necessary while discussing the meta-analysis: Zaharieva et al. [41] was included in the INT group as their protocol alternated continuous exercise with other exercises at different intensities. However, their exercise was based on a circuit training protocol and, therefore,

requiring a different muscular activation (e.g., isometric contractions). The main difference emerged with the studies of Campbell et al. [39] and Bally et al. [40] in the meta-analysis "time spent in hypoglycaemia" where the heterogeneity is evident visually in the figure and in the Q and T^2 statistic. This different protocol may produce slightly different outcomes and for the reported results, a better glycaemic control compared to END may be expected.

Separate to the meta-analysis, two studies [37, 40] reported the glucose variability measures (i.e., glucose standard deviation (SD), coefficient of variation (CV) and the mean amplitude of glucose excursion (MAGE)) but also in this case, there was no difference between INT and END. One study [39] reported the average maximum glucose levels but, as in the maximum and minimum CGM values overnight reported by Iscoe et al. [37], no statistical significance was found.

In contrast to what has been observed during the early recovery [53, 56], INT is not able to improve glycaemic control late after exercise and instead exacerbates hypoglycaemia as it occurs. The implications of these findings are crucial as they upset the misconception of INT as the best approach to reduce the risks related to exercise-induced hypoglycaemia. In fact, the beneficial effect of high-intensity bouts during END (i.e., COMB) is true only for the early recovery, while later the situation is inverted. Thus, we suggest caution in prescribing INT and advise against proposing it as an alternative to END if this is commonly performed.

The comparison between END and RES was proposed only in two studies. Furthermore, the reported outcomes are different and this makes it difficult to report on the findings. Yardley et al. [43] reported an increased number of participants experiencing hypoglycaemia and increased occurrence of hypoglycaemic events after RES compared to END. Furthermore, Reddy et al. [44] investigated END and RES but glycaemic control was a secondary outcome. They did not find differences in the two exercise types; however, they omitted to report the number of hypoglycaemic events or the number of patients experiencing hypoglycaemia. The limited evidence behind RES and the inability to compare the outcomes does not allow us to see more or fewer benefits in practising RES instead of END.

Yardley et al. [47] proposed the combination of RES ad END during the same session and investigated if performing RES before (RE) or after END (ER) may induce a different glycaemic response. They did not report differences in the frequency of post-exercise hypoglycaemia but there was a small trend for increased duration of hypoglycaemia after ER than after RE. Considering the variability of this outcome and no other studies supporting these findings, it is difficult to clarify whether the order of exercise affects glycaemic control during the late recovery from COMB exercise.

Gomez et al. [46] investigated the effect of diurnal variations on delayed glycaemic control performing END in the morning or in the afternoon. They reported about half of all the hypoglycaemic events for the group who exercised in the morning compared to afternoon and improved metabolic control (more time spent in euglycaemia) on the subsequent day. They also found that the majority of the hypoglycaemic events occurred 15-24 hour post-exercise suggesting a timeframe of increased risk. In light of this, exercise in the morning is encouraged while more attention will be necessary if END is performed in the afternoon. This conclusion has double utility as if people with diabetes know that a certain behaviour will increase the risk of experiencing hypoglycaemia, together with the timeframe in which it is more likely to happen, they could adopt strategies to prevent it [6].

Campbell et al [45] directly investigated the effect of RAIR on the post-exercise glycaemic control. They found that large pre and post-exercise RAIR preserved glycaemia and protected patients against hypoglycaemia up to 8 hours after END; however, the protective effect was not maintained later in the recovery. Other researchers adopted different magnitudes of RAIR (Table 1); usually reducing insulin from 20 to 75% of the usual dose before or after exercise. Even if this data cannot be meta-analysed, it seems that reducing rapid-acting insulin at 50% of the usual dose results in a better glycaemic control.

The lack of literature in this area did not allow us to perform other analyses or to identify sex-related differences in glycaemic response to exercise. The intensity proposed by the authors

varied from moderate to high and was in line with the ACSM recommendations [57] as was the duration; usually 45 minutes.

Following these findings, it is evident that exercise can significantly affect glycaemic control of people living with T1DM late after exercise. However, the heterogeneity of the studies and the selective reporting of the outcomes did not allow us to identify an approach to be preferred. Therefore, we suggest points to address in future studies and advocate authors to follow them in order to obtain comparable results and improve the quality and accuracy of exercise prescription in this population:

1. Use a common threshold to define hypoglycaemia (we suggest glucose levels equal to, or lower than 3.5 mmol/L).
2. Compare at least two exercise protocols and possibly include END as reference. Also including a no-exercise control may be helpful to evaluate the impact of exercise through network meta-analysis [58].
3. Do not include other interventions or, if other interventions like RAIR or nutrition are used, include a control group exercising only.
4. The exercise duration should be around 45 minutes to be in line with the majority of studies (unless the scope is to investigate different durations) and the intensity from moderate to high.
5. Report the number of patients experiencing hypoglycaemia and the number of hypoglycaemic episodes. Include also any other data collected with CGM or flash glucose monitoring (FGM) devices, even if there is no significant difference [59].
6. Report if exercise was executed in the morning or in the afternoon.
7. Investigate if glycaemic control differs between males and females [60].

In conclusion, from this systematic review and meta-analysis emerged that performing END at a moderate to high intensity for 45 minutes is the best exercise protocol for people living with T1DM

364 and that INT exposes people with T1DM to longer hypoglycaemic events. On the other hand, the
365 poor evidence behind RES and COMB did not allow any satisfactory conclusion and indicates the
366 necessity of further investigations. Preliminary results suggest that circuit-training protocols may
367 provide a better outcome than END and that performing exercise in the morning rather than in the
368 afternoon, together with a 50% RAIR, can reduce the risk of hypoglycaemia late after exercise.
369 Furthermore, as adequate exercise prescription is crucial to reduce risks and maximise benefits for
370 T1DM, in the final part of this review we provide advice to parties interested in analysing this topic
371 in future studies, with the aim to obtain comparable results and to improve the quality of exercise
372 prescription in T1DM.
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375 **Competing Interests**:
376 We have no competing interests to declare. This research did not receive any specific grant
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Table 1: Characteristics of studies included in the systematic review and meta-analysis

STUDY	COUNTRY	SAMPLE SIZE	AGE	SEX	P.A. level	HbA1c % (mmol/mol)	EXERCISE TYPE	DURATION
Gomez et al. (2015) [46]	Colombia	32	30.3 ± 12.6	M/F	NA	7.3 ± 1.0 (56)	Endurance	60 min (4 cycles of 15 min with 5 min break between)
Campbell et al (2013) [45]	UK	11	24 ± 2	M	Physically active	7.7 ± 0.3 (60)	Endurance	45 min
Campbell et al (2014) [48]	UK	10	27 ± 5	M	Physically active	6.7 ± 0.7 (50)	Endurance	45 min
Yardley et al. (2012) [47]	Canada	12	31.8 ± 15.3	M/F	Physically active	7.1 ± 1.0 (54)	Endurance and resistance (order)	45 + 45 min
Yardley et al. (2013) [43]	Canada	12 (11 and 10 for CGM post control and END)	31.8 ± 15.3	M/F	Physically active	7.1 ± 1.0 (54)	Endurance Vs resistance	45 min
Reddy et al. (2018) [44]	USA	10	33 ± 6.0	M/F	Physically active	7.4 ± 1.0 (57)	Endurance Vs Resistance	45 min
Iscoe et al. (2011) [37]	Canada	11	35.1 ± 3.5	M/F	Athletes	7.8 ± 0.4 (62)	Intermittent and Endurance	45 min
Moser et al (2015) [38]	Austria Germany	6	24 ± 5.3	M	Trained	7.4 ± 0.6 (57)	Intermittent Vs Endurance	30 min
Campbell et al (2015) [39]	UK	9	35 ± 4	M/F	Physically active	8.1 ± 0.2 (65)	Intermittent Vs Endurance	45 min
Bally et al. (2016) [40]	Switzerland	12	26.2 ± 3.9	M	Physically active	7.0 ± 0.6 (53)	Intermittent Vs Endurance	90 min
Zaharieva et al. (2017) [41]	Canada, USA	12 (8 for CGM)	32 ± 11	M/F	Physically active	7.0 ± 0.9 (53)	Intermittent Vs Endurance	40 min
Maran et al. (2010) [42]	Italy	8	34 ± 7	M	Physically active	7.1 ± 0.6 (54)	Intermittent Vs Endurance	30 min

Table 1: Continued

STUDY	INTENSITY	TIME PERIOD	POST EX. MONITORING	R.A.I.R. and FASTING	STUDY DESIGN	CONTROL SESSION
Gomez et al. (2015) [46]	Moderate	Morning Vs Afternoon	36 H	No No fasted	RCT	No
Campbell et al (2013) [45]	72% VO2peak	Morning	24 H	75% No fasted	RCT	No
Campbell et al (2014) [48]	70% VO2peak	Afternoon	24 H	50-75% No fasted	RCT	No
Yardley et al. (2012) [47]	60% VO2peak / 8 reps	Afternoon	25 H (data reported for 6 h overnight)	NA No fasted	RCT	Yes
Yardley et al. (2013) [43]	60% VO2peak / 8RM	Afternoon	24 H (data reported for 6 h overnight)	50% No fasted	RCT	Yes
Reddy et al. (2018) [44]	60% VO2max / 60-80% 1RM	Afternoon	24 H/Day (data reported for 12 h overnight)	No No fasted	RCT	Yes
Iscoe et al. (2011) [37]	50% Peak work rate interspersed with 15 sec of maximal bouts every 5 minutes / 55% Peak work rate	Afternoon	12 H	No No fasted	RCT	Yes
Moser et al (2015) [38]	Maximal sprint end active recovery / Below and above the first lactate turn point and below the second	NA	24 H	25-50-75% No fasted	NRT	No
Campbell et al (2015) [39]	Alternating 20 meters of walking, sprinting and running (up to 95% VO2peak) / 77% VO2peak	Morning	23 H	50% No fasted	RCT	No
Bally et al. (2016) [40]	10 s supramaximal sprints every 10 min at 50% VO2max / 50% VO2max	Morning	10 H	No No fasted	RCT	No
Zaharieva et al. (2017) [41]	Not quantifiable / 40-50% VO2max	Morning or afternoon	12 H	No No fasted	RCT	No
Maran et al. (2010) [42]	40% VO2max interspersed with 5 sec sprints at 85% VO2max each 2 min / 40% VO2max	Afternoon	20 H (data reported for 6 h overnight)	20% No fasted	RCT	No

P.A. physical activity, HbA1c glycated haemoglobin, R.A.I.R. rapid-acting insulin reduction, NA not available, min minutes, sec seconds, CGM continuous glucose monitoring, reps repetitions, 1RM one repetition maximum. In the case of more exercise interventions in the same study, exercise intensity was described following the order in which exercises are reported in the column "EXERCISE TYPE" and separated by the slash (/).

Table 2: quality of the outcomes

Meta-analysed Outcomes	N° of participants (Studies)	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	Evidence GRADE
N° of participants experiencing hypoglycaemia	20 (2)	/	/	/	/	/	High
Mean interstitial glucose levels	27 (3)	S	/	/	/	/	Moderate
Time spent in hypoglycaemia	29 (3)	S	/	/	/	/	Moderate
Time spent in hyperglycaemia	29 (3)	S	/	/	/	/	Moderate
Systematically-reviewed Outcomes							
N° of participants experiencing hypoglycaemia	50 (5)	S	/	/	/	/	Moderate
N° of hypoglycaemic events	92 (7)	/	/	S	/	/	Moderate
Time spent in euglycaemia	40 (2)	S	S	/	S	/	Very low
Time spent in hypoglycaemia	32 (1)	S	/	/	S	/	Low
Time spent in severe hypoglycaemia	10 (1)	VS	/	/	S	/	Very low
Nights where hypoglycaemic events occurred	10 (1)	VS	/	/	S	/	Very low
Nights where severe hypoglycaemia occurred	10 (1)	VS	/	/	S	/	Very low
Odds of hypoglycaemia occurring	10 (1)	VS	/	/	S	/	Very low
Area under the curve	42 (4)	S	/	/	/	/	Moderate
Mean interstitial glucose levels	23 (2)	/	/	/	S	/	Moderate
N° of participants who corrected blood glucose	11 (1)	/	/	/	S	/	Moderate
Average minimum glucose levels	9 (1)	/	/	/	S	/	Moderate
Average maximum glucose levels	21 (2)	/	/	S	S	/	Low
Duration of hypoglycaemia per episode	23 (2)	/	/	/	S	/	Moderate
Maximum CGM values overnight	11 (1)	S	/	/	S	/	Low
Minimum CGM values overnight	11 (1)	S	/	/	S	/	Low
Glucose standard deviation	23 (2)	S	/	/	/	/	Moderate
Glucose coefficient of variation	12 (1)	S	/	/	S	/	Low
Mean amplitude of glucose excursion	12 (1)	S	/	/	S	/	Low

N° number, CGM continuous glucose monitoring, / No, S Serious, VS very serious

Figure Legends

Figure 1. Literature search and study selection process.

Figure 2. Forest plots of the Meta-analysed outcomes. Meta-analysis of the hypoglycaemic events experienced among participants in the INT versus END (control) groups (2A), of standardised mean difference of the mean post-exercise interstitial glucose level (mmol/L) (2B), of standardised mean difference of the time spent in hypoglycaemia (percentage) (2C), of standardised mean difference of the time spent in hyperglycaemia (percentage) (2D). The vertical line represents no difference between the compared exercise conditions.CI confidence interval.

Figure 1

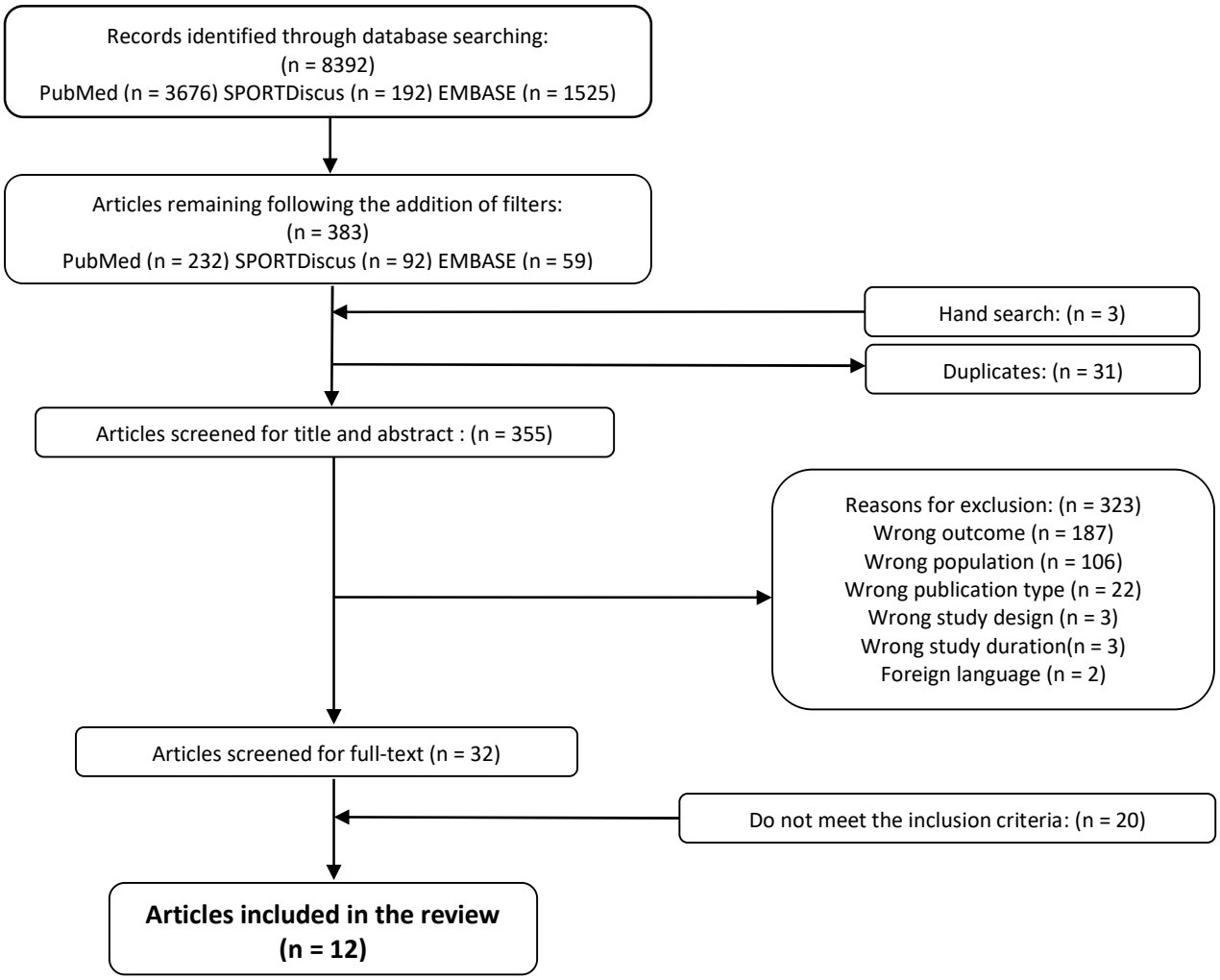
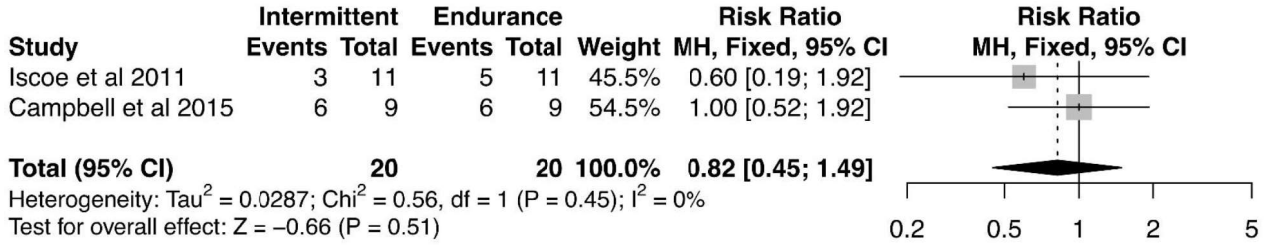
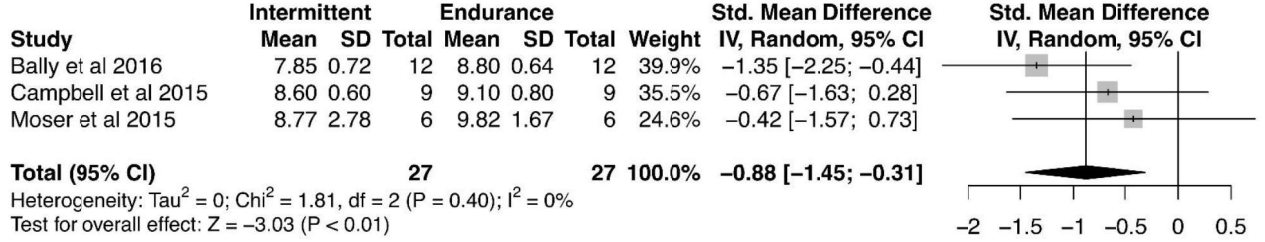

Records identified through database searching:
(n = 8392)
PubMed (n = 3676) SPORTDiscus (n = 192) EMBASE (n = 1525)
Articles remaining following the addition of filters:
(n = 383)
PubMed (n = 232) SPORTDiscus (n = 92) EMBASE (n = 59)
Hand search: (n = 3)
Duplicates: (n = 31)
Articles screened for title and abstract : (n = 355)
Reasons for exclusion: (n = 323)
Wrong outcome (n = 187)
Wrong population (n = 106)
Wrong publication type (n = 22)
Wrong study design (n = 3)
Wrong study duration(n = 3)
Foreign language (n = 2)
Articles screened for full-text (n = 32)
Do not meet the inclusion criteria: (n = 20)
Articles included in the review
(n = 12)

Figure 2

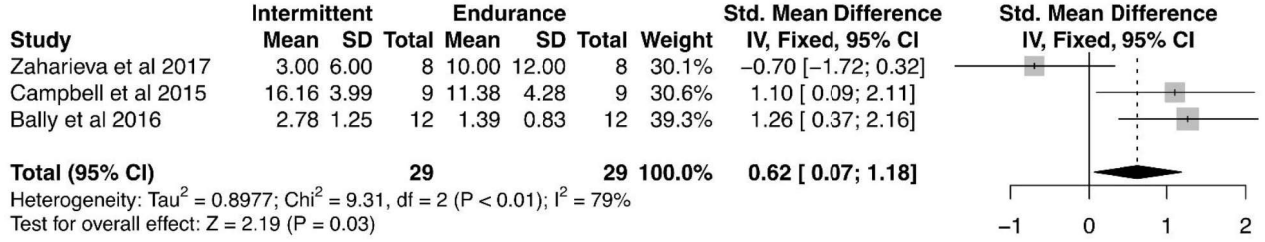
2A



2B



2C



2D