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Effect of metformin on exercise capacity: A meta-analysis

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ABSTRACT

Aims: To evaluate the effect of metformin on various parameters of exercise capacity [oxygen consumption (VO_2), peak oxygen consumption (VO_{2peak}), heart rate (HR), exercise test duration, respiratory exchange ratio (RER), rating of perceived exertion (RPE), lactate and ventilatory anaerobic threshold (VAT)].

Methods: Studies reporting change in VO_2 or VO_{2peak} after metformin administration were included. Subgroup analyses were performed as applicable. Mean difference with 95% CIs were pooled using random-effects model [RevMan (v5.3)].

Results: There were no changes in VO_2 and VO_{2peak} in the overall population [VO_2: n = 388, mean difference: −0.12 ml/kg/min, 95% CI: −0.74, 0.51, $p = 0.71$ ($i^2 = 0\%$, $p = 0.99$); VO_{2peak}: n = 345, mean difference: 0.41 ml/kg/min, 95% CI: −0.51, 1.33, $p = 0.38$ ($i^2 = 0\%$, $p = 0.89$)], healthy volunteers and patients (type 2 diabetes mellitus, insulin resistance, impaired glucose tolerance/impaired fasting glucose and metabolic syndrome). For patients with insulin resistance, there was a decrease in VO_{2peak}, but not VO_2. In the overall population, there was a significant decrease in HR and RER, a significant increase in RPE, and no changes in exercise test duration and VAT. In addition, there was an increased VAT in the healthy volunteers.

Conclusions: In the overall population, metformin did not affect VO_2, VO_{2peak}, exercise test duration and VAT, although it significantly decreased HR, RER and increased RPE.

1. Introduction

Physical activity is recommended as an initial mode of therapy in the prevention of type 2 diabetes mellitus (T2DM) [1]. Exercise is known to enhance both the delivery and utilization of oxygen to raise cardiorespiratory fitness (i.e., VO_2, and VO_{2peak}) [2]. Exercise training results in numerous adaptations to skeletal muscles that are important for glucose

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uptake and oxidation [3]. Further during high-intensity, short-duration exercise, muscle glycogen is used as the first source of energy [4]. In these type of exercises, glucose used by the active muscle fibers comes from glycogenolysis. Exercise training reliably increases the capacity to oxidize glucose and fat [5,6]. Thus, changes in VO_{2peak} may influence glycemic control. Moreover, an increase in VO_{2peak}-related metabolic adaptations is associated strongly with increased sensitivity to insulin [7]. Metformin is one of the most commonly prescribed drugs in T2DM. The common adverse effects seen with metformin are nausea, indigestion, abdominal cramp, bloating and diarrhea, along with lower blood levels of vitamin B_{12} [8]. Rarely, it may cause life-threatening lactic acidosis in the presence of concomitant diseases like renal as well as liver impairment, sepsis, myocardial infarction, and congestive heart failure [8]. In addition, metformin is also known to reduce lactate threshold (LT) (i.e. exercise intensity at which there is a marked increase in lactate accumulation in blood) and ventilatory anaerobic threshold (VAT) (i.e. point during exercise at which ventilation starts to increase at a faster rate than VO_2 due to anaerobiosis and lactate accumulation) [9] during exercise through inhibition of gluconeogenesis and electron transport chain in mitochondria [10–12].

Exercise capacity is considered to be the maximum amount of physical exertion that an individual can sustain. To measure exercise capacity accurately, the maximal exertion should be sufficiently prolonged to have a stable and consistent effect on various parameters of the cardiovascular system [13]. VO_2 and VO_{2peak}, heart rate (HR), exercise test duration, respiratory exchange ratio (RER), rating of perceived exertion (RPE), LT, and VAT are the important parameters to determine exercise capacity [14].

Metformin and exercise capacity are linked in a complex manner. Muscle contraction leads to activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), and there is a growing evidence that metformin also increases AMPK activity in liver, muscle and other tissues [15]. Activation of AMPK is indirectly associated with reduced exercise capacity through inhibition of tissue respiration [16]. Metformin has been shown to decrease oxygen consumption (VO_2) and peak oxygen consumption (VO_{2peak}) [17], possibly by inhibiting the transfer of electrons from reduced nicotinamide adenine dinucleotide (NADH) to coenzyme Q10 of mitochondrial electron transport system [18–20]. Thus, metformin may compromise adenosine triphosphate (ATP) production in mitochondria, leading to an increase in the AMP/ATP ratio. As a result of this energy depletion, glycolysis and phosphocreatine energy systems are induced to maintain normal cellular metabolism [19,20]. This has led to the speculation that metformin could increase anaerobic metabolism and reduce exercise capacity.

Many studies have demonstrated that metformin deteriorates [21–25], while some other studies have revealed that it improves [26–29] various parameters of exercise capacity. However, there are few inconclusive as well as neutral studies with respect to metformin's effect on exercise capacity in healthy volunteers, diabetes patients and those with insulin resistance [30–32]. The effect of metformin on exercise capacity has not been addressed by any meta-analysis so far. Since a better understanding of the dynamics between metformin therapy and physical activity may lead to improved quality of life in T2DM patients, this meta-analysis was conducted to evaluate the effect of metformin on various parameters of exercise capacity in adults.

2. Materials and methods

2.1. Study design

This study was initiated after obtaining 'exemption from review' by the Institutional Ethics Committee, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. The study protocol can be accessed in PROSPERO (ID: CRD42018082696).

Completed and published randomized controlled trials (RCTs) (parallel group and cross-over studies), which evaluated the effect of metformin on exercise capacity were included. The inclusion criteria were: participants of both gender and age $\geq$ 18 years for whom VO_2 or VO_{2peak} was measured to evaluate exercise capacity after administration of metformin. The exclusion criteria were: the presence of any disease (apart from T2DM, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), insulin resistance or metabolic syndrome) or intervention (e.g. drugs like beta blockers, statins, etc.), which might interfere with exercise capacity. The primary outcomes of the study were changes in VO_2 and VO_{2peak}, while changes in HR, exercise test duration, RER, RPE, VAT, LT and adverse effects resulting from metformin treatment were considered as secondary outcomes.

2.2. Search strategy

MEDLINE/PubMed, IndMED, Cochrane Library [Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register] and International Clinical Trials Registry Platform and ClinicalTrials.gov were searched until 31st January 2018. The search terms used were: "metformin", "biguanide", "exercise", "exercise capacity", "exercise tolerance", "aerobic", "aerobic exercise", "oxygen", "oxygen consumption", "VO_2", "peak VO_2" and "VO_{2max}". These search terms were adapted for use with different bibliographic databases in combination with database-specific filters for studies, if available. The search strategy was used to obtain titles and abstracts of relevant studies in the English language, and they were independently screened by two authors (SD and AS), who subsequently retrieved abstracts, and if necessary, the full text of articles to determine suitability. Disagreement resolution was done by another two independent authors (SKB and SS).

2.3. Data extraction and management

Abstract reviewing and data extraction was carried out independently by three authors (SD, SKB, and AS) using a preformatted data extraction spreadsheet. No assumptions or simplifications were made during data extraction. The included studies were assessed for risk of bias by three authors (SD, SS, and SKB) using Cochrane Collaboration's tool

for assessing the risk of bias [33]. Meta-analysis was performed (SD) wherever adequate data were available for primary and secondary outcomes using Review Manager (RevMan) (v5.3). The entire analysis was interpreted by three more independent authors (ASX, NSN, SK, and JPS) who have also provided expert inputs. A random-effect model was used to ensure robustness of the model across various population and susceptibility to outliers. Mean difference and 95% CI were used to estimate the treatment effects. For insufficient data, descriptive statistics were used. Data regarding screened and randomized patients, as well as both intention-to-treat and per-protocol analysis, were carefully evaluated. Attrition rates, such as dropouts, lost to follow-up and withdrawals were investigated. Issues of missing data and imputation methods were critically appraised [33]. Heterogeneity was analyzed using χ^2 test on n−1 degrees of freedom, with an α error of 5% used for statistical significance and with i^2 test [34]. The i^2 values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity respectively. Funnel plots were used to assess the potential existence of small study effects and reporting bias [33,35]. Subgroup analyses for the primary outcomes were performed based on ethnicity, patient population (healthy volunteer, patients or those with insulin resistance alone), duration of metformin treatment and characteristics of the included studies (parallel group vs. cross-over studies). Of the secondary outcomes, subgroup analyses were performed for HR, exercise test duration, RER, and RPE according to the patient population (healthy volunteer or patients). The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) [36,37] was used to assess the quality of generated evidence.

3. Results

A total of 1353 studies were screened and finally, 9 studies [17,22,23,28,30,31,38–40] were included in the analysis (Fig. S1). Of these 9, five were cross-over studies and four were parallel group studies. All the included studies were of moderate to high quality. Authors' judgments about the risk of bias for each included study has been itemized in Fig. S2. The study characteristics, sub-classifications, nomenclatures used based on exercise parameters and other characteristic details are enumerated in Table 1.

In the included studies, where multiple treatment arms were present, data from metformin arm and placebo arm (if available) were extracted. Some parameters of exercise capacity before administering metformin (hereafter referred to 'pre-metformin') were compared to that of after administering metformin (hereafter referred to 'post-metformin'); whereas, some other parameters of exercise capacity after administering metformin ('post-metformin') were compared to that of after administering placebo (hereafter referred to 'placebo').

3.1. Primary outcomes

There were no changes in VO_2 in the overall population [n = 388, mean difference: −0.12 ml/kg/min, 95% CI: −0.74, 0.51, $p = 0.71$ ($i^2 = 0\%$, $p = 0.99$)] (Fig. 1A), healthy volunteers (Fig. S3), patients [those with T2DM, insulin resistance (IR), IGT/IFG and metabolic syndrome] (Fig. S4) and those with insulin resistance alone (Fig. S5). Among the Caucasians (Fig. S6) and non-Caucasians (Brazilians) (Fig. S7), there were no changes in VO_2 after treatment with metformin. Similarly, treatment with metformin for <2 weeks (Fig. S8) and ≥2 weeks (Fig. S9) showed no changes in VO_2. Likewise, VO_2 measured in the included parallel group studies (Fig. S10) and cross-over studies (Fig. S11) also showed no changes after treatment with metformin.

Similarly, there were no changes in VO_{2peak} in the overall (Caucasian) population [n = 345, mean difference: 0.41 ml/kg/min, 95% CI: −0.51, 1.33, $p = 0.38$ ($i^2 = 0\%$, $p = 0.89$)] (Fig. 1B), healthy volunteers (Fig. S12), patients (those with T2DM, insulin resistance, IGT/IFG and metabolic syndrome) (Fig. S13) and those with insulin resistance alone (Fig. S14). There was no change in VO_{2peak} in the overall population by treatment with metformin for <2 weeks [(Fig. S12), ≥2 weeks (Fig. S13), included parallel group studies (Fig. S15) and cross-over studies (Fig. S16). Heterogeneity was found to be meager across the studies included for assessing primary outcomes.

3.2. Secondary outcomes

There was a significant decrease in HR in the overall population [n = 320, mean difference: 2.00 per min, 95% CI: 0.23, 3.77, $p < 0.05$ ($i^2 = 5\%$, $p = 0.40$)] (Fig. 2A) and healthy volunteers (Fig. S17), but significant increase in HR in the patients (those with T2DM, insulin resistance, IGT/IFG and metabolic syndrome) (Fig. S18). There was significant decrease in RER in the overall population [n = 266, mean difference: 0.03, 95% CI: 0.02, 0.03, $p < 0.001$ ($i^2 = 0\%$, $p = 0.43$)] (Fig. 2B) and healthy volunteers (Fig. S19), but no change in RER in diabetes patients and those with insulin resistance alone (Fig. S20).

There were no changes in exercise test duration in the overall population who were all healthy volunteers [n = 96, mean difference: −2.46 sec, 95% CI: −39.18, 34.26, $p = 0.90$ ($i^2 = 76\%$, $p < 0.05$)] (Fig. 3A). There was significant increase in RPE in the overall population [n = 298, mean difference: −0.35, 95% CI: −0.62, −0.08, $p < 0.05$ ($i^2 = 56\%$, $p < 0.05$)] (Fig. 3B) and healthy volunteers (Fig. S21), but no change in RPE in diabetes patients and those with insulin resistance alone (Fig. S22).

There was a significant increase in VAT in the overall population who were all healthy volunteers [n = 56, mean difference: −3.00% of VO_{2peak}, 95% CI: −5.42, −0.58, $p < 0.05$ ($i^2 = 0\%$, $p = 0.66$)] (Fig. 3C) in the overall population. None of the included studies reported post-treatment changes in LT.

Higher heterogeneity was observed among the studies comparing exercise test duration and RPE. The funnel plots for all the parameters assessed in the meta-analyses are depicted in Figs. S23–S49. Only mild gastrointestinal adverse effects of metformin were reported. The GRADE of quality of evidence generated from this meta-analysis was high for some of the outcomes (change in VO_2 in the overall population and change in RPE), while for the others (change in VO_{2peak} in the overall population, change in HR, exercise test duration and RER) it was low.

Table 1 – Characteristics of the included studies.

Study no.	Author, year (country)	Type of study	Demographic details				Measurement of exercise capacity		
			Age (years)	BMI (kg/m^2)	Condition	Metformin dose in mg (duration in days)	Equipment (protocol)	Duration of exercise	Exercise intensity/type
1	Boulé et al., 2011a (Canada) [30]	Randomized cross-over study	58 ± 6	28.6 ± 5.3	T2DM	2000 (28)	Treadmill (modified Balke-Ware protocol)	Until patient could continue	Low
	Boulé et al., 2011b (Canada) [30]	Randomized cross-over study	58 ± 6	28.6 ± 5.3	T2DM	2000 (28)	Treadmill (modified Balke-Ware protocol)	Until patient could continue	Moderate
	Boulé et al., 2011c (Canada) [30]	Randomized cross-over study	58 ± 6	28.6 ± 5.3	T2DM	2000 (28)	Treadmill (modified Balke-Ware protocol)	Until patient could continue	Vigorous
2	Boulé et al., 2013d (Canada) [31]	Randomized parallel group study	54.9 ± 7.1	33.3 ± 5.5	T2DM	1654 ± 616 (180)	Treadmill (exercise stress test at 75% maximum HR)	45 min thrice a week for 180 days	Aerobic
	Boulé et al., 2013e (Canada) [31]	Randomized parallel group study	54.9 ± 7.1	33.3 ± 5.5	T2DM	1654 ± 616 (180)	Strength tests (7 exercises/session, up to 2–3 sets at maximum weight that could be lifted 7–9 times)	Maximum weight that could be lifted 8 times for 180 days	Resistance
	Boulé et al., 2013f (Canada) [31]	Randomized parallel group study	54.9 ± 7.1	33.3 ± 5.5	T2DM	1654 ± 616 (180)	Treadmill and strength test (as mentioned in the above two rows)	As mentioned in the above two rows for 180 days	Combined
	Boulé et al., 2013g (Canada) [31]	Randomized parallel group study	54.9 ± 7.1	33.3 ± 5.5	T2DM	1654 ± 616 (180)	Not mentioned (pre-study activity levels)	–	Pre-study activity
3	Braun et al., 2008 (USA) [17]	Randomized cross-over study	27.9 ± 3.3	24.1 ± 3.6	Healthy volunteers	2000 (7–9)	Cycle ergometer or treadmill (continuous incrementally graded protocol: cycle resistance: 25–50 W increments in early stages and 25 W increments as test progressed beyond first few stages, treadmill grade: +2% increments at every 2 min until a maximal voluntary effort was achieved)	Until maximal voluntary effort was achieved	–
4	Cadeddu et al., 2014 (Italy) [22]*	Randomized parallel group study	46.2 ± 11	29.7 ± 4.8	IGT/IFG/insulin resistance	1000 (84)	Electrically braked stationary cycle ergometer (ramp protocol)	Until exhaustion (at least 10 min)	Graded exercise test
5	Johnson et al., 2008h (Canada) [38]	Randomized cross-over study	29.9 ± 3.7	25.2 ± 8	Healthy volunteers	1000 (1)	Cycle ergometer (pedal at 75–80 rpm and resistance of 160 W and increased by 40 W every 3 min)	Until exhaustion	Graded maximal exercise test
	Johnson et al., 2008i (Canada) [38]	Randomized cross-over study	29.9 ± 3.7	25.2 ± 8	Healthy volunteers	1000 (1)	Cycle ergometer (constant power output exercise test: power output over 45 min was set at 10–20% below power output of ventilatory threshold)	45 min	Constant workload exercise test
6	Learsi et al., 2015j (Brazil) [28]	Randomized cross-over study	23.5 ± .6	22.98	Healthy volunteers	500 (1)	Electromagnetically braked cycle ergometer (maximal incremental test, 6 submaximal constant workload tests at 40–90% VO_{2peak}, 2 supramaximal tests at 110% VO_{2peak} until exhaustion)	–	Last 30 sec
	Learsi et al., 2015k (Brazil) [28]	Randomized cross-over study	23.5 ± .6	22.98	Healthy volunteers	500 (1)	Electromagnetically braked cycle ergometer (maximal incremental test, 6 submaximal constant workload tests at 40–90% VO_{2peak} , 2 supramaximal tests at 110% VO_{2peak} until exhaustion)	–	First 110 sec
7	Malin et al., 2010l (USA) [23]#	Randomized cross-over study	25.0 ± 4.4	22.8 ± 2.7	Healthy volunteers	2000 (8–10)	Cycle ergometer (continuous progressive exercise: submaximal cycle workloads, starting at 30% peak work and increasing by 10% every 8 min to 70% peak work)	8 min	30% peak work
	Malin et al., 2010m (USA) [23]#	Randomized cross-over study	25.0 ± 4.4	22.8 ± 2.7	Healthy volunteers	2000 (8–10)	Cycle ergometer (continuous progressive exercise: submaximal cycle workloads, starting at 30% peak work and increasing by 10% every 8 min to 70% peak work)	8 min	40% peak work
	Malin et al., 2010n (USA) [23]#	Randomized cross-over study	25.0 ± 4.4	22.8 ± 2.7	Healthy volunteers	2000 (8–10)	Cycle ergometer (continuous progressive exercise: submaximal cycle workloads, starting at 30% peak work and increasing by 10% every 8 min to 70% peak work)	8 min	50% peak work
	Malin et al., 2010o (USA) [23]#	Randomized cross-over study	25.0 ± 4.4	22.8 ± 2.7	Healthy volunteers	2000 (8–10)	Cycle ergometer (continuous progressive exercise: submaximal cycle workloads, starting at 30% peak work and increasing by 10% every 8 min to 70% peak work)	8 min	60% peak work
	Malin et al., 2010p (USA) [23]#	Randomized cross-over study	25.0 ± 4.4	22.8 ± 2.7	Healthy volunteers	2000 (8–10)	Cycle ergometer (continuous progressive exercise: submaximal cycle workloads, starting at 30% peak work and increasing by 10% every 8 min to 70% peak work)	8 min	70% peak work
8	Malin et al., 2012 (USA) [39]*	Randomized parallel group study	45.0 ± 7.5	33.9 ± 5.2	IGT	2000 (84)	Cycle ergometer (continuous progressive exercise test: warming up on for 5 min, cycling at 70% of pre-training HR peak for 45 min, resistance exercise at 70% 1-RM, ~5% weight increased when 2 sets of 12 repetitions could be lifted)	–	Aerobic and resistance
9	Sharoff et al., 2010q (USA) [40]*	Randomized parallel group study	33 ± 9.5	30.3 ± 4.7	Insulin resistance	2000 (14)	Cycle ergometer (YMCA protocol, workload increased every 3 min based on the average heart rate during the last 2 min of each stage)	30 min	65% VO_{2peak}
	Sharoff et al., 2010r (USA) [40]*	Randomized parallel group study	33 ± 9.5	30.3 ± 4.7	Insulin resistance	2000 (14)	Cycle ergometer (YMCA protocol, workload increased every 3 min based on the average heart rate during the last 2 min of each stage)	10 min	85% VO_{2peak}

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; BMI: body mass index; HR: heart rate; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; RER: respiratory exchange ratio; RM: repetition maximum; rpm: rotation per minute; T2DM: type 2 diabetes mellitus.

Age, BMI and dose of metformin (for study nos. 2 and 5) are expressed as mean ± SD.

* Patients with insulin resistance were included.

\# Data collected at were not included.

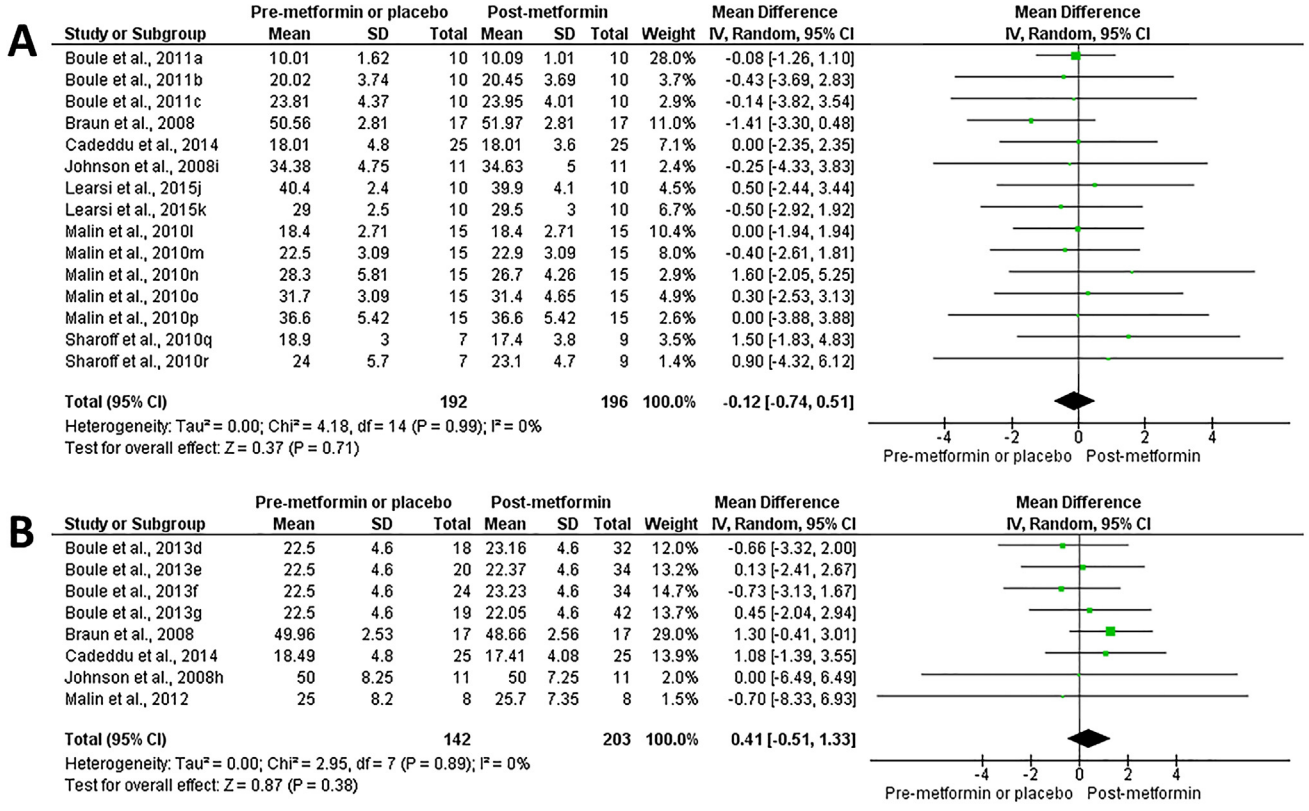

Fig. 1 – Forest plots showing primary outcomes. (1A): Effect of metformin on VO_2 (ml/kg/min) in the overall population (for Cadeddu et al., 2014 study, pre-metformin data have been compared to post-metformin data; for rest, post-metformin data have been compared to placebo data; for Johnson et al., 2008i study, body weight of healthy Canadian male was assumed to be 80 kg and VO_2 was calculated per kg body weight accordingly; for Braun et al., 2008 study, standard deviation of VO_2 was calculated from figure). (1B): Effect of metformin on VO_{2peak} (ml/kg/min) in the overall population, the whole population was Caucasians [for Boulé et al., 2013 (d–g) and Malin et al., 2012 studies, pre-metformin data have been compared to post-metformin data; for rest, post-metformin data have been compared to placebo data; for Boulé et al., 2013 (d–g) study, post-metformin data was calculated from the pre-metformin data and the reported differences; the standard deviations for post-metformin data were assumed to be same as that of pre-metformin data].

4. Discussion

This meta-analysis has demonstrated that metformin does not affect VO_2 and VO_{2peak} in the overall population, healthy volunteers, patients (those with T2DM, insulin resistance, IGT/IFG, and metabolic syndrome) and those with insulin resistance alone. Some previous studies have also demonstrated that metformin does not significantly affect VO_2 and VO_{2peak} [22,23,30,31,40]. However, it was observed in an earlier study that exercise capacity is only affected by metformin at or near maximal workloads [17]. Hence, it is unlikely that exercise capacity will be impaired by metformin with exercises of lesser intensities, which was the scenario in many of our included studies. Subgroup analyses showed that metformin does not affect VO_2 and VO_{2peak} irrespective of the ethnicity [Caucasians and non-Caucasians (Brazilians)], duration of treatment (<2 weeks and ≥2 weeks) and characteristics of the included studies (parallel group vs. cross-over studies).

In this study, metformin showed a significant decrease in HR in the overall population and healthy volunteers, but a significant increase in the patients. It is to be considered that a reduction in HR by 2 per min in the overall population might not be clinically significant. There are pieces of evidence from *in vitro* and *in vivo* animal studies to suggest that metformin has several roles in the heart involving electric activity, energy metabolism, ischemia-reperfusion injury, cardiac remodeling as well as systolic and diastolic functions. Previous studies have demonstrated that metformin at therapeutic doses is unlikely to produce major changes in the myocardial substrate utilization. However, the mechanism of direct effect of metformin on electrical activity of cardiomyocytes is not known [41]. This review exhibited that metformin does not have any significant effect on exercise test duration in the overall population who were all healthy volunteers, which might be because of its nominal effect on fatigue index [30]. Some previous studies have also demonstrated that metformin does not significantly affect the exercise test duration [23,30,32].

There was a significant decrease in RER and a significant increase in RPE in the overall population and healthy volunteers in this study without any changes in the patients (diabetes and those with insulin resistance alone). RER is the

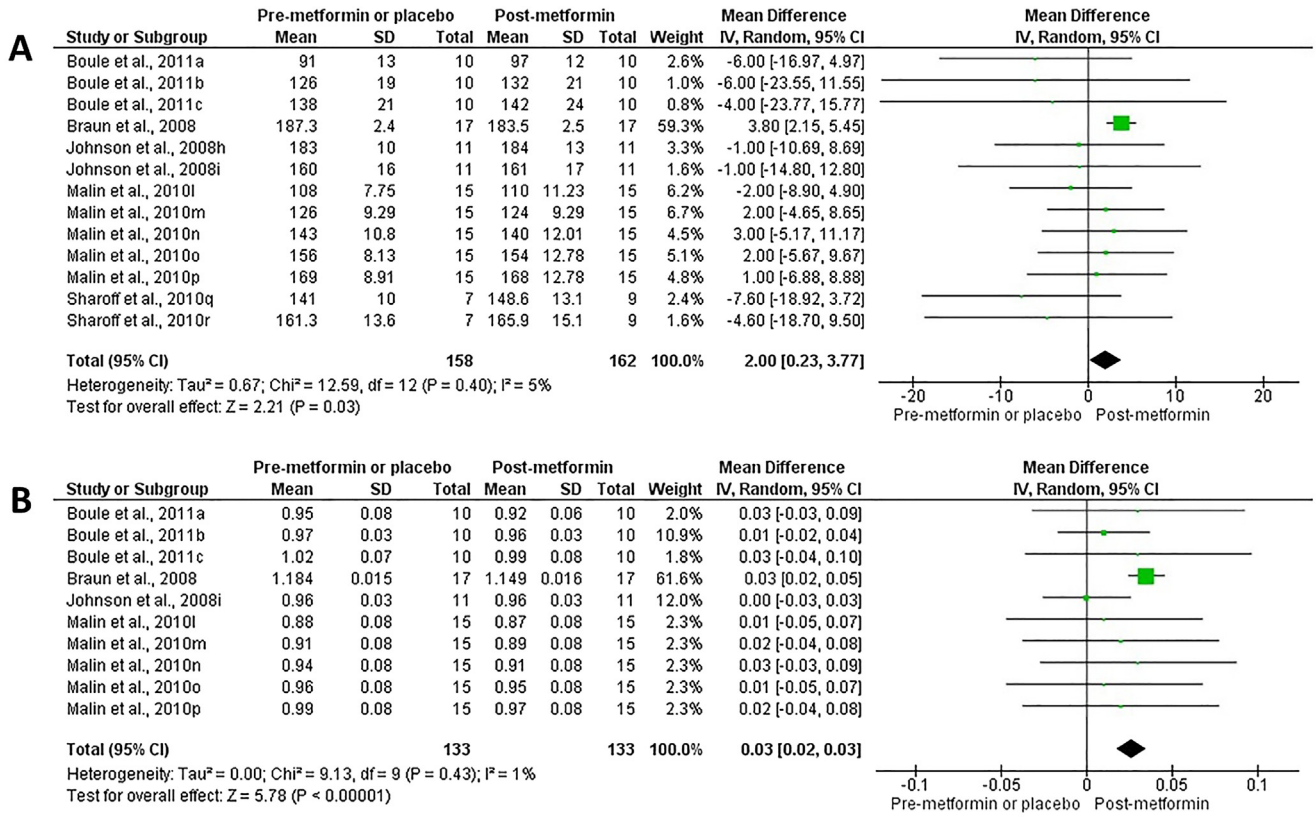

Fig. 2 – Forest plots showing secondary outcomes. (2A): Effect of metformin on HR (per min) in the overall population (for all studies, post-metformin data have been compared to placebo data). (2B): Effect of metformin on RER in the overall population [for all studies, post-metformin data have been compared to placebo data; for Malin et al., 2010 (l-p) study, the standard deviation of RER was calculated from figure].

ratio between the amount of CO_2 produced and O_2 used during metabolism. It increases with exercise intensity and under steady state conditions, it is used to indirectly determine the relative contribution of carbohydrate and lipids to overall energy expenditure [42,43]. A high RER indicates that carbohydrates are being predominantly used, while a low RER suggests lipid oxidation [42,43]. RER at the end of maximal exercise has been shown to have a significant correlation with changes in exercise capacity [44]. From the present study, it can be conferred that metformin lowers RER by increasing lipid oxidation, which is a normal adaptation during exercise [30]. Few previous studies have demonstrated that metformin lowers RER [21,23], while some studies have shown that metformin has no effect on RER [30,32,45].

RPE, on the other hand, is a quantitative measure of the intensity of physical activity [46,47]. In the present review, metformin has been shown to increase RPE. This reduced exercise capacity could be attributed to inhibition of tissue respiration by metformin-induced activation of AMPK [16] and an increase of anaerobic metabolism by inhibition of transfer of electrons in the mitochondrial electron transport system [18–20]. If the perception of the same intensity of exercise appears difficult with metformin, individuals may be less likely to comply with exercise training in conditions like T2DM. If this difference in RPE turns out to be a common side-effect of metformin, physicians may need to adjust exercise prescription. There are contradicting results in the literature regarding the effect of metformin on RPE as some studies have demonstrated an increase in RPE [23,30], while others have shown no effect on RPE with metformin [38,40].

Metformin increases anaerobic metabolism by inhibition of transfer of electrons in the mitochondrial electron transport system [18–20]. However, in our study, metformin has shown increased VAT in the in the overall population who were all healthy volunteers. However, this finding is based on the results obtained in two studies with 7–9 days (Braun et al., 2008) and a single dose (Johnson et al., 2008h) of metformin administration in a small sample size. Hence this finding needs to be confirmed by larger studies. Though metformin is thought to increase lactate production and reduces LT during exercise [10–12], recent evidence suggest that accumulated lactate during exercise does not cause any detrimental effect, rather it is found to be protective against muscle fatigue [48,49]. Although LT could not be analyzed in this present study because of lack of data, this could open up new research possibilities of investigating the role of metformin in modulating blood lactate level and correlation with exercise-related fatigue.

There is limited evidence describing the interaction between pharmacologic disease management and lifestyle approaches, such as diet and physical activity for conditions like T2DM. Further, it remains to be evaluated at what dose

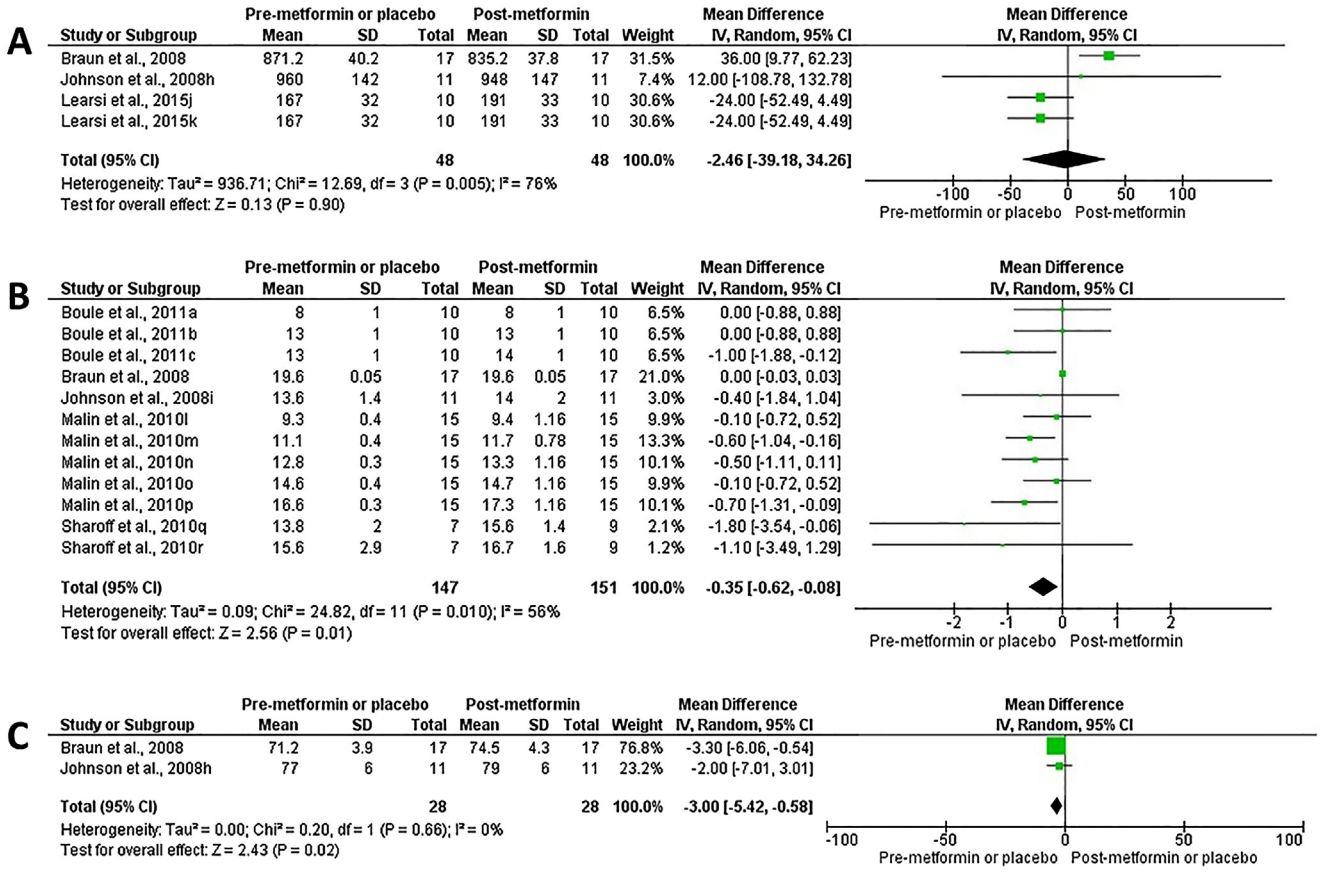

Fig. 3 – Forest plots showing secondary outcomes. (3A): Effect of metformin on exercise test duration (sec) in the overall population, the whole population was healthy volunteers (for all studies, post-metformin data have been compared to placebo data). (3B): Effect of metformin on RPE in the overall population (for all studies, post-metformin data have been compared to placebo data; for Braun et al., 2008 study, standard deviation of VO_2 was calculated from the figure). (3C): Effect of metformin on VAT in the overall population, the whole population was healthy volunteers (for all studies, post-metformin data have been compared to placebo data).

metformin needs to be combined with exercise to maximize health benefits. The findings of this meta-analysis, that metformin does not change exercise capacity will be reassuring the physicians to follow the current diabetes treatment guidelines without concerns about its effect on exercise tolerance. This finding further adds to the safety data of metformin. Mechanistic studies are needed following metformin and exercise treatment to investigate mitochondrial biogenesis and/or blood flow to better understand the mechanism behind these co-prescribed therapies on improving chronic disease management, such as T2DM [50]. The impact of metformin on VO_{2peak} in relation to glycemic control and cardiovascular risk reduction remains an area to be further explored. Individual RCTs in healthy as well as diseased population (T2DM, metabolic syndrome and IGT/IFG) for a prolonged period are warranted to evaluate the effect of metformin on different parameters of exercise (aerobic and anaerobic) capacity.

To the best of our knowledge, this is the first meta-analysis to demonstrate the effect of metformin on various parameters of exercise capacity in healthy volunteers as well as patients with T2DM, metabolic syndrome, and IGT/IFG. However, this study has certain limitations. Primarily, all the studies (parallel group and cross-over) have been combined in the overall analyses, resulting in low GRADE evidence for some of the outcomes. Higher heterogeneity was observed among the studies comparing exercise test duration and RPE. Further, the pre-metformin group was compared either with post-metformin or placebo groups depending on the study design to analyze the various parameters. Although the dose of metformin used was more or less uniform, the duration of therapy varied across different studies (1–180 days). In addition, different types (aerobic and anaerobic) and intensities of exercises were included in the final analyses, though metformin is known to have altered effects on different types of exercises [28]. In studies of aerobic exercise physiology or behavior, the exercise intensity was almost always controlled by scaling it as a percentage of maximal aerobic capacity [21,51–53]. Precise comparison of any outcome variables between metformin and placebo groups could have been confounded by the different relative exercise intensity in each condition. Several studies measured parameters of exercise capacity at different time points or at different intensities in the same participants, thereby giving a chance of overestimation of

the treatment effects. Finally, many of the included studies, including the different subgroup analyses had less sample size, and all the studies could not be used for comparison of all the outcomes due to unavailability of data. Notwithstanding these limitations, this study has demonstrated that metformin did not affect VO_2, VO_{2peak}, HR, exercise test duration and VAT, although it significantly decreased HR and RER, and increased RPE in the overall population. In addition, there was an increased VAT in the healthy volunteers.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Author contributions

SS has conceptualized the review; SD and SS have drafted the study protocol; SD and AS were involved with literature search and study selection; SKB and SS were involved with disagreement resolution and finalization of included studies; SD, SKB, and AS have extracted data from studies; SD, SS, and SKB performed the risk of bias analyses; SD and NSN have performed the analyses; SD, SKB, ASX, SS, SK, JPS, and NSN have interpreted the analyses; SD, SKB, ASX, and SS have drafted the review; SS, SK, JPS, and NSN have provided expert inputs and updated the final review. SS takes responsibility for the contents of this article.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.08.022.

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