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Effect of metformin on exercise capacity: A meta-analysis

Saibal Das [a], Sapan Kumar Behera [a], Akila Srinivasan [b], Alphienes Stanley Xavier [a], Sandhiya Selvarajan [a,*], Sadishkumar Kamalanathan [c], Jaya Prakash Sahoo [c], N Sreekumaran Nair [d]

[a] Department of Clinical Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
[b] Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
[c] Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
[d] Department of Biostatistics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

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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

* Corresponding author at: Department of Clinical Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry 605 006, India.
E-mail address: sandhiya_s@jipmer.edu.in (S. Selvarajan).
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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