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# Interactive effects of exercise and metformin on lactic metabolism in type 2 diabetes

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**Objective** Lactic acidosis is typically caused by an imbalance in lactic metabolism. This may be attributed to several reasons and is usually a result of complex interactions. There may be an increased risk for lactic acidosis in type 2 diabetes mellitus (T2D) patients when metformin treatment and physical exercise are combined since both metformin and exercise acutely affect lactic metabolism. As timing of exercise following metformin ingestion may determine the magnitude of long-term metabolic adaptations, this study aimed to test the acute effects of exercise performed at different times following metformin ingestion on lactic metabolism in T2D patients with a randomized crossover time series study design.

**Methods** Participants were recruited from two clinical health-care centers in China using a two-step screening procedure. First, approximately 2 523 patients with T2D were screened from the local diabetes database and clinical outpatient registration with inclusion criteria being men and women (30–65 years old) diagnosed with T2D no more than 5 years ago and treated with metformin (maximal daily dose of 2000 mg). Out of 100 potential participants who met the inclusion criteria, 56 were interested and invited to a laboratory visit. Finally, 34 patients participated in the study and of those, 26 patients (14 women and 12 men, mean age = 53.8 ± 8.6 years) completed all testing procedures.

All patients visited the laboratory on 4 occasions, each separated by at least 48 hours. Initially a control visit was performed and consisted of metformin administration only (Metf) and a maximal incremental cycle ergometer test in the afternoon. Thereafter, all participants performed a high-intensity interval training session (HIIT, 3 minutes at 40% followed by 1 minute of 85% of maximum power output) 30 minutes (EX30), 60 minutes (EX60), and 90 minutes (EX90) post breakfast and metformin administration, respectively, in a randomized order.

Serum lactate and glucose concentrations were assessed enzymatically, while insulin was assessed by an electrochemiluminescence immunoassay and superoxide dismutase (SOD) activity was determined by spectrophotometry. Measurements were performed before breakfast as well as both before and immediately after each exercise bout. In addition, capillary blood glucose concentrations were measured immediately after sampling using Omron AS1 glucose test strips (HGM-114) and lactate concentrations were assessed by ARKRAY Lactate Pro 2 test strips throughout each measurement day. Dietary intake was standardized on the evening prior to each laboratory day as well as between 8:00 a.m. and 4:00 p.m. during each testing day. This trial is registered with ChiCTR-IOR-16008469 on 13th of May 2016.

**Results** During all three-exercise sessions, the capillary lactate concentrations were significantly increased to a similar extent. However, sixty minutes following metformin administration, serum lactate levels began to accumulate to the highest level, where 30% of patients showed lactate concentrations above resting values (≥2 $mmol \cdot L^{-1}$). The increased lactate concentrations were statistically associated with increased glucose when exercise was performed 60 minutes post metformin administration ($r=0.384$, $p=0.048$). Furthermore, in EX60 and EX90 lactate concentrations were 19% and 8% higher, respectively, compared to EX30. In addition, we found that after exercise but not before exercise, the lactate level was positively correlated with SOD (EX30 $r=0.478$ and $p=0.012$, EX60 $r=0.562$ and $p=0.002$, EX90 $r=0.562$ and $p=0.003$, respectively).

**Conclusions** We found that the changes of lactate concentrations were related to the timing of exercise post meal and after metformin ingestion. Thus, timing of exercise appears to be an important factor to be considered when prescribing exercise for T2D patients treated with metformin. In the present study, the optimal timing of HIIT exercise was 30 minutes after metformin administration, which was indicated by a minimized fluctuation of both glucose and lactate levels in T2D patients. Our results also suggest that lactic metabolism and oxidative stress could be among the main underlying molecular mechanisms that elucidate the combinational therapy of exercise and metformin treatment on T2D. Since both acute exercise and metformin may induce opposite effects on ATP production and reactive oxygen species formation, it is important to conduct further studies in an attempt to define the "safe time" for exercise after metformin administration.