

Metformin and Exercise: no Additive Effect on Blood Lactate Levels in Healthy Volunteers

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Metformin administration has been associated with substantial rises in blood lactate concentrations in individual Type 2 diabetic patients. Exercise also leads to increases in blood lactate levels. The objective of this study was to determine whether metformin administration augments the rise in plasma lactate concentrations during intermittent exercise in healthy subjects, when compared to placebo. Twelve healthy males (age 28 ± 5 years, body mass index $22.7 \pm 1.3 \text{ kg m}^{-2}$) took either 1.7 g metformin or placebo daily for 4 consecutive days before being subjected to strenuous intermittent exercise. On the morning of the fourth day exercise was performed on an upright bicycle ergometer at a work load of 200 W for 2 min alternating with 2 min rest for an overall duration of 60 min. Maximal plasma lactate levels during exercise (metformin: $4.1 \pm 2.6 \text{ mmol l}^{-1}$, placebo: $4.5 \pm 2.6 \text{ mmol l}^{-1}$), areas under the plasma lactate curve (207 ± 121 vs $222 \pm 133 \text{ mmol l}^{-1} \text{ h}^{-1}$), blood pyruvate levels at the end of exercise (0.06 ± 0.04 vs $0.07 \pm 0.04 \text{ mmol l}^{-1}$), lactate/pyruvate ratio (65 ± 41 vs 60 ± 36), serum insulin (25.4 ± 8.9 vs $32.3 \pm 13.0 \text{ pmol l}^{-1}$), and plasma glucose (4.4 ± 0.3 vs $4.5 \pm 0.3 \text{ mmol l}^{-1}$) did not differ significantly between metformin and placebo administration. Administration of metformin did not lead to an augmented rise in endogenous plasma lactate concentrations during intermittent exercise in healthy fasting subjects under the experimental design chosen.

KEY WORDS Metformin Exercise Plasma lactate Lactic acidosis

Introduction

Use of biguanides in the treatment of diabetic patients is overcast by the reports of rare fatal lactic acidosis. Thus, the use of phenformin and buformin was discontinued in most of Europe and in the US in the 1970s. Treatment with metformin is also associated with lactacidosis albeit less frequently than phenformin.¹⁻⁴ Although previous studies have addressed the issue of blood lactate levels, biguanides and exercise, they offer little guidance for today's practitioners.⁵⁻¹¹ The biguanides used are for the most part no longer on the market, the duration of the exercise challenge was short, the work load administered was mild, and the results are contradictory.

This study readdresses this issue using intermittent strenuous exercise which results in relatively constant increases of plasma lactate over 1 h.¹² The aim of the present study was to determine if 1.7 g of metformin administered for 4 days results in an additional increase in plasma lactate concentrations induced by exercise in fasting healthy volunteers when compared to placebo.

Patients and Methods

Twelve healthy male non-athletic volunteers were recruited at the University of Düsseldorf (age 28 ± 5 years, BMI $22.7 \pm 1.3 \text{ kg m}^{-2}$ (mean \pm SD)). Participants were initially informed of study aims, procedures, risks, and possible side-effects of metformin administration. Written informed consent was obtained. Subjects were then examined and routine serum biochemistry was obtained. The study protocol was reviewed and approved by the local ethical committee.

Subjects either ingested 1.7 g metformin ($2 \times 850 \text{ mg}$; Glucophage-Retard®, Lipha, Essen, Germany) or placebo (Lipha) after breakfast on the 4 days prior to an exercise study. Each subject performed two exercise studies, one with metformin and one with placebo, in random order. On the morning of the fourth day, exercise was performed after an overnight fast and 30 min after administration of metformin or placebo, which were given with 100 ml of tap water and no food. Participants were requested to avoid alcohol on the evening before testing and were asked not to smoke or drink coffee or tea on the morning of the study. The minimum time between study phases (wash out period) was 7 days.

Exercise was performed on an upright bicycle ergometer (Conditronic 30, Keiper Dynavit, Rockenhausen, Germany). The 60 min of strenuous intermittent exercise consisting of 2 min at 200 W resistance at 50–60 rev

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min⁻¹ alternating with 2 min rest were begun after a 10 min warm up period. The warm up period consisted of 5 min cycling at 50 W and 5 min at 100 W. During the rest periods subjects sat on the ergometer without pedalling. After completion of the intermittent exercise subjects rested for another 60 min in a reclining chair (total study duration = 160 min).

All free-flowing venous blood samples were drawn from an indwelling intravenous cannula (Viggo-Spectramed, Helsingborg, Sweden, 1.4 mm (17G)) which was inserted into a forearm vein upon arrival at the exercise laboratory. The cannula was kept patent by the slow infusion of physiological saline. Initial venous blood samples were obtained half an hour after metformin or placebo administration. Further samples were drawn following the 10 min warm up, at 4 min intervals during the intermittent exercise immediately at the onset of the 2 min rest periods, and 15, 30, and 60 min after the exercise challenge (total blood loss during each test = 200 ml). During the study period blood pressure was measured intermittently by an automatic registering device (TM-2420, Bosch & Sohn, Jungingen, Germany). While exercising, blood pressure measurements were performed during the last minute of the exercise periods.

Blood samples were assessed for hormones and metabolites that characterize the exercise response. Plasma glucose was measured immediately after blood collection by a glucose oxidase method (Glucose-Analyser II, Beckman Industries, Fullerton, USA). Aliquots of blood for all other parameters were stored on ice prior to further work up. Venous blood for the plasma-lactate assay was collected into fluoride-EDTA, and for blood pyruvate, acetoacetate and β -hydroxybutyrate into ice cold 1 M perchloric acid. Plasma lactate concentrations were measured amperometrically (YSI Model 27 Lactate-Analyzer, Yellow Springs, USA). Ketone bodies and pyruvate were determined microfluorometrically. Aliquots for the measurement of serum insulin, serum C-peptide and plasma glucagon were stored at -20°C pending standard radioimmunoassay. Similarly, aliquots for total free fatty acid measurement were frozen and were determined photometrically at a later date (WAKO, Neuss, Germany). Acid base determinations were carried out immediately using a pH/blood gas analyser (Series 2000, Ciba-Corning, Fernwald, Germany). For the measurement of plasma metformin the thawed plasma aliquots were deproteinized with 10% trichloroacetic acid, centrifuged for 3 min by 10 000 rev min⁻¹ and 70 μ l of the clear supernatant were assayed by HPLC (Schimadzu HPLC with pump (LC-9 A, autosampler (SIL-6B, UV-detector SPD A6)) and integrator (C-R 4 AX), cation exchange column Partisil (SCX, 10 μ m, 4.6 \times 25, Biscoff, Germany) utilizing a mobile phase of 100 mM ammoniumdihydrogenphosphate after 6.5 to 7.5 min, under a flow of 4 ml min⁻¹). The sensitivity for the procedure is given as 20 μ g l⁻¹. Plasma metformin measurements were performed by Sycomp Laboratories, Augsburg, Germany.

Statistical Analysis

All results are presented as mean \pm SEM. The area under the curve (AUC) was calculated by the trapezoidal rule. Statistical analysis made use of the students paired *t*-test and analysis of variance for repeated measurements.

Results

Beginning at comparable initial plasma lactate values prior to exercise on both study days (Table 1), plasma lactate rose to maximal values of 4.1 \pm 2.6 mmol l⁻¹ 30 \pm 18 min after metformin administration and 4.5 \pm 2.6 mmol l⁻¹ ($p=0.247$) 35 \pm 18 min ($p=0.272$) after placebo administration. Mean plasma lactate concentrations during intermittent exercise did not differ between prior metformin or placebo administration (Figure 1). The AUC below the plasma lactate profile during intermittent exercise was comparable after metformin and placebo administration ($p=0.314$). After ending the exercise challenge plasma lactate concentrations fell more slowly following metformin administration than after placebo ($T=85$ min, metformin 2.2 \pm 1.5 vs placebo 1.7 \pm 0.9 mmol l⁻¹ ($p=0.063$); $T=100$ min, 1.8 \pm 0.9 vs 1.5 \pm 0.9 mmol l⁻¹ ($p=0.032$); $T=130$ min, 1.5 \pm 0.4 vs 1.4 \pm 0.4 mmol l⁻¹ ($p=0.345$)). However, AUCs were not different after end of exercise ($p=0.091$). Plasma pyruvate levels did not differ following metformin or placebo administration when expressed as individual concentrations or as AUCs for the intermittent exercise or recovery period. The lactate/pyruvate ratio, which allows an approximation of cytosolic NAD⁺/NADH ratio and thus redox status, was also comparable between metformin or placebo administration.

After metformin administration, initial plasma metformin concentrations were 807 \pm 305 μ g l⁻¹ at the beginning of exercise and rose to 1715 \pm 578 μ g l⁻¹ at the end of exercise ($p<0.001$). Following placebo administration plasma metformin concentrations were below the sensitivity of the method (<20 μ g l⁻¹). Maximal plasma lactate levels or mean plasma lactate levels during exercise did not correlate with plasma metformin concentrations.

Blood pH values remained constant during the whole study period (Table 2). Base excess fell to a minimum at the end of exercise but basal values were reached again at the end of the study. Intermittent exercise induced a moderate decline in endogenous insulin secretion, as shown by lower serum insulin and C-peptide levels after exercise. AUC for the free fatty acids during the exercise period ($p<0.033$) and the AUC for glucagon ($p<0.013$) differed significantly. In contrast, glucose, acetoacetate, and β -hydroxybutyrate levels were comparable following metformin or placebo administration. The increase in heart rate and blood pressure due to the intermittent exercise was comparable on both study days. Eight of the twelve subjects complained of common side-effects

Table 1. Changes in lactate and pyruvate levels induced by intermittent ergometry at a work load of 200 W for 60 min in comparison to baseline ($t=0$ min), start of ergometry ($t=10$ min; after warming up at 50 and 100 W for 5 min each), after ergometry ($t=70$ min), and the end of study after 60 min rest ($t=130$ min). The twelve healthy individuals received 1.7 g metformin or placebo for 4 days; mean \pm SD

	Baseline	Start of ergometry	After ergometry	End of study	AUCs	
					During	After ergometry
Lactate (mmol l^{-1})						
Metformin	1.30 \pm 0.30	1.62 \pm 0.75	3.66 \pm 2.71	1.46 \pm 0.42	207 \pm 121	136 \pm 76
Placebo	1.34 \pm 0.30	1.53 \pm 0.60	3.69 \pm 2.70	1.36 \pm 0.40	222 \pm 133	122 \pm 69
					(mmol l^{-1} h $^{-1}$)	
Pyruvate (mmol l^{-1})						
Metformin	0.05 \pm 0.03	0.05 \pm 0.02	0.06 \pm 0.04	0.04 \pm 0.03	3.6 \pm 1.6	2.6 \pm 1.2
Placebo	0.05 \pm 0.02	0.04 \pm 0.02	0.07 \pm 0.04	0.04 \pm 0.02	3.5 \pm 1.6	2.9 \pm 1.8
					(mmol l^{-1} h $^{-1}$)	
Lactate/pyruvate ratio						
Metformin	35 \pm 26	40 \pm 35	65 \pm 41	37 \pm 12	–	–
Placebo	32 \pm 10	40 \pm 11	60 \pm 36	40 \pm 21	–	–

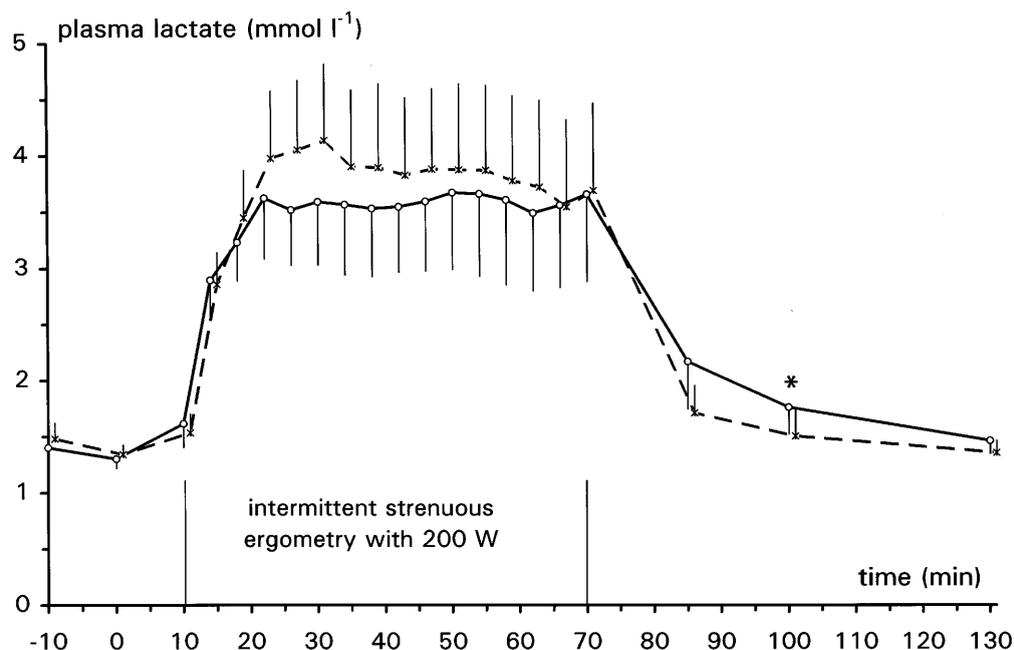


Figure 1. Plasma lactate concentrations during intermittent strenuous ergometry in 10 healthy subjects following administration of metformin (solid line) or placebo (broken line); mean \pm SE; asterisk = significant difference

of metformin such as nausea, abdominal discomfort or diarrhoea.

Discussion

Administration of metformin should lead to an augmented rise in plasma lactate concentrations during intermittent physical exercise if metformin interferes with lactate clearance. By subjecting healthy volunteers to 60 min of intermittent exercise a substantial and sustained increase

in plasma lactate concentrations was induced. This increase was not augmented by administration of metformin. Thus, the hypothesis of the study was not confirmed. However, administration of metformin did result in a slower decline of the raised lactate levels after exercise was stopped. This suggests that metformin administration does in some way interfere with lactate clearance.

Previous studies addressing the influence of biguanide administration on plasma lactate levels during exercise have reported an increase,⁹⁻¹¹ a decrease⁸ or no

Table 2. Changes in pH, base excess, insulin, C-peptide, glucagon, free fatty acids, γ -hydroxybutyrate, aceto acetate, heart rate, systolic and diastolic blood pressure induced by intermittent ergometry at a work load of 200 W for 60 min in comparison to baseline ($t=0$ min), start of ergometry ($t=10$ min; after warming up at 50 and 100 W for 5 min each), after ergometry ($t=70$ min), and the end of study after 60 min rest ($t=130$ min). The 12 healthy individuals received 1.7 g metformin or placebo for 4 days; mean \pm SD, AUCs were given where appropriate, significant differences between placebo and metformin

	Baseline	Start of ergometry	After ergometry	End of study	AUCs	
					During	After ergometry
Insulin (pmol l ⁻¹)						
Metformin	35.4 \pm 9.6	30.5 \pm 8.5	25.4 \pm 8.9	29.7 \pm 10.1	1.68 \pm 0.42	1.93 \pm 0.64
Placebo	39.5 \pm 10.0	33.4 \pm 10.0	32.3 \pm 13.0	31.6 \pm 8.8	2.08 \pm 0.69	2.13 \pm 0.65
					$\mu\text{mol l}^{-1} \text{h}^{-1}$	
C-peptide (nmol l ⁻¹)						
Metformin	0.52 \pm 0.11	0.46 \pm 0.10	0.43 \pm 0.14	0.42 \pm 0.12	80 \pm 21	82 \pm 24
Placebo	0.57 \pm 0.09	0.51 \pm 0.13	0.49 \pm 0.12	0.49 \pm 0.11	92 \pm 24	92 \pm 23
					$\text{nmol ml}^{-1} \text{h}^{-1}$	
Glucagon (pg ml ⁻¹)						
Metformin	245 \pm 192	259 \pm 259	282 \pm 218	253 \pm 184	16.6 \pm 13.9*	16.1 \pm 10.9
Placebo	243 \pm 221	225 \pm 192	245 \pm 222	222 \pm 160	15.0 \pm 13.7	14.5 \pm 11.0
					$\text{ng ml}^{-1} \text{h}^{-1}$	
Plasma glucose (mmol l ⁻¹)						
Metformin	4.5 \pm 0.4	4.4 \pm 0.3	4.4 \pm 0.3	4.3 \pm 0.4	266 \pm 20	279 \pm 22
Placebo	4.6 \pm 0.3	4.5 \pm 0.4	4.5 \pm 0.3	4.4 \pm 0.3	270 \pm 15	286 \pm 17
					$\text{mmol l}^{-1} \text{h}^{-1}$	
Free fatty acids (mmol l ⁻¹)						
Metformin	0.39 \pm 0.15	0.32 \pm 0.14	0.60 \pm 0.34	0.67 \pm 0.21	26.6 \pm 13.8*	39.2 \pm 13.2
Placebo	0.31 \pm 0.13	0.27 \pm 0.13	0.44 \pm 0.27	0.55 \pm 0.21	19.8 \pm 11.8	32.4 \pm 13.4
					$\text{mmol l}^{-1} \text{h}^{-1}$	
β -hydroxybutyrate (mmol l ⁻¹)						
Metformin	0.06 \pm 0.06	0.04 \pm 0.03	0.06 \pm 0.07	0.14 \pm 0.13	2.9 \pm 2.4	7.2 \pm 8.1
Placebo	0.04 \pm 0.02	0.03 \pm 0.02	0.04 \pm 0.03	0.08 \pm 0.08	2.1 \pm 0.9	4.5 \pm 3.6
					$\text{mmol l}^{-1} \text{h}^{-1}$	
Aceto acetate (mmol l ⁻¹)						
Metformin	0.10 \pm 0.06	0.08 \pm 0.05	0.09 \pm 0.06	0.12 \pm 0.11	6.4 \pm 3.8	3.6 \pm 3.1
Placebo	0.07 \pm 0.02	0.06 \pm 0.02	0.06 \pm 0.03	0.09 \pm 0.06	4.6 \pm 1.2	2.7 \pm 1.4
					$\text{mmol l}^{-1} \text{h}^{-1}$	
pH						
Metformin	7.39 \pm 0.03	7.41 \pm 0.03	7.39 \pm 0.03	7.38 \pm 0.03	–	–
Placebo	7.39 \pm 0.02	7.39 \pm 0.02	7.41 \pm 0.06	7.38 \pm 0.03	–	–
Base excess (mmol l ⁻¹)						
Metformin	1.39 \pm 1.46	1.27 \pm 1.36	-0.85 \pm 3.39	0.99 \pm 2.61	–	–
Placebo	2.38 \pm 2.46	1.43 \pm 3.17	-0.17 \pm 3.57	2.44 \pm 2.71	–	–
Heart rate (beats min ⁻¹)						
Metformin	80 \pm 19	98 \pm 28	136 \pm 36	78 \pm 12	–	–
Placebo	84 \pm 14	88 \pm 24	126 \pm 35	77 \pm 9	–	–
Systolic blood pressure (mm Hg)						
Metformin	125 \pm 12	151 \pm 28	202 \pm 39	118 \pm 18	–	–
Placebo	117 \pm 13	138 \pm 34	184 \pm 27	108 \pm 13	–	–
Diastolic blood pressure (mm Hg)						
Metformin	76 \pm 5	79 \pm 11	66 \pm 12	76 \pm 8	–	–
Placebo	71 \pm 16	72 \pm 13	70 \pm 16	73 \pm 6	–	–

difference,^{5,6} with one author emphasizing substantial variability in response.⁷ Because of differing experimental protocols, variable responses of basal lactate levels to biguanide administration and the use of agents no longer available, the conclusions that can be drawn from these studies are limited. The current study distinguishes itself

from the previous research in the duration and magnitude of the exercise challenge. In the earlier studies, exercise was customarily performed for 15 min at a work load of between 45 and 110 W. Given that lactate production, other things being equal, depends on duration and degree of exertion, the lactate flux generated during the

intermittent strenuous exercise of our study must be greater than that generated in the earlier studies. Furthermore the time period for which the subjects were exposed to high blood lactate levels were longer than previously reported. A cumulative effect of metformin and increased lactate flux on plasma levels may be a slow process, occurring over more than 15 to 20 min. Increasing the work load and extending the exposure to high lactate levels for over 60 min, however, did not lead to a more pronounced rise in lactate levels following metformin administration. It is conceivable that a possible impairment of lactate clearance inflicted by metformin was counterbalanced by lactate oxidation during the intermittent rest periods. This is in line with the observation that the greatest oxygen uptake is in the first minute of rest following each exercise period. The loading with metformin was followed in accordance with the available pharmacokinetic data.^{13,14} Due to a rapid enteral absorption and early renal elimination of metformin we chose to start the exercise soon after drug administration. As shown by the plasma metformin levels, therapeutic biguanide concentrations were already established at the onset of exercise and increased progressively and significantly during exercise. This increase in metformin levels is attributable to the ongoing absorption of metformin, possibly enhanced in the fasted state by exercise. A standardized test meal, which may have facilitated splanchnic lactate output, was not used, in order to avoid the variability in plasma metformin concentrations associated with inhomogeneous enteral absorption.

Plasma lactate concentrations were measured to evaluate changes in non-erythrocyte lactate levels. Contamination by lactate of erythrocyte origin was minimized by careful handling of samples to prevent haemolysis. Analysis of the hormone and substrate concentrations in our study showed that plasma glucose, serum insulin, and serum C-peptide concentrations tended to be lower following metformin administration than after placebo. In contrast ketone body, free fatty acid and glucagon levels tended to be higher, suggesting an increase in hepatic gluconeogenic substrate flux. These observations suggest that metformin does have an impact on glucoregulation during exercise in healthy individuals, even if this is not reflected in an augmented rise in plasma lactate concentrations during exercise. An alternative explanation may be that enhanced insulin sensitivity for glucose metabolism resulted in lower insulin levels, allowing higher ketogenesis and lipolysis.

In conclusion, in healthy individuals in the fasting state administration of metformin for 4 days does not induce an additional increase in plasma lactate during intermittent exercise in comparison to that seen with placebo. Although this study does not directly address the role of metformin in lactate metabolism in exercising diabetic patients, it does not support the hypothesis that metformin administration amplifies the lactate response to exercise.

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