

Serum lactate levels in Libyan patients with type 2 diabetes mellitus receiving metformin therapy

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Introduction

Metformin is the most commonly used glucose lowering drug in patients with type 2 diabetes [1]. Its anti hyperglycemic action is mainly achieved through a reduction in hepatic glucose production (gluconeogenesis) as well as increased glucose uptake in peripheral tissues [2]. These effects are translated clinically into a reduction in both fasting glucose and glycated hemoglobin and to lesser extent a reduction in postprandial glucose [3]. Metformin has an excellent safety profile with rare incidence of hypoglycemia and neutral effects on body weight that made it the first line therapy for hyperglycemia in patients with type 2 diabetes [1]. However metformin has been linked for years with the rare development of the life-threatening complication of lactic acidosis [2]. Metformin may increase plasma lactic acid by blocking lactate utilization through gluconeogenesis and may also reduce non oxidative and oxidative lactate utilization leading to lactate accumulation [4]. In conditions where there is increased production and/or decreased utilization of lactates (e.g liver, renal or heart failure) lactate accumulation is greater leading to development of lactic acidosis [5]. In this study we determine whether metformin therapy in otherwise healthy subjects with type 2 diabetes increases the levels of serum lactate.

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ABSTRACT

Objective: Metformin is the most widely prescribed anti-hyperglycemic agent. It has been linked to the development of lactic acidosis. However the incidence of this condition is thought to be very low in metformin-treated patients. The aim of this study to assess the levels of serum lactate in metformin-treated patients with type 2 diabetes.

Methods: Thirty patients with type 2 diabetes receiving metformin therapy were recruited to the study from out-patients attending Benghazi Diabetes Center. Thirty age-matched and sex-matched healthy controls were selected for comparison. Serum lactate was determined in both groups

Results: Metformin-treated patients with type 2 diabetes had higher mean serum lactate levels compared with age-matched and sex-matched healthy subjects (1.87 mmol/l vs 1.49 mmol/l, $P < 0.05$). There is no effect of duration of treatment or the dose of metformin on serum lactate.

Conclusions: Metformin therapy is associated with small increase in serum lactate levels that seems to be dose-independent and not affected by treatment duration. This increase is far less than the levels known to be associated with lactic acidosis

KEY WORDS:

**Metformin
Biguanides
Lactate
Lactic acidosis**

Materials and methods

This cross-sectional study was conducted on 30 out-patients with type 2 diabetes mellitus attending Benghazi Diabetes Center, Benghazi, Libya. Fifteen males and fifteen females were randomly selected. All patients were on metformin. Patients with risk factors for development of lactic acidosis (chronic renal disease, liver disease or hypoxia) were excluded. The age, duration of diabetes, and duration and dose of metformin were recorded.

Thirty healthy subjects matched for age and sex were included as a control group. All study subjects underwent thorough history, physical examination, and laboratory evaluation including urine routine examination, renal and liver function tests. Five milliliters of venous blood were drawn from fasting subjects without tourniquet and collected in heparinized syringes, 0.5 ml of metaphosphoric acid (as protein precipitant) was added. Serum lactate was measured in the collected blood using a spectrophotometric assay. The assay was based on enzymatic oxidation of serum lactate by lactate dehydrogenase with reduction of NAD⁺ to NADH. The spectrophotometric measurement of the formed NADH at 340 nm serves as amount of lactate. The assay has 100% sensitivity and 95% specificity.

Statistical Analysis

Data were expressed as mean standard deviation and statistical analysis was performed using t-test with results considered significant if $p < 0.05$.

Results

Ten patients were on 500mg of metformin per day, 14 patients were on 1000mg/day and 6 patients were on 1500mg/day. Sixteen patients were on metformin for one year or less while 14 patients were treated with metformin for more than 1 year. Metformin-treated patients with type 2 diabetes had higher mean serum lactate levels compared with age-matched and sex-matched healthy subjects (1.87 mmol/l vs 1.49 mmol/l, $p < 0.05$). Among those on metformin there was no statistically significant difference in serum lactate levels between those on different doses (500mg/day vs. 1000mg/day vs. 1500mg/day) or those with different durations of metformin therapy (<1 year vs. >1 year). Results are displayed in table 1.

Discussion

Biguanides including metformin have been linked to the development of lactic acidosis, a condition associated with high mortality rate [2]. Although phenformin, the prototype member of biguanide group was withdrawn because of high incidence of lactic acidosis, different studies failed to show clear association between metformin and lactic acidosis [6]. The incidence of lactic acidosis with metformin is 10-20 times lower than with phenformin, a level

that is in many studies comparable to that of the background diabetic population [7]. In this study, patients treated with metformin but without lactic acidosis have significantly higher serum lactate levels than their age-matched and sex-matched health control. This increase in serum lactate was also observed in other different studies [8-11].

Table 1. Mean serum lactate in the study patients and control subjects.

	Numbers	Mean serum lactate (mmol/l) ± SD	P Value
Patients vs. control			
Patients	30	1.87 ± 0.68	<0.05
Healthy controls	30	1.49 ± 0.059	<0.05
Dose of Metformin			
500 mg/day	10	1.7 ± 0.65	NS
1000 mg/day	14	2.00 ± 0.72	NS
1500mg/day	6	1.8 ± 0.80	NS
Duration of metformin therapy			
≤ 1 year	16	1.76 ± 0.062	NS
> 1 year	14	1.99 ± 0.72	NS

However this increment in serum lactate did not reach the level diagnostic threshold of lactic acidosis (i.e. 5mmol/l or above). This is again in line with observations from other studies [12]. Only 10% of our patients had serum lactate above the normal level of 2.44 mmol/l, and none reached levels above 3.5 mmol/l.

In a study by Marchitti et al [13], there was a positive effect of metformin dose on serum lactate. However no such effect was observed in our study, as serum lactate levels at dose of 500 mg were similar to those at doses of 1500 mg. The absence of dose-related effect of metformin on serum lactate levels was also observed by other investigators. [11,14]. There was no recognizable difference on serum lactate with respect to duration of metformin treatment in our patients. The serum lactate levels among patients treated for one year or more were similar to patients treated for less than one year, indicating that metformin has no cumulative effect. This observation was also seen in another previous study [14]. In conclusion, metformin therapy may be associated with small increase in serum lactate levels that seems to be dose-independent and not affected

by treatment duration. This increase is far less than the levels known to be associated with lactic acidosis. This can explain the rare incidence of metformin-associated lactic acidosis.

Conflict of Interest

We declare that we have no conflict of interest.

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