

METFORMIN USE IN DIABETES MELLITUS WITH CHRONIC KIDNEY DISEASE - IS LACTIC ACIDOSIS A REAL CONCERN?

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Introduction^{1,2}

- Metformin use in type 2 diabetes mellitus with chronic kidney disease (CKD) is limited by concerns of it causing lactic acidosis.
- Metformin is associated with reduced cardiovascular mortality¹ & its stoppage results in poor glycemic control.
- Link between metformin & lactic acidosis has not been established in normal or in CKD populations².

Objective

To study whether metformin use in CKD is associated with raised serum lactate levels.

Methodology

Study Design: Prospective Observational

Study duration One year

Study site: Department of Nephrology, Kasturba Hospital, Manipal.

Study subjects:

Inclusion criteria:

- Adult type 2 diabetes mellitus with CKD [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m²] inadvertently receiving metformin.

Exclusion criteria:

- active sepsis, malignancy or any other drugs causing lactic acidosis.

Data Collection:

- Clinical, demographic, lab data from case records.
- Serum lactate & relevant investigations were done.
- Arterial Ph & serum bicarbonate were done in patients with raised serum lactate.
- Screening for other side effects of metformin

Data Analysis: On SPSS version 15 with p value less than 0.05 considered significant.

Results

Table 1 : Demography (number = 40)

Characteristics	Mean ± SD
Age (years)	56 ± 8.24
Body mass index (kg/m ²)	25.27 ± 3.80
Duration of diabetes mellitus (months)*	60(24 to 120)*
HbA1C % (number = 21)	7.01 ± 0.56
Serum creatinine(mg/dl)	3.5 ± 1.81
Creatinine clearance ml/min(CKD EPI)	27.82 ± 12.93
Metformin dosage (mg/day)	896.25 ± 350.16
Duration of Metformin use (months) *	24 (12.5 to 60)*
Serum lactate (mg/dl) *	12.25(10 to 15.75)*

*Median with Inter quartile range

Correlation between serum lactate level and dose of metformin

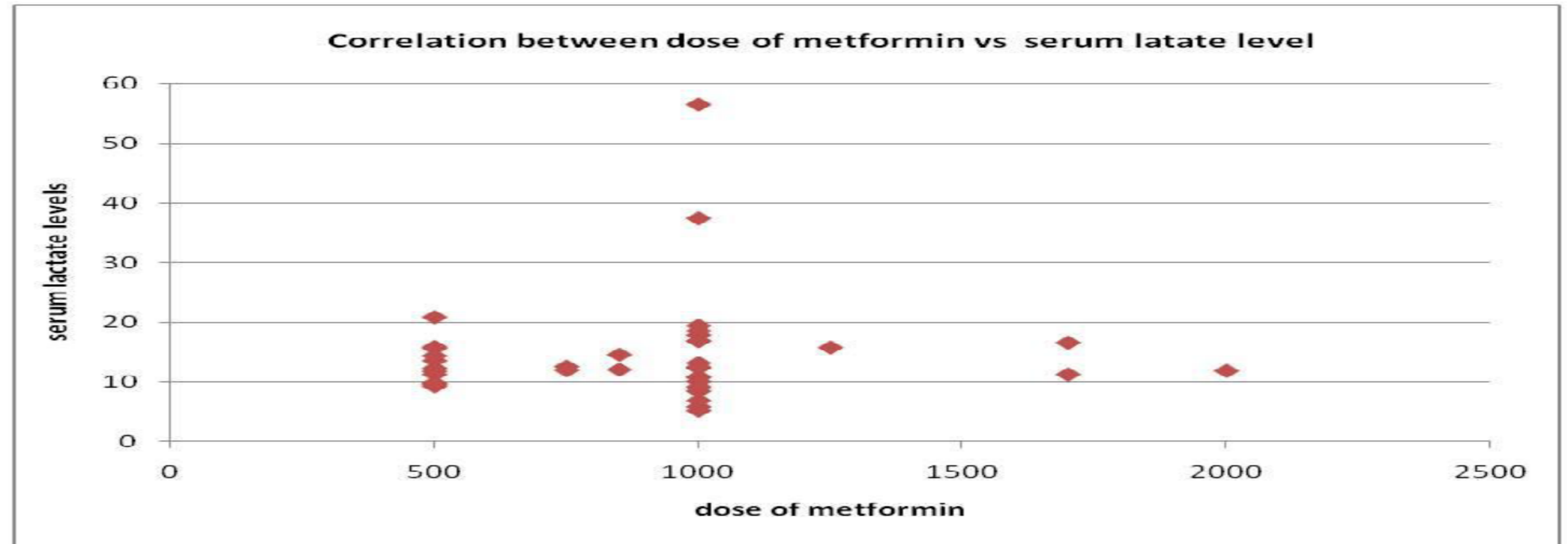


Table 2. Correlation between Metformin dose and serum lactate levels in each stage of CKD

CKD Stage	Number (%)	Pearson's correlation	p value
3	19(47.5)	0.11	0.63
4	11 (27.5)	-0.10	0.75
5	10 (25)	0.14	0.68
Total	40	0.63	0.69

Discussion

- Prescribing guidelines contraindicate the use of metformin in men and women with serum creatinine concentrations ≥ 1.5 and ≥ 1.4 mg/dL respectively.
- In this cohort of 40 patients with type 2 Diabetes mellitus & CKD on metformin in dose range 500 to 2000 mg/day for average of 2 years serum lactate was raised in only two.
- Serum lactate level did not correlate with metformin dose or CKD stage (Figure 1 & table 2).
- The two patients with raised serum lactate were asymptomatic & had normal arterial Ph & serum bicarbonate.
- No significant gastrointestinal or other adverse effects related to metformin therapy were observed.
- An updated Cochrane review has not found any cases of lactic acidosis associated with metformin use².
- Pharmacokinetic studies of metformin in renal insufficiency have shown reduced clearance of metformin³ but no correlation with lactic acidosis or mortality⁴. Metformin use in CKD has not been assessed in a controlled fashion⁵.

Conclusion

- In this small cohort of patients of Diabetes Mellitus and CKD stages 3 to 5 metformin was well tolerated.
- There was no correlation between metformin dose and serum lactate levels or CKD stage.
- There is a case for conducting larger trials of metformin use in diabetic CKD to enable revision of guidelines for use of this drug in CKD.

References

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