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CORRELATION BETWEEN METFORMIN USAGE AND PLASMA LACTATE LEVEL OF TYPE II DIABETES MELLITUS PATIENTS IN A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Background: Metformin is a widely used anti-hyperglycemic agent recommended for Type II Diabetic patients regardless of age. The most serious adverse effect associated with metformin is acknowledged to be lactic acidosis. The objective of the study was assess correlation between Metformin usage and plasma Lactate level of Type II Diabetes mellitus patients in a tertiary care teaching hospital. **Method:** This was a prospective observational study including 193 patients for a period of 6 months in Government Medical College, Trivandrum. Patients of age ≥30 who had type 2 Diabetes Mellitus with all co-morbidities enrolled in this study. The demographic data, disease data and laboratory data fasting plasma lactate was noticed. Pearson correlation was used to assess relationship between metformin and fasting plasma lactate. **Results:** The study population was predominantly female (59.5%) and nearly a third (59.5%) belonged to the age group of 51-60 years. Pearson correlation coefficient of plasma lactate with duration of metformin therapy was 0.479 the scatter gram indicated that there is a moderate positive relationship between two variables. Plasma lactate concentration increases with increasing duration of metformin therapy. This result was found to be statistically significant at the P value of 0.000 (P<0.01). **Conclusion:** In Conclusion, this study suggests that metformin therapy may be associated with small increase in serum lactate level seems to be duration of therapy and not affected by daily dose of metformin.

KEYWORDS: Diabetes mellitus, Metformin, Fasting plasma lactate level, Comorbidities.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to defect of insulin secretion, insulin action or both. Chronic hyperglycemia leads to dysfunction and failure of various organs especially the eyes, kidney, nerves heart and blood vessel.[1]

Metformin is the most commonly prescribed oral anti-hyperglycemic medication in the world and it has been considered as the first line therapy for newly diagnosed type 2 diabetes mellitus.[3] Anti-hyperglycemic action of metformin is mainly achieved through a reduction of hepatic glucose production as well as increasing glucose uptake in peripheral tissues as a result reduction in both fasting glucose and glycated hemoglobulin and to lesser extent a reduction in post prandial glucose.[4]

Metformin has excellent safety profile with proven efficacy in reducing hyperglycemia but rarely it causes hypoglycemia and neutral effects on body weight. Majority of studies showed that metformin monotherapy leads to reduction in diabetes mellitus related end points and mortality rate compared with other anti diabetic agents. However, biguanides has been linked for years with the rare development of the life threatening complication of lactic acidosis.[4]

Lactic acidosis defined as a plasma lactate concentration >5.0mmol/L together with arterial blood pH <7.35 and electrolyte disturbance with an increased ion gap. It has been recommended that the measurement of blood lactate be used to assess whether a change in symptoms reflects incipient acidosis.[6]

The divergence opinion about metformin linked with lactic acidosis mainly because of earlier biguanide, phenformin hydrochloride was withdrawn from the market because it associated with lactic acidosis.[7]

MALA developed by blockade age of lactate utilization through gluconeogenesis and may also reduce non-oxidative and oxidative lactate utilization leading to lactate accumulation further, it may cause lactic acidosis.[4]

Certain factors that are indirectly related to diabetes treatment such as obesity, hypertension, renal function and hyperglycemia itself have also been associated with raised plasma lactate in diabetes patients. Without knowledge of relative importance of these factors, the interpretation of a fasting plasma lactate concentration is difficult.[6]

The aim of the present study was to determine the relationshipbetween metformin and plasma lactate level in type 2 diabetes patients in a tertiary care referral center and teaching institute.

MATERIALS AND METHODS

The objective of this study was correlation between metformin usage and plasma lactate level of type 2 diabetes mellitus patients. Study conducted in internal medicine department of government medical college hospital, Thiruvananthapuram, Kerala.

Inclusion criteria

All type 2 diabetes mellitus cases of age group above 30 years attended in our internal medicine department.

Exclusion criteria

- Type 1 Diabetes mellitus
- Patients those who were non-adherant to metformin
- Pregnancy and breast feeding

Study procedure

The study was conducted after obtaining ethical clearance from the institutional ethics committee of government medical college, Thiruvananthapuram. Patients of age ≥30 who had type 2 diabetes mellitus with co-morbidities enrolled in the study. Informed consent was taken from all study subjects fulfilling the criteria. During the first visit patients basic data are collected using prescribed profoma. Assess patients knowledge about diabetes by using a validated questionnaire, Diabetes Knowledge Questionnaire-24 item (DKQ-4). On the next review routine laboratory values (Random Blood Sugar, Serum creatinine) and fasting plasma lactate was noticed.

Statistical analysis

IBM SPSS version 16 software package was used for data stratification and analysis, descriptive statistics were used. Pearson correlation was used for factor analysis.

RESULT AND DISCUSSION

Of the 173 patients recruited to the present study, there were 70 males and 103 females. The mean age was 56.92. All of them were type 2 diabetic patients taking metformin as their usual treatment with the dose ranges between 500-1500mg OD/BD.

Table 1: Details of patients diabetes and associated laboratory values, Data are in mean ± s.d.

	Mean ± s.d
Age	56.92 ± 10.36
Body mass index	22.08 ± 3.38
Duration of metformin	8.77 ± 7.1
Therapy	1.48 ± 0.27
Fasting plasma lactate	246.2 ± 116.86
RBS Serum creatinine	0.694 ± 0.7
Creatinine clearance	98.65 ± 32.7

Fasting plasma lactate and correlation with metformin.

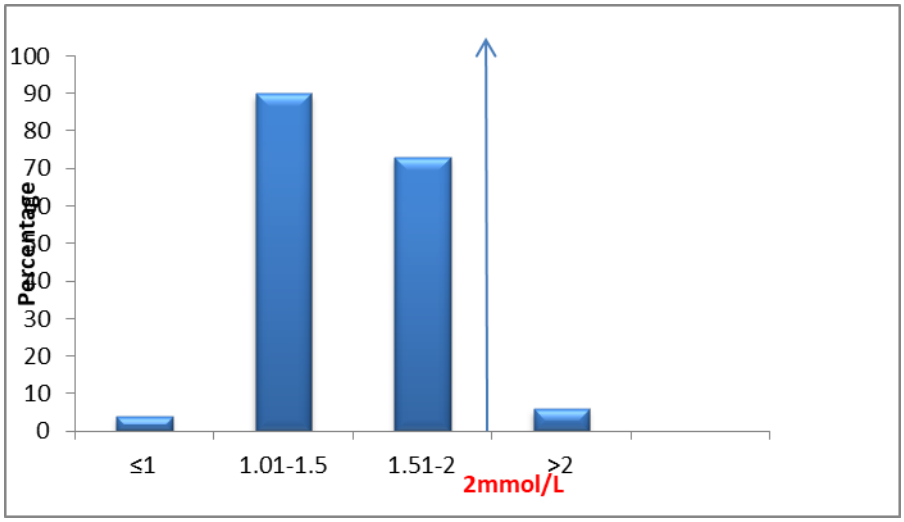

Figure 1: Percentage distribution of sample according to fasting plasma lactate concentration.

The mean ± s.d was 1.48 ± 0.27. Among this 3.46% of cases plasma lactate was above the upper limit of reference range, (0.5-2mmol/L). The highest value observed was 2.18mmol/L.

Pearson correlation is used to determine the relationship between plasma lactate and variables.

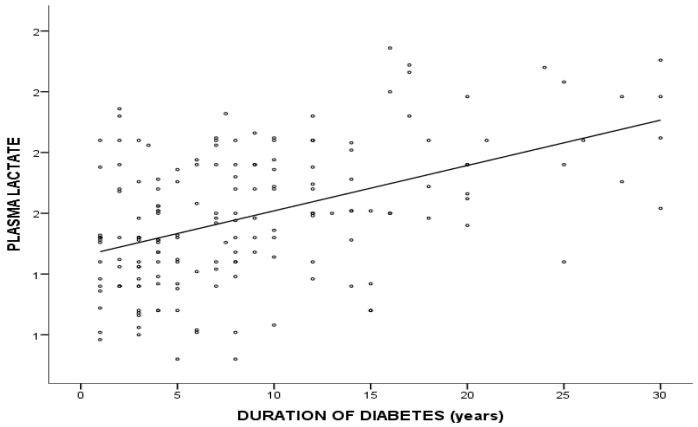

Figure 2: Relationship of fasting plasma lactate with duration of metformin therapy.

Pearson correlation, r between fasting plasma lactate and duration of diabetes is about 0.479, P =0.001. (P=0.000, P<0.01). which indicates that there is a moderate positive relationship between the variables.

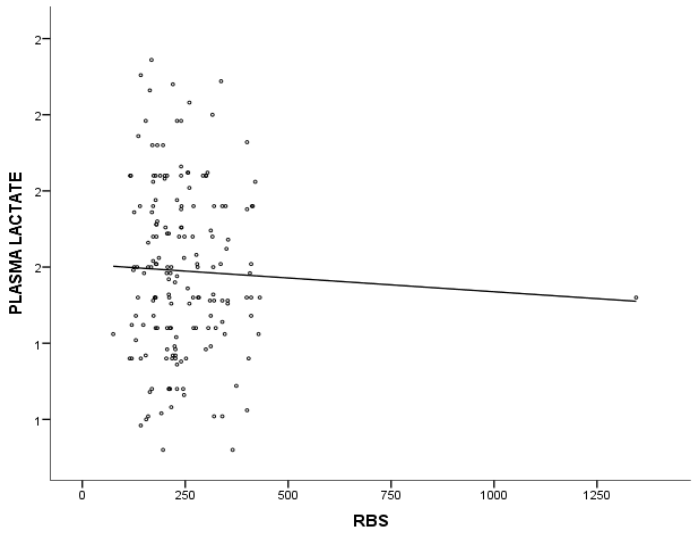

Figure 3: Relationship with Random blood sugar.

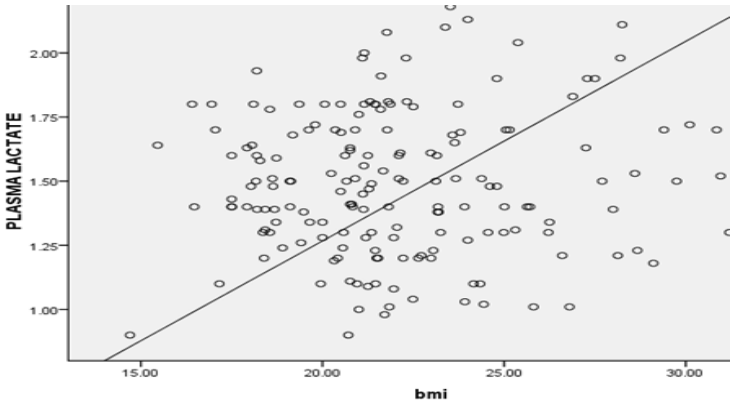

Figure 4: Relationship with body mass index.

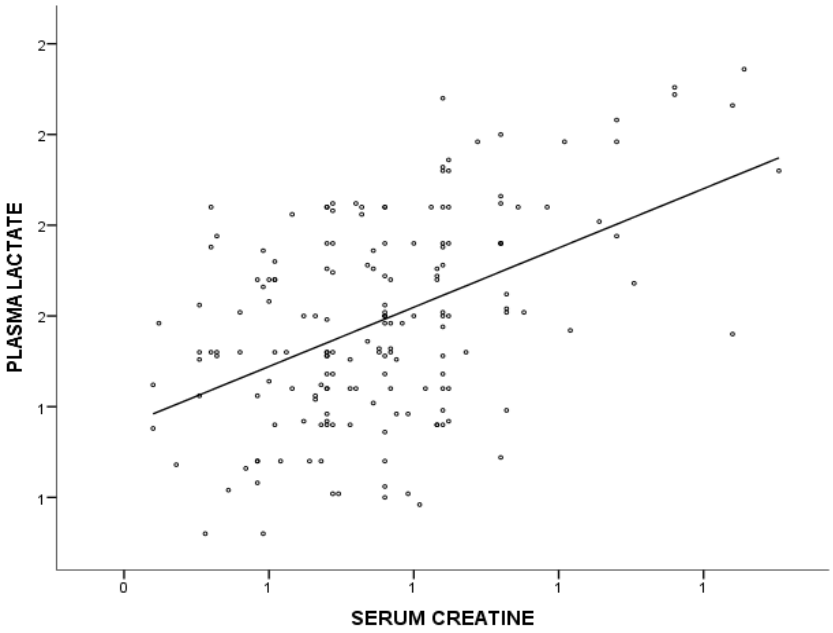

Figure 5: relationship with serum creatinine.

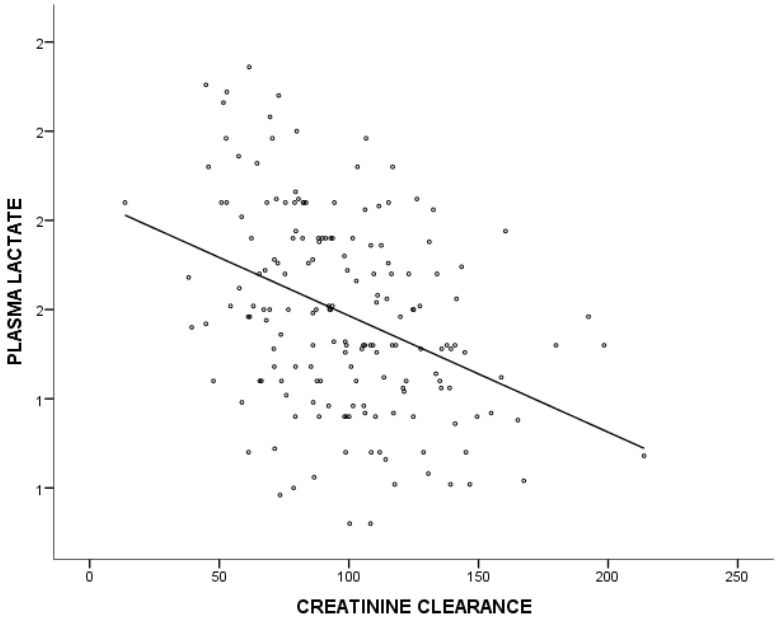

Figure 6: relationship with creatinine clearance.

Table 2: Pearson correlation coefficient matrix for factors associated with plasma lactet in present study.

	Age	Gender	Dietary habit	Weight	RBS	Duration of metformin therapy	Dose of metformin	Serum creatinine	Creatinine clearance	Plasma lactate
Gender	-0.171*									
Dietary habit	-0.28	0.043								
Weight	0.086	-0.385**	0.000							
RBS	-0.034	0.030	0.28	-0.018						
Duration of metformin therapy	0.259**	-0.120	-0.139	0.146	-0.080					
Dose of metformin	-0.168*	-0.146	0.060	0.011	-0.025	-0.020				
Serum creatinine	0.170*	-0.273**	-0.041	0.241**		0.429**	-0.028			
Creatinine clearance	-0.307**	-0.062	-0.007	0.302**	-0.070 0.042	-0.327**	-0.017	-0.702**		
Plasma lactate	0.200**	-0.165*	0.21	0.066	-0.038	0.479**	-0.078	0.480	-0.0386**	

The present result shows that metformin therapy is associated with an increasing the fasting plasma lactate concentration in patients with type 2 diabetes mellitus. The mean age of the patients was 56.925 ± 10.361, similar result were found in a study conducted by Eppenga etal.

Biguanides including metformin have been linked to the development of lactic acidosis, a condition associated with high mortality rate.[25] 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.[7] In our study outcome of the therapy was assessed using patients laboratory values, prescription and DKQ-24 item. The results show that duration of metformin therapy is associated with elevation in the plasma lactate concentration in patients with type 2 diabetes mellitus. A small increase in the plasma lactate concentration, 0.6mmolL^{-1} is observed with upper limit of normal value 2mmolL^{-1}. The mean duration of metformin therapy is 8.77 years with a standard deviation of 7.108. maximum duration of therapy was 30 years (Table 10: distribution of sample according to duration of metformin therapy). **Imhemed etal (2015)** conducted a study, there was no recognizable difference on serum lactate with respect to duration of metformin treatment.[4]

In the present study the mean plasma lactate is observed is 1.48mmolL^{-1} with a standard deviation of 0.276 (Table: distribution of sample according to plasma lactate level). From the histogram of plasma lactate concentration, the straight line indicating the upper limit of normal plasma lactate concentration 0.5-2mmolL^{-1}. A total of 173, 6 (3.46 %) patients shows lactate level >2 mmolL^{-1}.

Correlation between metformin usage and plasma lactate concentration

Pearson correlation is used to determine the relationship between plasma lactate and variables.

In these results, Pearson correlation coefficient of plasma lactate with duration of metformin therapy was 0.479 (Table). The scatter gram (Fig) indicated that there is a moderate positive relationship between two variables. Plasma lactate concentration increases with increasing duration of metformin therapy. This result was found to be statistically significant at the P value of 0.000 ($P<0.01$).

In a study by **Marichetti etal (1990)** 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 dose of 1000mg (Table). Other variables that were independently

associated with plasma lactate level were RBS, body weight, serum creatinine and creatinine clearance.

The relationship between
plasma lactate and glucose concentrations can be confusing. Via some mechanisms, changes in plasma glucose can drive changes in lactate, while via different mechanism, changes in lactate can drive changes in glucose concentration.[26] In the present study mean RBS was 246.20 with a standard deviation of 116.86 (Table). Majority of patients have blood sugar level in a range of 201-300. There was a weak negative linear relationship between and plasma lactate concentration and RBS value. The Pearson correlation coefficient $r_=$ -0.038 with a P value 0.618 and its insignificant as P value >0.05. In addition, the RBS doesn't alter plasma lactate concentration markedly. Which is similar to findings reported by **Timothy ME Davis etal (2001).**

Known predisposing factor for MALA or elvated plasma lactate concentration include impaired renal function, chronic liver disease, alcoholism and decreased tissue perfusion due to infection, heart failure, or other causes.[26,27]

Florent F etal (2014) conducted a large scale study to evaluate the incidence of LA by renal function in patients receiving metformin in an observational setting. Of the 23 patients with LA and moderately reduced kidney function.[28] In case of serum creatinine, it shows a weak negative correlation with plasma lactate concentration (r=-0.01) and was insignificant.[6] We used the serum creatinine is a simple index of chronic kidney diseases. The mean creatinine of patient was 0.694 ± 0.700 (Table).In our study, total 173 patients 11 having chronic kidney disease. From the data maximum creatinine value is 1.38mmolL^{-1} and corresponding plasma lactate was 2.13mmolL^{-1}. The Pearson correlation of plasma lactate with serum creatinine show moderate positive linear relationship with correlation coefficient , $r_=$0.480 with P value of 0.000. There is a significant improvement of plasma lactate with serum creatinine.

In our study creatinine clearance is one of the another variable observed along with serum creatinine clearance and was calculated by using Cockroft gault fomula. 8 (4.12%) of total patients had creatinine clearance were 98.65 ± 32.70 (table). 38.18 ml/min was the lowest value observed. It has a significant weak linear association with lactate concentration. When Pearson correlation coefficient, $r_=$ -0.386 with a P value of 0.000 (<0.01).

Body mass index of the patients was analyzed for this study. The mean BMI of patient was 22.08 with a standard deviation of 3.38. largest number of patients had normal range of BMI belongs to the group 20-25. Maximum BMI of patient was 31.58. Correlation of BMI with plasma lactate shows very weak positive relationship with a P value of 0.655 and was insignificant.

We included type 2 diabetes mellitus patients with their comorbidities for this study. There was no relationship was observed with plasma lactate and co-morbidities except CKD. A total of 173 patients 6.35% experienced with chronic kidney diseases. While assessing co-morbidities , we found that majority of patients attending in our internal medicine department hypertension was the most commonest co-morbidity associated with diabetes followed by dyslipidemia.

Diabetic neuropathy was one of another major problem. From these results we found patients had lack of awareness about life style diseases. Proper awareness and patient education about diabetes and life style modification may help the patient become healthier.

CONCLUSION

The study reveals that correlation between use of metformin tablet and plasma lactate concentration in type 2 DM patients. Plasma lactate concentration was collected from patients laboratory data and determine whether it has any relation with other corresponding variables, by using Pearson correlation. From the outcome variables duration of metformin therapy shows a moderate positive relationship that means, there was statistically significant increase in plasma lactate concentration. CKD was the common co-morbidity found in patients with elevated lactate concentration of >2 mmolL^{-1}, so serum creatinine and creatinine clearance were assessed as simple index of CKD. The result shows elevated plasma lactate concentration significantly increased in patients with mild to moderate renal insufficiency. In conclusion, our study suggests that metformin therapy may be associated with small increase in serum lactate level seems to be durationof therapy and not affected by daily dose of metformin. This should be confirmed in future research, preferably in a study in which lactate concentrations, renal function, and metformin exposure are frequently assessed and in which all potential risk factors are accurately determined and recorded.

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