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RESEARCH ARTICLE

LACTIC ACIDOSIS IN TYPE 2DIABETES PATIENT WITH AND WITHOUT RENAL IMPAIRMENT TREATED WITH METFORMIN

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Diabetes, Lactic Acidosis, Renal Impairment

Abstract

Metformin is a widely used antihyperglycemic agent recommended by both the American Diabetes Association and the European Association for the Study of Diabetes as the first-line type 2 diabetes treatment in all patients receiving a new diagnosis, regardless of age Lactic acidosis (LA) is a rare event, with an estimated incidence of 4.3 cases per 100,000 person-years in metformin users LA is caused by the buildup of lactic acid in the bloodstream. It is characterized by an arterial lactate level ?5 mmol/L and a blood pH ?7.35, and occurs when oxygen levels in the body drop (hypoxia). The occurrence of LA in type 2 diabetes is of great concern because the mortality rate of LA can be as high as 50% .To determine whether the use of metformin in type 2 diabetic patients with various kidney functions is associated with an increased risk of lactic acidosis (LA). Lactic acidosis occurs in patients taking metformin who have renal failure. In our study, metformin was used in CKD stage 1 to 3b patients. Most of them were in stage 3. There is statistically significant association between stages of kidney disease and serum lactate level($P<0.05$) .There Is statistically significant association between stages of kidney disease and arterial blood gas analysis.

Introduction:-

Metformin is a widely used antihyperglycemic agent recommended by both the American Diabetes Association and the European Association for the Study of Diabetes as the first-line type 2 diabetes treatment in all patients receiving a new diagnosis, regardless of age [1]. It enhances the sensitivity of both hepatic and peripheral tissues to insulin. In addition, metformin improves glycemic control and the oxidative disposal of glucose and lactate in the body, without altering muscle lactate metabolism, plasma lactate concentration, or plasma lactate turnover Metformin is eliminated primarily unchanged by the kidneys by both filtration and active tubular secretion Renal clearance of metformin decreases in proportion to decreasing renal function, which can be measured by the estimated glomerular filtration rate (GFR). One of the most important known risk factors for elevated metformin concentration is the inability to clear the drug efficiently due to renal impairment The relationship between metformin clearance and estimated GFR indicates that the maximum dosage of metformin should be decreased in line with impaired renal function. All diabetic patients, especially those with chronic kidney disease (CKD), may be at risk for more rapid decline in their renal function, and 10–40% of those with type 2 diabetes eventually experience kidney failure [2]

Lactic acidosis (LA) is a rare event, with an estimated incidence of 4.3 cases per 100,000 person-years in metformin users LA is caused by the buildup of lactic acid in the bloodstream. It is characterized by an arterial lactate level ≥5

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mmol/L and a blood pH ≤7.35, and occurs when oxygen levels in the body drop (hypoxia). The occurrence of LA in type 2 diabetes is of great concern because the mortality rate of LA can be as high as 50% [3]

There is a significant divergence in opinion about whether metformin is associated with LA, mainly because a prior biguanide-phenformin was removed from the market as a result of a strong association with LA.

Objectives:-

To determine whether the use of metformin in type 2 diabetic patients with various kidney functions is associated with an increased risk of lactic acidosis (LA).

Materials & Methods:-

Study design:
Case control study

Study setting:
General medicine and Nephrology department of KarpagaVinayaga institute of Medical sciences and research centre , chengalpattu district, Tamilnadu

Study duration:
6 MONTHS

Study population:
Patients attending **Nephrology and General medicine**opd of KarpagaVinayaga institute of Medical sciences and research centre and also inpatients under medicine department after verifying inclusion and exclusion criteria

Inclusion criteria
1. Type 2 diabetic patients
2.Patient on metformin
3.CKD Stage1to 3b
4.Those who have not received any forms of renal replacement therapy

Exclusion criteria:
1. Incomplete medical record
2.Type 1 diabetes
3.CKD Stage 4 and 5

Sample size with calculation methods:
The prevalence of patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) stage 3a as 7.5% by RavindraAtturPrabhu (2019) in the recent edition of International Urology and Nephrology. With this reference and assuming a 95% confidence interval, 5% absolute precision value, and with the available population size of 360, the minimum required sample size will be 82 ~ 90.

Data analysis
Descriptive statistics like mean, median, standard deviation and percentages were calculated approriately. The association between variables was calculated by chi-Square test at 5% level of significance .

Results:-

Table 1:- Age wise distribution of study participants.

Age	Male (n=66)	Female (n=24)
21-30	2	1
31-40	8	2
41-50	9	1
51-60	26	14
61-70	21	6

Table 2:- Distribution of serum lactate in different stage s of kidney disease.

CKD(stage 1 to 3b)	SERUM LACTATE(Mean mmol/l)	TOTAL	P value
Stage 1	0.5	22	0.03
Stage 2	1.2	33	
Stage 3a	2.3	25	
Stage 3b	3.8	10	

Figure 1:- Distribution of serum lactate in different stage s of kidney disease.

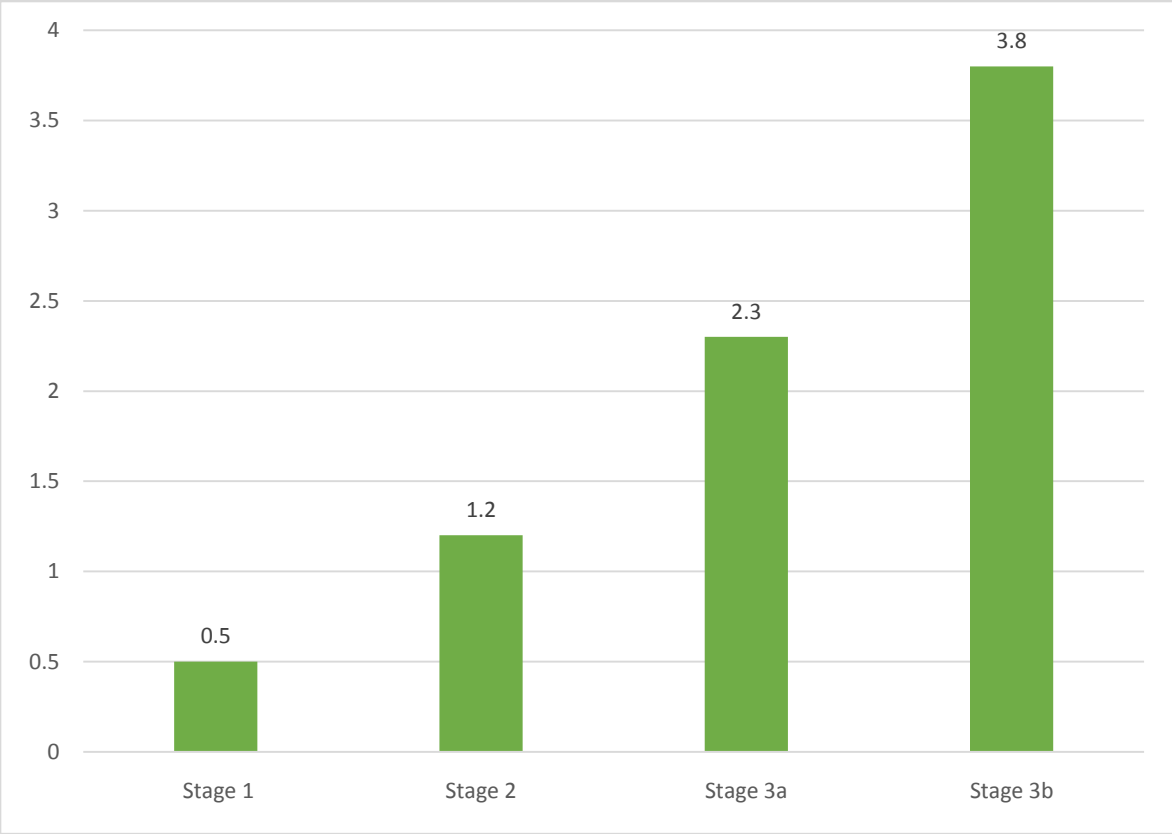
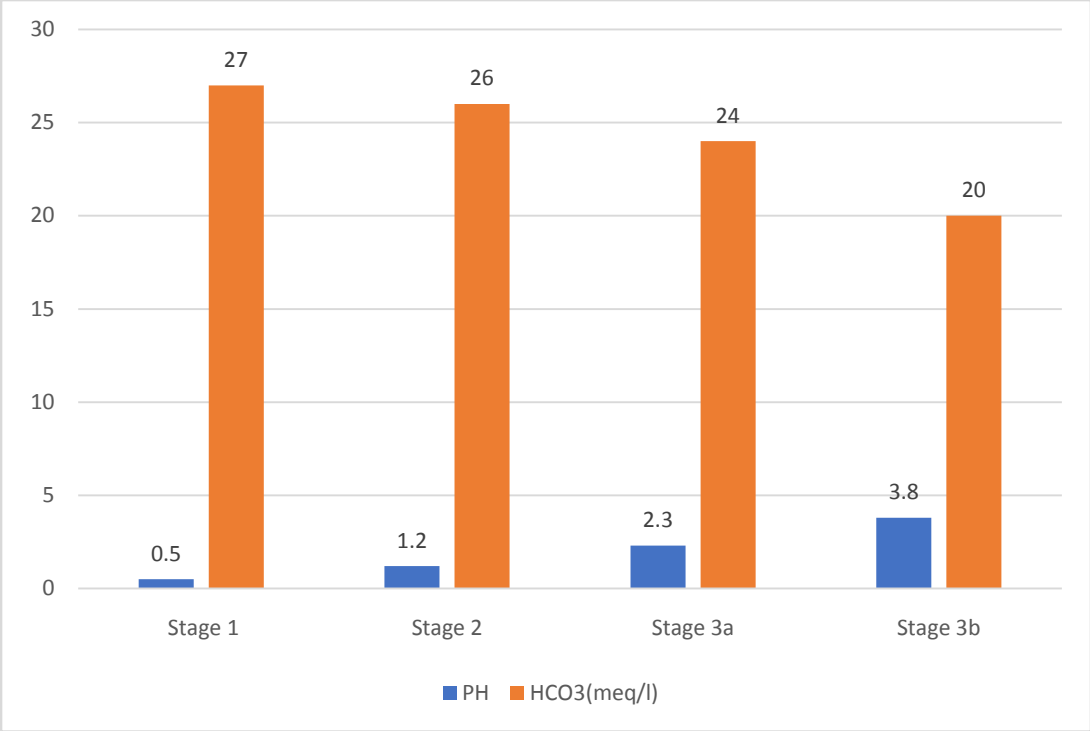


Table 3:- Arterial blood gas analysis in different stages of Kidney disease.

CKD(stage 1 to 3b)	PH	HCO3(meq/l)	TOTAL
Stage 1	0.5	27	22
Stage 2	1.2	26	33
Stage 3a	2.3	24	25
Stage 3b	3.8	20	10
P value	o.o4	0.01	

Figure 2:Arterial blood gas analysis in different stages of Kidney disease



Results And Discussion:-

Lactic acidosis occurs in patients taking metformin who have renal failure. In our study, metformin was used in CKD stage 1 to 3b patients. Most of them were in stage 3. There is statistically significant association between stages of kidney disease and serum lactate level($P<0.05$) .There is statistically significant association between stages of kidney disease and arterial blood gas analysis.

Another study was done in Denmark on 10,652 diabetic patients (non-CKD), conducted for 14 years; 163 experienced an acute hospitalization due to LA corresponding to an increased rate of 391/100,000 person/years [4] Although metformin is presumed to increase the risk of LA, we were unable to confirm this finding. The overall incidence of lactic acidosis in metformin users ranges from 3-47/100,000 person-years in the non-CKD population However, as far as the rate of hospitalization due to acidosis is concerned, we did not find any difference between CKD patients on metformin and those not on metformin (p-value 0.4).

DM itself causes increased concentration of lactate levels in the blood, so patients who are on metformin don't experience a predisposition to developing MALA . Several large observational studies have traversed the connection between metformin and LA [5,6]but did not find any significant association. In studies on patients continuing to receive metformin, even when they have GFR of less than 30-60ml/min, LA was a very rare complication, and risk for LA was similar to the risk seen with other agents in patients with similar degrees of renal impairment [7,8]

Ekstrom et al. studied 51,675 diabetic CKD patients and followed them for almost four years. They found that patients with eGFR between 45-60ml/min and metformin therapy had a lower risk of acidosis, severe infections, and all-cause mortality [9]. Overall the use of metformin for type 2 diabetic patients with decreased renal function remains controversial. One study showed metformin increases the risk of LA in patients with mild to moderate CKD, and this study highlighted that those patients who showed signs of dehydration or were on diuretics were more likely to develop MALA [10]. Their analysis showed that lactate levels were normal in patients with mild to moderate CKD who were on metformin therapy.

Conclusions:-

Metformin is used routinely in type 2 diabetic patients. The relationship between metformin clearance and estimated GFR indicates that the maximum dosage of metformin should be decreased in line with impaired renal function. More studies to be conducted in future to find out temporal association.

Limitations

In our studysample size is small can't be projected for large scale populations

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