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# SAFETY OF METFORMIN IN DIABETIC HEMODIALYSIS PATIENTS BETWEEN FACTS AND FICTION: A MULTI CENTER OBSERVATIONAL STUDY

**Nephrology**


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## ABSTRACT

**Objective:** Over decades, Metformin was accused of causing lactic acidosis in end-stage renal disease (ESRD) patients and in spite of its well known benefits; its use in this group of patients is still restricted. Little is reported about the effect of hemodialysis (HD) on metformin clearance and the fear of lactic acidosis deprives ESRD patients from metformin therapeutic advantages. Dialysis in general and HD in particular may save ESRD patients from this hazard.

**Material and Methods:** The study was conducted on 61 HD patients with type-2 diabetes mellitus in 3 centers. Metformin was administered in a single dose 0f 250-500 mg three times weekly post HD. Patients were monitored for glycemic control. Plasma lactic acid and plasma metformin levels were monitored on a scheduled basis. The relation between plasma metformin and plasma lactate was studied in addition to the effect on mortality.

**Results:** Mean fasting blood sugar (FBS) was 12.4 + 0.5 and 8.2 + 0.6 mmol/L, and the mean HgA1C was 8.1 + 0.7 and 6.7 + 1.1 at beginning and end of the study, respectively ($p < 0.001$). The mean body mass index (BMI) was 29.3 + 3.7 and 27.4 + 3.5 at the beginning and at the end of the study respectively ($p < 0.001$). There was no relationship between plasma metformin and lactate levels. The overall mean plasma lactate level across all blood samples was 1.48 + 0.5 and plasma samples > 2 mmol/L but < 3 mmol/L was found in 13.4% and 3-3.8 mmol/L in 2.7% plasma samples. None of our patients had lactic acidosis (levels > 5 mmol/L). Age > 65 and negative fluid balance were predictors for hyperlactemia.

**Conclusion:** Metformin may be used with caution in a particular group of ESRD who are on regular hemodialysis. Metformin allows better diabetic control with significant reduction of BMI. The relationship between metformin and plasma lactate levels is lacking. HD may protect ESRD patients from metformin-associated lactic acidosis.



## KEYWORDS

ESRD, HD, type-2 diabetes mellitus, metformin, lactic acidosis, Hemoglobin A1-C, BMI.

## Introduction

The statement 'Metformin is contraindicated in dialysis patients due to the risk of lactic acidosis' is not referenced and is perhaps not supported by the available evidence. This oral antidiabetic agent has been evaluated in hundreds of clinical studies in diverse patient populations during approximately five decades of clinical use and randomized controlled studies demonstrated (evidence level A) significant reductions of blood sugar levels and body weight with metformin, relative to baseline or comparator agents (1-15). Stopping metformin often results in poorly controlled glycemia and/or the need for other agents with their own adverse-effect profiles. Metformin-associated lactic acidosis is exceedingly rare based on the available literature, and even though the use of metformin has not been comprehensively assessed in individuals with chronic kidney disease (CKD), there is extensive evidence that this agent often is used without adverse effects in those with moderately reduced renal function (16). In the context of rising concerns regarding other glucose-lowering therapies (17), safety restrictions over the use of metformin in this population may result in the drug being stopped prematurely and unnecessarily in some patients. A review of metformin in chronic kidney disease nicely summarizes the issue. It cites two small studies of metformin use in dialysis patients and recommends 250 mg daily and 500 mg post dialysis for PD and HD patients respectively (18). The Cochrane Systematic Database review (19) did not find enough evidence to link lactic acidosis with metformin use. Same was concluded in a very recent study by Lee EY and colleagues (20). In fact almost all the reports that augmented such fears were limited to case reports or physicians letters to drug safety committees (21, 22). Schousboe K, et al (23) successfully treated four patients with severe lactic acidosis by HD. Supporting this was the study by Lalu JD, et al. (24) who found that hemodialysis efficiently removes metformin and corrects metabolic acidosis in patients with metformin-induced lactic acidosis. We conducted this prospective study to evaluate the safety of metformin use as a glycemic control in ESRD hemodialysis patients.

## Patients and Methods

This observational study of patients with type-2 diabetes and ESRD on regular hemodialysis was performed according to *Helsinki's Declaration* at King Fahd University Hospital, Al-Khobar, Saudi Arabia. The study was conducted from February 2014 through March 2017 with prior approval by *King Fahd Hospital Human Ethical committee*. All patients were above 18 years of age and written informed consents were obtained from every patient after full explanation of the aim of the study, the side effects of metformin and the expected outcomes. Patients with chronic heart disease, chronic respiratory disease, chronic liver disease, ongoing sepsis, those using alpha-glucosidase inhibitors as well as pregnant ladies were excluded from the study (Figure-1). All 61 patients were type-2 diabetes mellitus on insulin; Glargine (insulin lantus) or premix insulin. As the minimally recommended daily dose is 0.5 gm; metformin was added to their regimen with a dose between 250 mg to 500 mg per day as needed. On dialysis days, metformin was administered post dialytic treatment. Fasting blood glucose was measured once per week predialysis session and HgA1-C every three months. While serum lactate levels were measured on weekly basis for 8 weeks then monthly until the end of the study (normal levels: 0.4-2.0 mmol/l); metformin plasma levels monitored at the beginning, every 3 months and at the end of the study; a level of 0.5-1 mg/l was considered as therapeutic (25). Metformin was hold in case of infection or acute illness and resumed after resolution. Dialysis was carried out through a permanent internal jugular catheter, arteriovenous fistula or graft (Table 1). All Patients were on three times per week dialysis and their dialytic prescription consisted of four hours dialysis; blood flow 350-400 ml/min, dialyzer were all high flux (Gambro Dialysatoren, Holger-Craford-Strasse, Hechingen, Germany). Acid concentrate (ADAMCO, limited, SA) and bicarbonate (Bicart, Gambro, Lundia AB, Sweden) were used in all patients. The acid concentrate contains 100 mmol/L sodium, 1-3 mmol/L potassium, 2-4 mmol/L calcium, 0.375 mmol/L magnesium, 105.75 mmol/L chloride and 2 gm/L glucose. Patients received unfractionated heparin at the beginning of and during hemodialysis as needed. Both lactate and metformin levels were measured predialysis.

**Lactate assay**: Blood was collected predialysis in tubes containing sodium fluoride/potassium oxalate, and the specimen immediately chilled and plasma separated within 15 minutes. If tests could not be performed immediately, the separated plasma samples were refrigerated at temperature less than 4 C$^{o}$ awaiting analysis. The kits used are LA Flex Reagent Cartridge. Cat DF16, Dimension Clinical Chemistry System. All samples were collected from patients in fasting and complete resting state. Normal plasma lactate levels were considered in the range of 0.4 - 2.0 mmol/L

**Metformin assay**: Metformin concentrations were measured in duplicate in the same laboratory using Quantitative Reverse Phase HPLC with Diode-Array Detection and Tandem Mass Spectrometry (ARUP's Laboratory). Fasting plasma metformin levels between 0.5-1.0 mg/L were accepted as therapeutic.

## Statistical analysis

Continuous variables are expressed as mean $\pm$ SD or median (IQR) and categorical variables are expressed as percentage. Non parametric Spearman Rank test was used for continuous variables correlation and Mann-Whitney test used for comparison of two groups. P values were not adjusted for multiple testing and therefore should be considered descriptive. Multivariate linear regression was used to study the relationship between metformin level, age, duration of ESRD, blood sugar level and duration of metformin therapy and lactic acid concentration. The statistical analysis was performed using SPSS for Windows version 20 *(IBM Inc. New York, USA).*

## Results

The study involved a total of 96 patients with ESRD and diabetes mellitus type-2. Twenty-eight patients were excluded from the study because of chronic heart disease (CHD) (n=4), chronic respiratory disease (CRD) (n=4), chronic liver disease (CLD) (n=3), ongoing sepsis (n=4), alcohol intake (n=2), pregnancy (n=2), patients on alpha-glucosidase inhibitors at the time of study (n=3) or patients' refusal (n=6). Seven patients dropped during the study period; 3 of sepsis and 4 patients because of kidney transplantation. The remaining 61 (28 incident and 33 prevalent) patients were eligible for inclusion in the study (Figure-1). Four (6.6%) patients died before completing the study; the cause of death was cerebral hemorrhage in one and acute myocardial infarction in two and pulmonary embolism in one. In 5 (8.2%) metformin was temporarily discontinued because of acute chest infection in 3 and unstable angina in 2 patients, it was resumed once the acute illness was resolved. The median (IQR) duration of discontinuation was 11 (9-13) days. All patients were on insulin but not metformin at the time of the study. Forty-two (68.9%) patients were on Glargine insulin (Lantus) and 19 patients (31.1%) on premix insulin. The demographic characteristics of patients are illustrated in table-1. The mean body mass index (BMI) was 29.3 $\pm$ 3.7 and 27.4 $\pm$ 3.5 at the beginning and at the end of the study respectively ($p < 0.001$). Mean fasting blood sugar (FBS) was 12.4 $\pm$ 0.5 and 8.2 $\pm$ 0.6, and the mean HgA1C was 8.1 $\pm$ 0.7 and 6.7 $\pm$ 1.1 at beginning and end of the study, respectively ($p < 0.001$). The mean creatinine clearance was 7.1 $\pm$ 2.5 ml/minute and 6.8 $\pm$ 2.6 ml/minute at metformin introduction and at the end of the study period, $p > 0.05$ (Table-2).

The overall mean plasma lactate level across all blood samples was 1.48 $\pm$ 0.5. The mean lactate level was 1.44 $\pm$ 0.7 mmol/L, (range 0.8-3.4 mmol/L) and 1.46 $\pm$ 0.6 (range 0.6-3.1) one month after beginning and at the end of the study, respectively ($p > 0.05$). Plasma lactate level $\leq$ 2 mmol/L was found in 1436 out of 1712 (83.9%) plasma samples, more than 2 mmol/L but below 3 mmol/L in 230 (13.4%) and 3-3.8 mmol/L (the maximum lactate level) in 46 (2.7%) plasma samples (Figure 2). hyperlactemia (level > 2 & $\leq$ 5 mmol/L) was not associated with overt acedemia. Thirty-one out of 46 plasma samples (67.4%) with lactate levels above 3 belonged to patients with a dry weight less than planned ($p < 0.001$). None of our patients had plasma lactate level of 5 mmol/L or more. Multivariate analysis of hyperlactemia controlling for age, gender, hypertension, negative fluid balance, duration of diabetes, blood sugar level, HgbA1C, and plasma metformin level found, only age (RR, 0.41; 95% CI, 0.21 to 0.76; $p = 0.011$) and negative fluid balance (RR, 44; 95% CI, 0.19 to 1.1; $p = 0.009$) were significant predictors for hyperlactemia. The mean anion gap was 12.9 mmol/L $\pm$ 2.4 and 11.3 mmol/L $\pm$ 1.7 ($p > 0.05$) and the mean pH was 7.27 $\pm$ 0.1 and 7.31 $\pm$ 0.08 ($p > 0.05$) at the beginning and at the end of the study respectively (Table-2 and Figure-3). The overall mean plasma metformin concentration was 5.32 $\pm$ 3.27 mg/L (range 0.1 to 13.0 mg/L) with a mean concentration of 5.19 $\pm$ 4.22, 5.14 $\pm$ 4.19 and 5.14 $\pm$ 3.97 at the end of the 1$^{st}$, 2$^{nd}$ and 3$^{rd}$ years respectively ($p > 0.05$) (Table-2 & Figure-4). Seven patients had plasma metformin concentrations below 1 mg/L (below the level for the recommended dosage) and In contrast, 11 patients had plasma metformin concentrations of at least 10 mg/L (i.e. 10 times the recommended

level) (Table-2). A correlation between metformin and plasma lactate levels was lacking (Figure-5). The overall survival rate in our patients was 93.4% (57 of 61 patients). There was no difference in mean lactate levels between patients who survived (1.41 ± 0.88 mmol/L) and those who died (1.40 ± 0.78), whereas the mean plasma metformin concentration was about 2 times higher in the surviving patients (5.14 vs. 2.62 mmol/L) .

**Discussion**

If a therapeutic agent carries a potential rare and non-specific complication, it is difficult to develop a definitive evidence base for the risk–benefit analysis. This may lead to guidelines, in the face of uncertain risk, emphasizing 'first do no harm' rather than balancing the benefits against the risks, unreasonably denying a patient the benefits of that therapeutic agent. The guidelines for the use of metformin in patients with impaired renal function [e.g. avoid with an estimated glomerular filtration rate (eGFR) < 30 ml/min and with caution < 40 ml/min)] (26), to our minds, and the minds of others (16, 27, 28), reflect a mismatch between the benefits of metformin against the risks of utilization, predominately the risks of lactic acidosis (29). Metformin use has been advocated in the treatment of type 2 diabetes as well as in obese patients and it has been shown to slow cardiovascular complications associated with diabetes (30, 31). By decreasing excess hepatic gluconeogenesis without raising insulin levels, it rarely leads to significant hypoglycemia when used as monotherapy (30-32). The independent effect of metformin on the development of lactic acidosis remains unclear. The Cochrane group Comparative Outcomes Study of Metformin Intervention versus Conventional Approach (COSMIC) study (33), and the United Kingdom Prospective Diabetes study (34) have disputed the existence of lactic acidosis in the presence of metformin and hence the term metformin-induced lactic acidosis has subsequently been changed to metformin associated lactic acidosis (MALA). A systematic review and meta-analysis showed no evidence that metformin therapy is associated with an increased risk of lactic acidosis or with increased levels of lactate compared with other anti-hyperglycemic treatments if the drug is prescribed under study conditions (35). Of 194 studies considered, there were no cases of fatal or nonfatal lactic acidosis in 36,893 patient-years in the metformin group or in 30,109 patient-years in the non-metformin group (35). The role of metformin in glucose lowering has been associated with a reduction in cardiovascular events (36, 37) and a previous systematic review (38) demonstrated low rates of cardiovascular mortality in people randomized to metformin in six trial of more than 11,000 patients. Furthermore, in the 10-year study conducted by Holman RR, et al. (39) a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed in the metformin study group during 10 years of post-trial follow-up. In fact even in the setting of moderate renal insufficiency, metformin itself has not been linked to mortality in users developing lactic acidosis during metformin use, which perhaps reflects a primary effect of other underlying causes of the acidosis (40). Metformin effect on body weight has been remarkable. In 10-year follow- up of metformin-treated overweight patients in the UK Prospective Diabetes Study (UKPDS) (41) the difference of weight gain between metformin and glibenclamide groups was highly significant. A Diabetes Progression Outcomes Trial randomized a population of 4360 patients uncontrolled by lifestyle intervention to monotherapy with metformin, glibenclamide or rosiglitazone for 4 years (42). Patients in the metformin group lost weight, on average, while weight gains occurred in the other treatment groups. In our study, weight loss was undeniable and highly significant ($p < 0.001$) and was not attributed to fluid removal as the patients' weight was always recorded post-dialysis. The concerns about lactic acidosis in chronic kidney disease are simply based on case reports. The previous US prescribing guidelines warn against the use of metformin in patients with a serum creatinine ≥ 1.5 mg/dl (≥ 133 mmol/l) in men or ≥ 1.4 mg/dl (≥ 124 mmol/l) in women as cases of lactic acidosis have been described in patients with chromic kidney disease (43). There are reports, however, considering these thresholds as too tight and suggested its safe use in patients with moderate renal impairment (44, 45); in the UK, for instances, the National Institute for Health and Clinical Excellence guidelines are less restrictive and more evidence-based than those in the USA, allowing its use down to GFR at 30 ml/min (46). Duong, et al. (47) in their study indicated that using metformin at stable creatinine clearances as low as 20 ml/min is safe and provides a basis for undertaking larger, controlled trials of metformin in patients with CKD. Studying the pharmacokinetics of metformin; the same authors demonstrated that with appropriate dose reduction, metformin can be safely administered to patients with creatinine clearance as low as 15 ml/min without lactate concentrations increasing (48). More recently, Dissanaiaki et al (49) conducted an important study on the safety of metformin in stage 4 CKD and they were supportive of the liberalization of metformin use in stable moderate to severe CKD, as well as raising the question of the more widespread use of metformin assays to demonstrate tolerance of supratherapeutic but safe metformin concentrations and subsequent personalized metformin dosing. Literature concerned with metformin use in hemodialysis patients is scarce. In the study of Peters and colleagues (50) hemodialysis was used to treat patients with MALA. The mortality rate in MALA was not altered by hemodialysis. This may be a reflection of the small size of this study. Upon closer inspection of the data, those patients who were dialyzed were more acutely ill as they had higher values on the SAPS II (Simplified Acute Physiology Score II). Furthermore, those who were dialyzed trended toward having a larger burden of comorbidities (Charlson index) and more severe acidosis. Their data strongly suggest that hemodialysis may be of benefit in MALA. Only 3 publications have presented data concerning metformin removal by extracorporeal treatment. Lalau and Race (51) reported removal of 1105 mg, 694 mg, and 688 mg by HD in 3 patients. Barrueto *et al.* (52) reported 3.5 g removal by continuous venovenous hemodialysis in 10.5 hours and Ayoub et al. (53) showed that high-efficiency dialysis provides enhanced metformin clearance and substantial metformin removal. Other reports by Roberts D and Scalzo AJ showed that high-efficiency hemodialysis provide metformin clearance that surpasses 120 ml/min and a metformin half-life of approximately 4 hours (54 & 55). In comparison, metformin clearance with continuous renal replacement therapy is usually about one-fourth of that obtained with HD, and the half-life is at least 3 times as long (52 & 56-60). In a previous report (61), we studied 35 diabetic ESRD patients on peritoneal dialysis in whom metformin was used for over three years. None of the 83 patients developed lactic acidosis and few had lactate level above 2.0 mmol/L. In our study, metformin was well tolerated; plasma lactate concentrations (along with other markers of acidosis) were relatively constant. None of our patients had lactic acidosis and only few had lactate levels above 2 but < 5 mmol/L. Recently we analyzed 83 patients with type 2 diabetes mellitus and ESRD on PD and similar results were obtained (62). One patient in Duong's cohort was also on hemodiafiltration and had no elevation of metformin or lactate concentrations (47). A recent study by Smith, et al (63) showed that metformin is readily removed from plasma during hemodiafiltration and, at appropriately reduced doses may be safely administered to patients with type-2 diabetes mellitus on dialysis and recommended monitoring of pre-hemodiafiltration metformin plasma concentrations. Regolisti, et al (64) reported a case of metformin intoxication, severe lactic acidosis, and acute kidney injury in a diabetic patient with pre-existing chronic kidney disease stage 3, treated effectively with sustained low-efficiency dialysis. With continuous dialysis modalities, Similar results were reported by Alivanis P, et al (65). Supporting the feasibility of metformin use in ESRD dialysis patients, Duong, et al. (47) reported that none of their patients on dialysis therapy had lactic acidosis. The relation between metformin concentrations and lactate plasma concentrations was lacking in our study. Lalau, et al. (66) studied metformin therapy in patients with chronic kidney disease, noticed large inter-patient variability in metformin concentrations and they were generally much higher than the therapeutic range. However, these authors did not specify the timing of blood samples. Lalau, et al. (67) and others suggested that apart from poor compliance, at least two additional factors may have contributed to the variable concentrations of metformin. First, the oral availability of metformin is highly variable, ranging at least threefold (68, 69). Second, there is substantial scatter in the relationship between the renal clearance of metformin and creatinine (69, 70). Therefore monitoring metformin concentrations may not be that helpful due to the large variability in its pharmacokinetics. The study of Lalau, et al. showed that in the patients receiving dialysis and low doses of metformin (250 mg daily), neither metformin nor lactate concentrations were elevated. This is despite lactate being present in the solutions used for dialysis. A major strength of our study is that it was conducted over a long observation period in a controlled situation. In addition, we not only separately evaluated the influence of renal function, the effect of hemodialysis and the level of metformin intake, but also did so in combination with serum lactate levels. The study is one of the very few that explores the sensitive issue concerning metformin use in ESRD who are on hemodialysis. Like most observational studies, our study is not without limitations. First, there is the potential issue of the selection and inaccurate estimation of our outcome measure. A second limitation is that we could not get adequate information about all potentially relevant risk factors for

lactic acidosis during metformin use and third, our study population is relatively small making it difficult to get strong recommendations.

**In conclusion**, we demonstrated herein that metformin may be used with caution in small doses in ESRD patients who are treated with hemodialysis and that the risk of lactic acidosis in metformin users of this group of patients needs to be revised. It is possible that HD may protect ESRD patients from metformin-associated lactic acidosis. Older age and excess fluid removal may predict hyperlactemia. Further prospective studies are needed to elucidate the direct role of metformin on the development of lactic acidosis in subjects with ESRD and type-2 diabetes.

## DISCLOSURES

The authors have no financial conflicts of interest to declare.

**Table 1: Demographic characteristics of the study population**

| Age (years), mean ± SD | 55 ± 11.8 |
|---|---|
| Female/Male (female %) | 23/61 (37.7) |
| Smokers (%) | 19.7 |
| HTN (%) | 73.8 |
| BMI at beginning, mean ± SD | 29.3 ± 3.7 |
| Duration of DM, years<br><br>(mean ± SD) | 14 ± 7.8 |
| Insulin type, n (%)<br><br>Lantus<br><br>Premix | 42 (68.9)<br><br>19 (31.1) |
| Indication of dialysis<br>Volume overload, n (%)<br>Uremia, n (%)<br>Hyperkalemia, n (%) | 11 (18.0)<br>43 (70.5)<br>7 (11.5) |
| *Duration of HD, months<br><br>(mean ± SD) | 29 ± 8.1 |
| Overall FBS, mmol/L (mean ± SD) | 9.3 mmol/L ± 1.2 |
| Overall Hgb A1C % (mean ± SD) | 7.2% ± 0.7 |
| Overall Cr Cl, ml/min, (mean ± SD) | 7.0 ± 2.2 |
| Overall plasma metformin concentration, mg/L<br><br>(mean ± SD) | 5.32 ± 3.27 |
| Overall plasma lactate level,<br><br>mmol/L (mean ± SD) | 1.48 ± 0.5 |
| Hyperlactemia plasma samples (level 2- ≤5<br><br>mmol/L), n (%) | 276 (16.1) |
| Mortality, n (%) | 4 (6.6%) |

**HTN:** hypertension, BMI: Body mass index, DM: diabetes mellitus, HD: hemodialysis, FBS: fasting blood sugar, Cr Cl: Urine creatinine clearance. * Duration of HD was calculated at the end of study

**Table 2: Table 2-Patients' clinical features at baseline and at the end of the study**

| Variable | At baseline | At the end of study | *p* |
|---|---|---|---|
| BMI, kg/m$^2$ , median (IQR) | 29.3 ± 3.7 | 27.4 ± 3.5 | o.ooo7 |
| Insulin requirements (units)<br>Lantus, mean ± SD<br>Premix, mean ± SD | 18 ± 3.1<br>25 ± 5.2 | 11 ± 1.1<br>15 ± 3.0 | 0.0004 |
| FBS, mmol/L, mean ± SD | 12.4± 0.5 | 8.2 ± 0.6 | 0.0004 |
| Hgb A1C%, mean ± SD | 8.1 ± 0.7 | 6.7 ± 1.1 | 0.0008 |
| Cr Cl (ml/min) , mean ± SD | 7.1 ± 2.2 | 6.8 ± 2.1 | 0.2423 |
| pH, mean ± SD | 7.27 ± 0.1 | 7.31 ± 0.08 | 0.7538 |
| AG, mmol/L, mean ± SD | 12.9 ± 2.4 | 11.3 ± 1.7 | 0.5067 |
| *Plasma metformin concentration, mg/L (mean ± SD) | 5.19 ± 4.22 | 5.14 ± 3.97 | 0.8403 |
| *Plasma lactate, mmol/L (mean ± SD) | 1.44 ± 0.7 | 1.46 ± 0.6 | 0.8955 |

* Baseline plasma metformin levels represent values of one month after starting the study and baseline plasma lactate levels represent values taken one week after starting the study. BMI: body mass index, FBS: fasting blood sugar, Cr Cl: urine creatinine clearance, AG: anion gap.

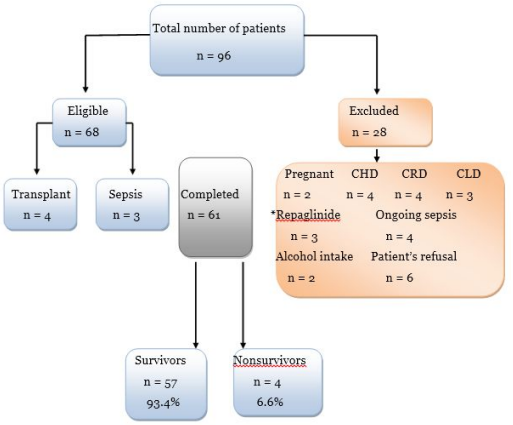


**Figure-1**: Consort diagram demonstrating study design and patients' progress

**CHD:** chronic heart disease, CRD: chronic respiratory disease, **CLD:** chronic liver disease, Repaglinide: represents alpha-glucosidase inhibitors.

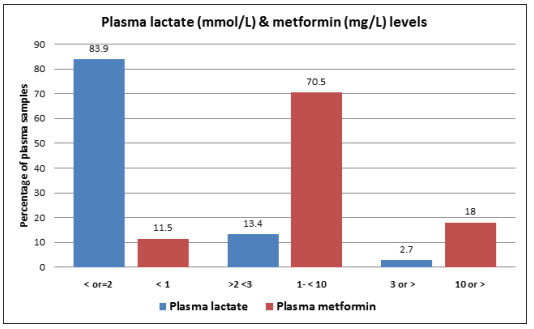


**Figure-2: Distribution of plasma lactate and metformin levels in the study population**

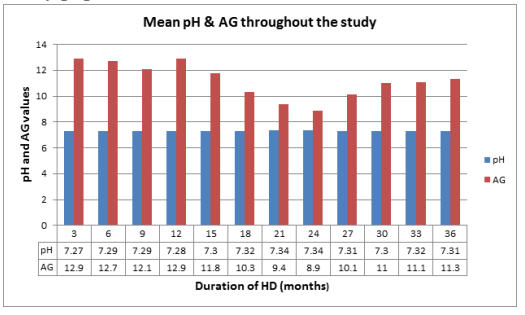


**Figure-3: Mean pH & anion gap throughout the study (p = 0.2304)**

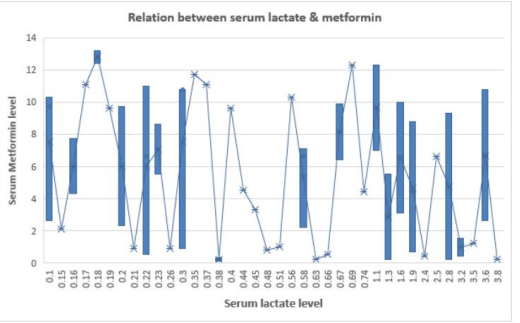

**Figure 4: Relation between serum metformin and serum lactate levels**

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