A Contraindication to Metfromin Therapy: Renal Impairment - Adherence to Prescribing Guidelines at a Hospital in Turkey

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ABSTRACT

Objective: The aim of this study was to investigate whether renal functions of the patients were monitored and checked before and during metformin treatment as recommended in guidelines or whether they were disregarded and metformin was prescribed despite the contraindication of renal impairment in a hospital in Turkey.

Method: This retrospective cross-sectional study was conducted among the patients who were hospitalized at a university hospital, diagnosed with type 2 diabetes mellitus and had metformin included in their treatment between 2015-2016. The total number of patients with this diagnosis and treatment between these years was determined as 66 and all the patients were taken into the study. Renal functions of these patients were assessed by measuring serum creatinine levels and calculating GFR using the Cockcroft - Gault formula.

Results: During the duration of metformin treatment 10 patients (15%) were not monitored for their serum creatinine. The 56 patients who were monitored for their serum creatinine were at 1, 2, 3, 4, 5 (end-stage) renal failure stages with the rates of 30, 36, 30, 4, 0 % respectively.

Conclusion: Assessment of renal function, adjustment of drug doses accordingly and termination of the treatment when contraindicated, are essential strategies for metformin therapy to prevent medication errors. However, this study showed that adherence to these prescribing rules are low and in some patients renal function was not monitored, placing them in increased risk of lactic acidosis.

Keywords: Metformin, Renal Function, Lactic acidosis

INTRODUCTION

According to American Diabetes Association (ADA) guideline[1] and a position statement on the management of hyperglycemia in patients with type 2 diabetes published by ADA and European Association for the Study of Diabetes (EASD),

metformin is stated as the preferred first-line antidiabetic pharmacologic agent for the treatment of type 2 diabetes if it is tolerated and not contraindicated [2]. This information is also emphasized by the guideline of National Institute for Health and Clinical Excellence (NICE)[3]. Unlike some other antidiabetic agents such as sulfonylureas, thiazolidinediones and insulin, metformin is weight-neutral which makes it an attractive choice of drug for obese patients as well. It reduces the risks and rates of cardiovascular events and death. It also has low cost, proven safety record and effectiveness. During the management of type 2 diabetes mellitus (DM) hypoglycemia can occur and cause complications; however, metformin monotherapy rarely leads to hypoglycemic attacks when compared with insulin and sulfonylureas [1, 2, 4-7].

Metformin and phenformin, the two main biguanides, became available for DM treatment in the 1950s [8]. In the late 1970s all biguanides, except metformin, were withdrawn because of links to lactic acidosis and increased cardiac mortality. Ongoing research and its minimal clinical use fostered the approval of metformin by Food and Drug administration (FDA) in 1995. Especially The UK Prospective Diabetes Study (UKPDS) in 1998 set metformin to its current position [9].

Metformin is noticed as an antihyperglycemic agent because it lowers blood glucose concentrations in type 2 DM and it is also frequently described as an insulin-sensitizer, leading to reduction in insulin resistance by increasing insulin-stimulated glucose uptake of skeletal muscle and adipose tissue. Metformin exerts its antidiabetic effects mainly by reducing hepatic glucose production through inhibition of gluconeogenesis which is upregulated in type 2 DM. Reduction of hepatic glucose production by metformin is mediated by inhibition of mitochondrial respiratory chain resulting in a decrease in cellular ATP [7, 8, 10].

Metformin is a small molecule that is not bound to plasma proteins and it does not undergo relevant biotransformation in the liver or biliary excretion. It has low lipid solubility and high volume distribution. Excretion of unchanged drug in urine is the major mode of elimination of metformin. It is cleared by renal tubular secretion and glomerular filtration. As predicted, in case of impairment in renal function, clearance of metformin will reduce and accumulation may occur [11].

Although it has advantages metformin has some adverse effects and contraindications that narrow down the segment of the type 2 diabetic population that can benefit from this drug. The most frequent adverse effects, affecting approximately 30 % of the patients, result from gastro-intestinal (GI) disturbances including anorexia, metallic taste, nausea, abdominal discomfort and diarrhea. However, GI side effects are usually transient and can be minimized by slowly titrating the dose and administering the drug with or after food [10, 12].

Metformin and Lactic Acidosis

Lactic acidosis is a rare but serious adverse effect of metformin with a reported incidence of ≤10 cases per 100,000 patient-years which is estimated to be 20 times less than with phenformin, however it is life-threatening and associated with overall mortality of 25 to 50% [4, 13-16]. It is an anion-gap metabolic acidosis defined by plasma lactate level greater than 5 mmol/L and pH less than 7.35 [16, 17]. When severe, it is associated with multi-system organ dysfunction particularly neurologic (stupor, coma, seizures) and cardiovascular (hypotension, ventricular fibrillation) and carries a high mortality risk [17].

Predisposing factors of lactic acidosis are considered to be contraindications and precautions of metformin. For instance, in patients with kidney disease, liver function abnormalities, congestive heart failure, peripheral vascular disease, pulmonary disease, acute myocardial infarction, septicaemia, hypovolemia, shock, or other causes as these conditions may increase the risk of tissue anoxia and therefore the development of lactic acidosis [4, 16]. For the same reason it is recommended that metformin should be withdrawn in patients undergoing major surgery or requiring investigation using radiographic contrast media and should only be restarted once renal function has been evaluated and determined as within acceptable limits [11].

Metformin Treatment Preference in Renal Impairment

The prescribing information for metformin in the current label specifies the contraindication of renal disease or renal dysfunction as serum creatinine (SCr) levels≥1.5mg/dL (for males) and SCr levels≥1.4mg/dL (for women) [18]. According to FDA Revised Warning in April 2016, metformin can be used in patients with mild kidney impairment (Stage 2: 90>GFR≥60) and in some patients with moderate (Stage 3: 60>GFR≥30) impairment. It is also recommended to use estimated glomerular filtration rate (eGFR) instead of a single laboratory value such as a SCr to measure kidney functions in order to determine if patients can receive metformin [1, 19].

The updated Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation are perfectly consistent with the label adding that a recent advice was adopted by the British National Formulary and the Japanese Society of Nephrology proposing that metformin use be reevaluated when GFR is 45 mL/min/1.73 m^2 and stopped when 30 mL/min/1.73 m^2 [20].

NICE guideline allows the use of metformin with eGFR less than 60 mL/min/1.73m^2, recommends to review the dose of metformin if the eGFR is below 45 mL/min/1.73m^2 in adults with type 2 diabetes, to stop metformin if the eGFR

is below 30 mL/min/1.73m², and to prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 mL/min/1.73m² [3].

Lastly Lipska et al[6] proposed recommendations for metformin use based on eGFR taking into consideration the eGFR thresholds of NICE guideline, Canadian Diabetes Association and the Australian Diabetes Society (Table 1).

Table 1. Proposed recommendations for metformin use based on eGFR [6]

Stage	Description	eGFR mL/min/1.73m²	Action
1	Kidney damage with normal or high GFR	≥ 90	No renal contraindication to metformin Monitor renal function annually
2	Kidney damage with mild low GFR	<90 and ≥60	No renal contraindication to metformin Monitor renal function annually
3	Moderate decreased GFR	<60 and ≥45	Continue use Increase monitoring of renal function (every 3-6 months)
3	Moderate decreased GFR	<45 and ≥30	Prescribe metformin with caution Use lower dose Closely monitor renal function Do not start new patients on metformin
4	Severe decreased GFR	<30 and ≥15	Stop metformin
5	Kidney failure	< 15 (or dialysis)	Stop metformin

Stages of chronic kidney failure by the National Kidney Foundation [21]; eGFR: estimated glomerular filtration rate.

In view of these worldwide ambiguities about metformin use in presence of renal impairment, the aim of this study was to investigate whether renal functions of the patients were monitored and checked before or during metformin treatment as recommended in guidelines and if the treatments were adapted accordingly or whether they were disregarded and metformin was prescribed despite the contraindication of renal impairment in a hospital in Turkey.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted among the patients who were hospitalized at a university hospital, diagnosed with type 2 diabetes mellitus and had metformin included in their treatment between 2015-2016. The total number of patients with this diagnosis and treatment between these years was determined as 66 and all the patients were taken into the study. This study was

approved by the Ethics committee of the hospital. Relevant permissions were obtained to access patient data. Patient information was de-identified and just the investigators kept a confidential document revealing the identity of each patient. The data was collected by retrospective review of the hospital's electronic patient charts and included 1-year data. From the patients' chart, demographic data (age, gender, and diagnoses) and laboratory data (serum creatinine) were collected. Researchers used serum creatinine, when available on charts, and calculated CrCl using Cockcroft - Gault formula to estimate renal function of each subject. The number of patients who have not received a renal function assessment was identified. The number of cases of failure to de-prescribe metformin when contraindicated was also determined.

RESULTS

There were a total of 66 patients who met the inclusion criteria. When looked through the demographic characteristics of the patients enrolled in this study, 64 % were male. According to eGFR calculations, the 56 patients who were monitored for their serum creatinine were at 1, 2, 3, 4 and 5 (end stage renal failure) renal failure stages (Table 1) with the rates of 30, 36, 30, 4, 0 % respectively (Figure 1). It was determined that for 10 out of 66 patients (15%) who were on metformin treatment, a serum creatinine measurement and therefore renal function assessment was not performed. The study identified that according to eGFR calculations, 2 patients were contraindicated for having stage 4 kidney failure and according to SCr levels 2 more patients would be contraindicated for having a SCr level higher than 1.5 mg/dL although they were at stage 3 kidney failure and it is not accepted as a contraindication according to eGFR calculation.
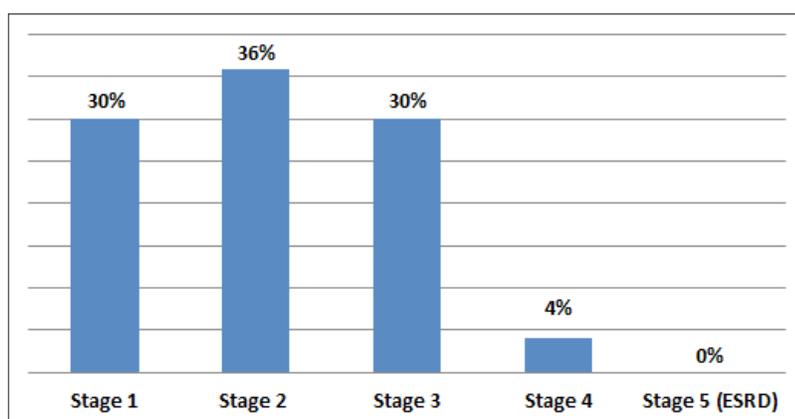

Figure 1. Renal Function Statutes of the patients (according to eGFR).

DISCUSSION AND CONCLUSION

The fear of lactic acidosis as an adverse effect originates from the experience with phenformin, although incidence of lactic acidosis is low with metformin. It has been interpreted that this experience led the physicians to be more cautious and lowered the incidence of metformin-associated lactic acidosis [14]. Studies reviewed by Inzucchi et al. [17] and Holstein et al [22] show that in real-life practice, recommendations to avoiding contraindications, including renal impairment, are not followed accordingly. The review also mentions that even though metformin clearance is reduced in the presence of chronic kidney disease, metformin levels remain within therapeutic range (0.47 – 2.5 mg/L) when eGFR is greater than 30 mL/min/1.73m². Richy et al [23] has noted that in their study the majority of metformin-treated patients (92.2%) had some level of renal impairment including severely reduced function. On the other hand, Eppenga et al [16] demonstrated in their retrospective cohort study that patients with all stages of renal impairment were treated with metformin, but they concluded mentioning the importance of current recommendations about renal function monitoring.

The approach towards the use of metformin in patients with renal impairment varies and the guidelines are not consistent in describing the contraindications as well [1,3,6,18-20]. It is shown that the recommendations of the guidelines are disregarded by the physicians in clinical practice. Studies conducted among patients on metformin treatment reveal that 25-28% of them had renal impairment as a contraindication [24-26]. Several reasons thought to cause this disregard, include 1) controversial ideas about the cause of MALA and the role of metformin [17, 26], 2) the low incidence of MALA, 3) high number of patients being deprived from the advantages of metformin treatment [6, 17, 22], 4) the thought that contraindications are unnecessarily strict because of the experience with phenformin [22], 5) antidiabetic drugs alternative to metformin might not be safer or better for these patients [17, 22]. This uncertainty shows the need to review the guidelines. Although the prescribing rules can be softened it must be acknowledged that lactic acidosis can lead to death and renal impairment is an inevitable complication of uncontrolled diabetes [27]. In the light of this study, the confusion worldwide seems to affect the physicians in Turkey as well. Examining different wards of departments in a hospital in Turkey revealed that the renal functions were not even monitored for 15 % of the patients. Although the guidelines aren't consistent about the approach to metformin use in the presence of renal impairment it is agreed by all that metformin must be stopped when eGFR is below 30 mL/min/1.73m². It is necessary to monitor the renal function initially to avoid this certain contraindication, besides there were also 2 patients with stage 4 renal failures. This might be explained as a lack of knowledge rather than a disregard.

Lack of clinical pharmacists serving in hospitals in Turkey presently, which is another factor increasing the risk of such oversights.

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