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Satyanarayana *et al.*
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Original Article

A Study on Inappropriate use or Cessation of Metformin in Type 2 Diabetic Patients with Renal Impairment

Prathyusha D [1], Parvaz Khanam P [1], Venkata Tejaswini K [1], Suresh P[1],Satyanarayana V [*], J N Suresh Kumar [2]

[1] V Pharm.D Students, Department Of Pharmacy Practice, Narasaraopeta Institute Of Pharmaceutical Sciences, Yallamanda(P),Narasaraopet , Guntur(Dt), Andhra Pradesh , India-522601.

[2] Principal, Narasaraopeta Institute Of Pharmaceutical Sciences, Yallamanda(P), Narasaraopet, Guntur (Dt), Andhra Pradesh, India-522601.

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ABSTRACT

Introduction: Diabetes is the leading cause of CKD , which makes estimation of renal function crucial. Metformin is the only biguanide extensively used these days and has become the first-line oral drug in the type 2 diabetes, however it is considered unsafe in patients with renal insuffiency because of fears about lactic acid accumulation. Because, the kidney excretesmetformin, any degree of kidney dysfunction would increase the level of metformin and subsequent lactic acid production. We evaluated the risk of CKD among adults who were prescribed metformin for NIDDM, using CKD-EPI equation to estimate kidney function and examined who were potentially stopped or inappropriately using metformin. **Methods:** We conducted a single centered observational analysis of adults age above 18 years who were prescribed with metformin from august 2016-january 2017 at Vedanta hospital, mangalagiri road, Guntur. CKD was defined using National Kidney Foundation- Kidney Disease outcome Quality Initiative Criteria. GFR was calculated using the CKD-Epidemiology(EPI) collaboration equation. **Main results:** A larger proportion of patients had renal impairment (eGFR 30-59 ml/min/1.73 m2). Only eleven patient in the entire study had severe renal impairment (eGFR < 15 ml/min/1.73 m2). There was a greater proportion of cessation of metformin in patients with eGFR <60 ml/min/1.73 m2. **Conclusion:** Most patients were found to have renal insufficiency. Patients with severe renal impairment stopped receiving the metformin after eGFR decline. CKD is common in adults prescribed metformin for type 2 diabetes, so medication safety deserves greater consideration.

Keywords: Type 2 diabetes, Chronic Kidney Disease, Metformin, GFR, CKD-EPI equation.

1. INTRODUCTION

Diabetes Mellitus is the leading cause of Chronic Kidney Disease. The National Kidney Foundation (NKF) defines CKD as either kidney damage (pathologic abnormality or markers of damage including abnormal blood,urine and imaging test) or GFR (Glomerular filtration rate) <

Corresponding author *
Mr.V. Satyanarayana[M.Pharm(Ph.D)]
Assistant Professor, Department of Pharmacy Practice ,
Narasaraopeta Institute of Pharmaceutical Sciences,
Narasaraopet, Guntur(D.t), A.P. India-522601.
E-mail: veeragandamsatya@gmail.com

60ml/min/1.73m^2 for ≥ 3 months [1]. For decades, a mainstay of therapy against diabetes has been metformin. Metformin is a biguanide used to lower blood glucose levels in patients with non-insulin dependent diabetes mellitus (NIDDM).

Metformin notably has certain advantages over sulfonylureas because it does not cause hyperglycemia,nor does it promote weight gain/hyperinsulinemia [2]. It also appears to have beneficial effects on blood lipid levels [3]. Because of these advantages, metformin use is widely promoted for the treatment of NIDDM. Nevertheless a potential complication of metformin us is its rare association with lactic acidosis, a condition that has a mortality rate of approximately 50% [4, 5].

Metformin exerts its activity by increasing peripheral glucose uptake and utilization and decreasing hepatic gluconeogenesis.By decreasing pyruvate dehydrogenase activity and mitochondrial reducing agent transportation.Metformin enhances anaerobic metabolism and increased production of tricarboxylic acid cycle precursors. Inhibition of pyruvate dehydrogenase subsequently decreases the channeling of these precursors into aerobic metabolism and causes increased metabolism of pyruvate to lactate and ultimately lactic acid production [6] .

In a patient with normal renal function, the excess lactic acid is simply cleared through kidneys. However in a patient with renal impairment, both metformin and lactic acid are cleared less effectively and may results in further accumulation of both [6]. The complication of lactic acidosis is serious and potentially fatal.

Current guidelines recommend cautious use of metformin in patients with renal impairment and metformin is contraindicated in patients with severe renal impairment [7]. Guidelines recommend discontinuation of metformin in patients with an estimated Glomerular Filtration Rate(eGFR) below 30ml.min/1.73m^2: but recommended eGFR thresholds that should trigger caution use and dose reduction , but not discontinuation , vary between 60 and 45 ml/min/1.73m^2 [8].

2. MATERIAL AND METHODS

2.1. Study design. The study was conducted at the Vedanta hospital, mangalagiri road, Guntur, between August 2016 to January 2017. We recorded all the patients who are using metformin for type 2 diabetes mellitus. Clinical data were collected. Renal function was evaluated. Serum creatinine and estimated glomerular filtration rate (eGFR) as calculated with the CKD-EPI equation were recorded. Patients were stratified according to the NKF-KDOQI criteria for CKD stages.

2.2. Objectives. Our primary goal is to estimate the prevalence of renal impairment and to estimate the glomerular filtration rate using serum creatinine and CKD-EPI equation. Secondary endpoints included changes in metformin use after decline in renal function, in metformin initiators.

2.3. Study method. Patient medication details were obtained from patient case sheets and required data is entered in data collection forms. The data was categorized based on various parameters like Gender, Age, GFR, Serum creatinine levels, Stages of renal impairment .A total of 100 patients receiving metformin in renal impairment were evaluated for information on appropriate use / cessation of metformin in renal impairment. The appropriateness is checked based on the Canadian diabetic association guidelines, stage of renal impairment and patient condition.

Equation used for the estimation of glomerular filtration rate

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for estimating the glomerular filtration rate.

CKD-EPI equation [9]

$GFR(ml/min/1.73m^2) = 141 \times \min(SCr/K,1)^{\alpha} \times \max(SCr/K,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.159$(if black)

SCr= serum creatinine ; K=0.7 for females and 0.9 for males ; α= -0.329 for females and -0.411 for males ; min indicates the minimum of SCr/K or 1 ; max indicates the maximum of SCr/K or 1.

3. RESULTS ND DISCUSSION

100 patients with type 2 diabetes mellitus who met the study's criteria were selected to participate, based on information from medical records at Vedanta hospital, mangalagiri road, Guntur. Out of this total, 29 patients were having eGFR >60ml/min/1.73m^2. 71 patients were having eGFR <60ml/min/1.73m^2, thirty seven men and thirty four female.

With regards to the social habits and medical history of the patients with type 2 diabetes mellitus, we observed that most diabetics were between 41-70years and had hypertension (52%) cerebrovascular accident (8%) and coronary artery disease (7%) associated with type 2 diabetes mellitus. The prevalence of smoking and drinking habits in the population studied was 6% and 10% respectively.

The assessment of renal function, according to serum creatinine and GFR calculated using CKD-EPI equation shows that the prevalence of serum creatinine above 1.5mg/dl was 58%.

Patients were stratified according to the NKF-KDOQI criteria for CKD stages and population who stopped using metformin after decline in GFR was shown in figure 1.

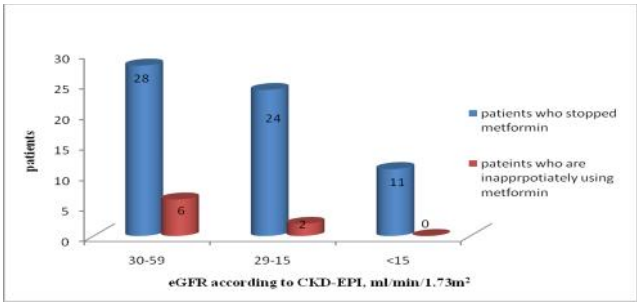

Fig 1: Patients who stopped or inappropriately using metformin after decline in their eGFR

4. CONCLUSION

The estimated prevalence of moderate to end stage renal disease was 71% in this study population of adults prescribed metformin for type 2 diabetes,which raises the possibility of potentially inappropriate metformin use. The CKD-EPI equation identified more subjects were having CKD. We observed major study population with renal impairment was stopped receiving the metformin for type 2 diabetes after decline in eGFR < 60ml/min/1.73m^2.

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