Original Research Article

Implication of Estimated Glomerular Filtration Rate for a rationale management in Type 2 Diabetes Mellitus.

Running title:

A study involving the renal parameters to obtain a nephroprotective therapeutic modalities in type 2 Diabetes Mellitus.

ABSTRACT

Introduction: Diabetic patients are at early risk of developing deterioration in renal function. The pharmacokinetics of antidiabetic drugs may get altered depending on the Glomerular filtration rate. **AIM:** The aim is to study the eGFR appropriateness in the management of type 2 DM. **Materials and Methods:** The study was conducted in the private diabetic care centre, Chennai. Blood urea, Sr creatinine, GFR and routine blood glucose investigations was estimated for all the participants. Based on the report, the therapeutic modalities were analyzed for their nephroprotection. Descriptive statistics was used & values were expressed in numbers and percentage. **Results:** Out of 148 patients, 87 diabetic patients were selected based on inclusion criteria. In which 55% were males & 45% females. Diabetes was observed to be highest 58.62% in the age group 40-59 years followed by 22.99% in 20-39 years and 18.39% in ≥60 years. 66 patients had creatinine level ≤1.1 and 21 patients had increased serum creatinine (>1.1). From the 87 study participants, 24 patient's treatment regimens were modified based on eGFR and HbA1C. **Conclusion:** Rationality in the management could be improved by including eGFR values in addition to glucose levels and HbA1C for type 2 diabetes mellitus.

KEY WORDS: Hypoglycaemic agents, Renal function tests, Diabetic nephropathy

Introduction:

One of the leading cause of end stage renal disease in the world is Diabetes mellitus. Diabetic patients are at early risk of developing deterioration in renal function.[1] About 30% of all

diabetics are affected by diabetic nephropathy.[2] Therefore, kidney function needs to be monitored regularly in all diabetic patients. When the glomerular filtration rate (GFR) is less than 60 ml/min, the pharmacokinetics of antidiabetic drugs may get altered. A quite number of oral hypoglycemic drugs undergoes renal metabolism and their metabolites are usually active. These active metabolites are retained in the body for long time in case of decreased GFR and cause hypoglycemia. Severe hypoglycemic episodes can prove fatal. The easily available tests in detection and prevention of diabetic kidney disease at an early stage are serum urea and creatinine.[3,4] It is also desirable to assess the renal function by estimating the glomerular filtration rate. Measurement of renal function by GFR is the best used and widely accepted measure.[5] Measurement of these parameters can limit the progression to end stage renal disease (ESRD). Literatures support the estimation of renal parameters and GFR in patients with chronic kidney disease. But the purpose of initiation of this study is to estimate the basic renal tests like serum creatinine and eGFR for all type 2 diabetic patients and obtain an appropriate treatment regimen. This would allow for early detection of derangement in renal function and allowing more rigorous management by the physician. Improved and continous monitoring of renal functions in diabetic patients, provides warning signals regarding the progression of disease. The eGFR based treatment in diabetic patients without nephropathy can slow the progression of developing chronic kidney diseases as well as prevent life threatening hypoglycaemic attacks.

Materials and methods:

This study was conducted in the private diabetic care centre, Chennai for a period of four months from July to October 2021. Institutional ethics committee approval was obtained. Informed consent was obtained from all the study participants.

Inclusion criteria

- Patients who are k/c/o type-II diabetes mellitus and are on antidiabetic agents.
- Both the genders.
- Age 18-80

Exclusion criteria

- Pregnant and lactating women.
- Patients with other co morbid conditions
- Patients with any long term nephrotoxic drugs
- Gestational diabetes
- Type 1 diabetes

All type 2 diabetic patients without any symptoms of renal disease and are on antidiabetic drugs were included in the study. Patients were choosen in such a way that they had minimum two values of Blood urea & Sr creatinine within a period of three months.

CKD- EPI equation [6,7] was selected to calculate the estimated glomerular filtration rate. This equation was found to give the best estimation of GFR when compared to the other formulas available to calculate eGFR.[8] Based on the eGFR values, their therapeutic modalities were analyzed for nephroprotection.

Stastical analysis: Descriptive statistics was used and values were expressed in numbers and percentage.

Results:

Out of 148 patients who visited the out-patient department, 87 diabetic patients were selected based on the inclusion criteria, in which 48 (55%) were males and 39 (45%) were females. Type II DM was observed to be highest (58.62%) in the age group of 40-59 years followed by 22.99% in the age group of 20-39 years and 18.39% in ≥60 years.

Out of the 87 patients, creatinine values in their records were observed to be normal (≤1.1) in 66 patients and around 21 patients had increased serum creatinine values. eGFR was obtained using CKD-EPI equation for all the 87 patients. 39 patients had e GFR ≥ 90 ml/min, 30 patients within the range of 60 -90 ml/min, 11 patients within 45-59ml/min, 4 patients within 30 -44ml/min, 2 patients within 15-29ml/min and 1 patient <15 ml/min as depicted in Table 1.

From the 87 included patients, 24 patients prescriptions were modified based on eGFR and HbA1C values to nephroprotective antidiabetic agents. 8 patients prescription was modified with other antidiabetic drugs, purely due to poor control of diabetes (based on HbA1C). Eventhough their eGFR values were able to tolerate all antidiabetic drugs. 16 patient

prescriptions were replaced with nephroprotective antidiabetic drugs depending on their eGFR values and glucose levels as shown in Table 2.

The most common monotherapeutic antidiabetic agent prescribed before estimation of e GFR was metformin followed by drugs of the sulfonylurea group. After estimation of eGFR, the monotherapeutic agents prescribed were Metformin, sulfonylureas except Glibenclamide. Inclusion of DPP 4 Inhibitors like Vildaglipin and increase in the prescription of Insulin after estimation of eGFR was observed as seen in figure 1.

The most common combination therapy given was glimepride and metformin before and after eGFR estimation. Newer drugs prescribed after eGFR estimation were gliptins with metformin, gliptins and insulin as shown in fig 2.

Table no 1: e GFR values of the study participants

e GFR values	n (%)*
≥ 90 ml/min/1.73m2	39 (44.8%)
60-90 ml/min/1.73m2	30 (34.5%)
45-59 ml/min/1.73m2	11 (12.6%)
30-44 ml/min/1.73m2	4 (4.6%)
15-29 ml/min/1.73m2	2 (2.3%)
<15 ml/min/1.73m2	1 (1.14%)

***indicates the number of diabetic patients without nephropathy and its expressed in percentage.**

Table no 2: Drug utilization Pattern of Antidiabetic drugs based on renal function tests and HbA1C

n (%)*	**e GFR values ml/min/1.73m^2**	**Nephroprotective drugs #**	**No. of pts already on nephroprotective**	**Number of patients treatment**

			antidiabetic agents	modified based on e GFR & HbA1C
39 (44.8%)	≥ 90	All antidiabetic drugs	37 (94.87 %)	2 (5.13%)
30 (34.5%)	60-90	All antidiabetic drugs	24 (80%)	6 (20%)
11 (12.6%)	45-59	Gliclazide, Repaglinide, Metformin, Exenatide, Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Pioglitazone, SGLT2 inhibitors, Insulin	1 (9.09%)	10 (90.91%)
4 (4.6%)	30-44	Sitagliptin, Saxagliptin, Linagliptin, Exenatide, Repaglinide, Insulin	1 (25%)	3 (75%)
2 (2.3%)	15-29	Saxagliptin, Sitagliptin, Insulin	0	2 (100%)
1 (1.14%)	<15	Insulin	0	1 (100%)

***indicates the number of diabetic patients without nephropathy and its expressed in percentage.**

 # Clinical practice recommendations by Anne zanchi *et al*

Figure No 1: Impact of e GFR on diabetic patients who received monotherapy

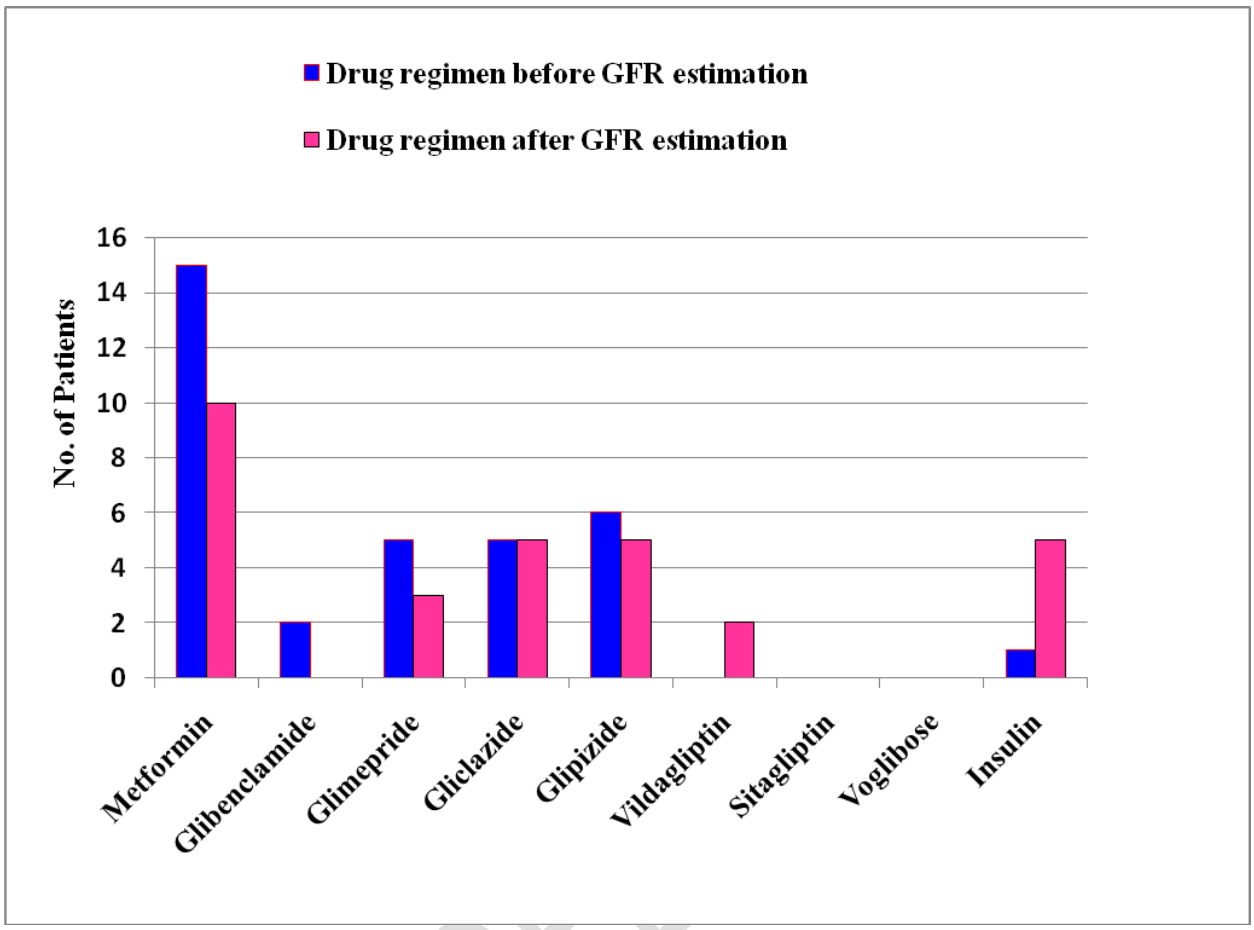
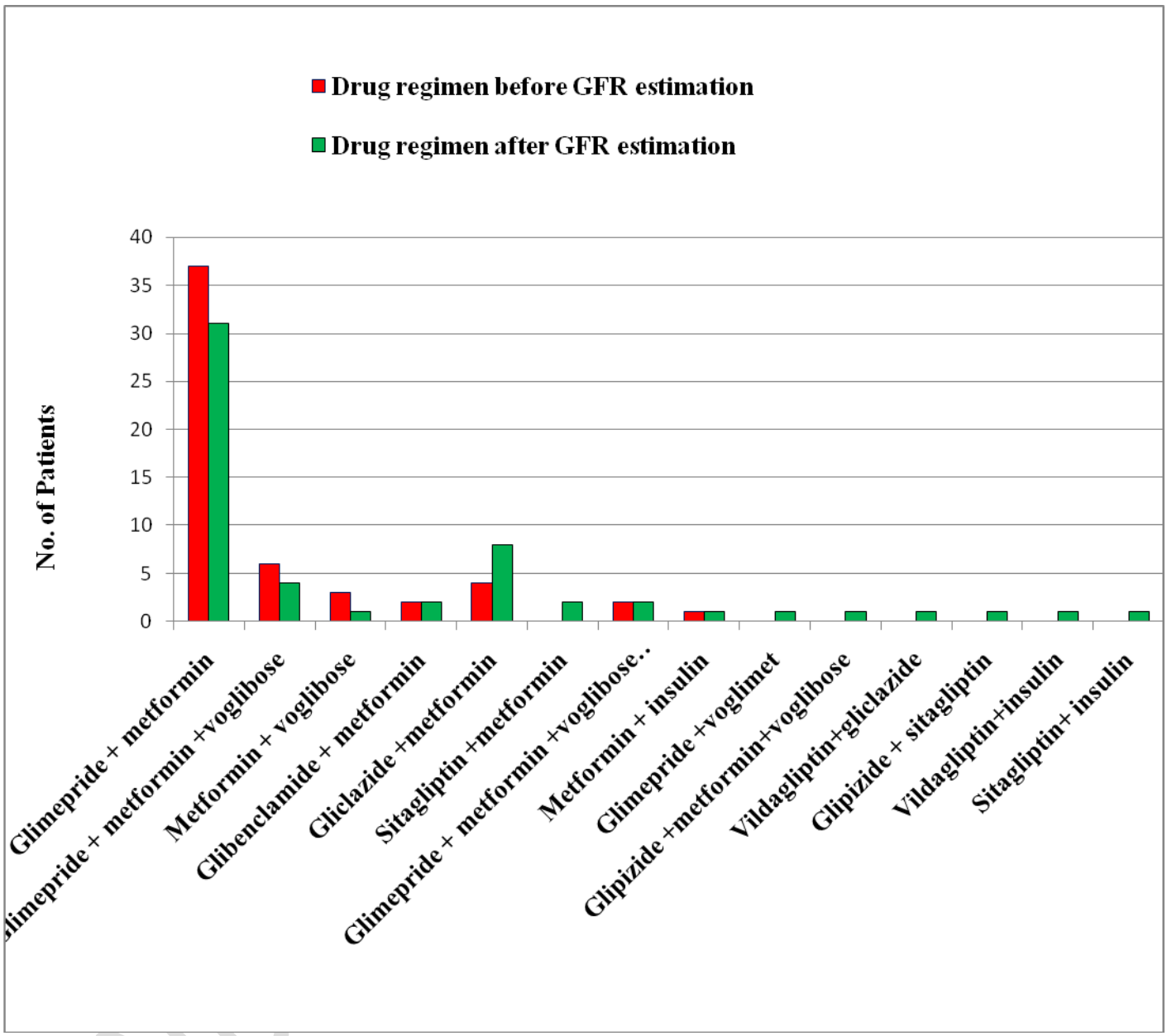


Figure No 2: Impact of e GFR on diabetic patients who received combination therapy


Drug regimen before GFR estimation
Drug regimen after GFR estimation
No. of Patients
40
35
30
25
20
15
10
5
0
Glimepride + metformin
Glimepride + metformin +voglibose
Metformin + voglibose
Glibenclamide + metformin
Gliclazide +metformin
Sitagliptin +metformin
Glimepride + metformin +voglibose..
Metformin + insulin
Glimepride +voglimet
Glipizide +metformin+voglibose
Vildagliptin+gliclazide
Glipizide + sitagliptin
Vildagliptin+insulin
Sitagliptin+ insulin

Discussion:

In this study we have attempted to describe the current prescription pattern and trend of antidiabetic drugs in Type 2 DM without any symptoms of kidney disease. Previous studies suggest that the prevalence of DM and CKD increases with age,[9, 10] highlighting the need for regular controls of kidney function in older diabetics.[11] But the present study is in contrast with the previous studies shows decline in e GFR in the age group of 20 -59yrs. A study by Geert Goderis *et al* also supported our findings of association of younger age with DCKD (Diabetic Chronic Kidney Disease).[12]

CKD is highly prevalent in patients with type 2 DM. Even though intense glycaemic control has proven to delay the onset and decrease the progression of CKD. But the exact pathogenesis remains complex and not completely understood. Current antidiabetic agents are directed towards delaying of the progression of diabetic nephropathy. However, there are only limited data regarding the renal protection provided by these therapeutic modalities.[13] Diabetic kidney disease without proteinuria is increasingly recognized.[14] Similar findings were observed in the present study, the diabetic patients included had no proteinuria but had decline in e GFR and increase in serum creatinine values.

Previous literatures states that, measurement of serum creatinine and blood urea are the easily available tests which can assess the detection and prevent the diabetic kidney disease in early stage.[3,4] Estimation of renal function tests is simple, economic and reliable that can be considered as an adjunct in the management of long term type 2 Diabetes Mellitus.[15,16] A study by Bamanikar *et al* proved that there was statistically significant rise in urea and creatinine values in diabetic patients when compared to non diabetics.[17] These findings were again supported by our present study showing decline in GFR and increase in creatinine values without any symptoms of CKD in diabetes patients.

The main objective in the management of Diabetes Mellitus is to achieve HbA1C of < 7% and ensuring that the antidiabetic drugs are in compatible with the renal functions.[18, 19] In our present study the prescription of antidiabetic drugs adhered to NICE guidelines, having Metformin as the most commonly prescribed monotherapy as well in combination with sulfonylureas.

Previous literatures state Glibenclamide should be used with caution in mild CKD (e GFR 60-90 ml/min) and contraindicated in e GFR < 60 ml/min (≥ 3 CKD stage). Glimepride contraindicated with GFR < 60 ml/min. Gliclazide used in subjects with GFR of 40-60 ml /min and stopped once GFR falls below 40ml/min. Repaglinide is not containdicated in patients with CKD. Metformin is indicated for patients with GFR of45 -60ml/min and stop it when GFR drops <45ml/min. Pharmacokinetic parameters of glitazones are not altered by renal impairment but their use was restricted due to the risk of water and sodium retention. Alpha glucosidase inhibitors are not recommended because of the risk of accumulation. Exenatide not to be used if GFR <30ml/min and Liraglutide not to be used in GFR <50ml/min. Among DPP4 inhibitors Saxagliptin and sitagliptin are the only two drugs which can be prescribed for e GFR <30 ml/min but dose reduction was required [1]. Based on e GFR and HBA1C, the prescription pattern in the present study led to more safer & nephroprotective antidiabetic drugs like Gliclazide, DPP4 inhibitors, Metformin and Insulin. Therefore there is always a need for the reevaluation of the treatment regimen based on the kidney functions.

Hence along with other routine markers of diabetes, Renal Function Tests and eGFR could aid in the management and long-term treatment of Type 2 diabetes mellitus. They should be recommended to be included in the panel of routine investigations for proper management of type 2 DM to prevent diabetic nephropathy.

Conclusion:

The eGFR and serum creatinine based treatment in diabetic patients without nephropathy can slow the progression of developing chronic kidney diseases as well as prevent life threatening hypoglycemic attacks. eGFR could be an early warning sign for renal impairment in diabetic patients. Treatment of type 2 DM based not only on glucose levels and HbA1C, but also with relation to eGFR and serum creatinine could be a most appropriate treatment protocol. This calls in creating awareness among the primary care physicians and other clinicians involved in the care of diabetic patients.

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