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Original Research Article

Role of Dapagliflozin, a SGLT2 Inhibitor in Early CKD Patients with T2DM in a Tertiary Health Care Centre

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Conflict of interest: Nil

Abstract:

Background: Chronic kidney disease (CKD) is a prevalent condition which affects 50% of the individual with T2DM (1). Dapagliflozin, a SGLT2 inhibitor is a class of antidiabetic remedy which has emerged to show effects in kidney disorders.

Aim: An observational study to identify the role of Dapagliflozin in Chronic Kidney Disease Patient with diabetes.

Method: A total of 49 patients were included according to the specified inclusion and exclusion criteria in the study. Their medical records were carefully examined, and relevant information was documented. Subsequently, statistical analysis was carried out using SPSS software using all the quantitative data.

Result: In this study, Dapagliflozin exhibited positive changes in biomarkers associated with CKD and Diabetes. Initially estimated glomerular filtration rate (eGFR) was low, but significant Improvement was seen over the second follow-up, suggesting improved renal function. Similarly, the level of HbA1C decreased from the initial measurement to the second follow-up which shows better glycaemic control. In the final follow-up, there were no patients in stages G4 or G5, and a notable decrease was observed in stages G3A and G3B. Moreover, the mean creatinine level also decreased significantly suggesting improved kidney function

Conclusion: Dapagliflozin has demonstrated efficacy in improving glycaemic control and offering renal protection. As a result, Dapagliflozin shows promise as a therapeutic solution for addressing the complex connection between CKD and T2DM.

Keywords: Chronic Kidney Disease, Diabetes Mellitus, Dapagliflozin, Glomerular Filtration rate.

Introduction

A persistent abnormality in the urine, anatomical abnormalities, or reduced excretory renal function that is suggestive of the loss of functional nephrons are all indicators of chronic kidney disease (CKD).[1] Between 8% and 16% of people worldwide are affected with chronic kidney disease (CKD), which is often overlooked by patients and medical professionals.[2]In extensive clinical trials including type 2 diabetes patients, sodium-glucose cotransporter 2 (SGLT2) inhibitors reduced glycated haemoglobin levels and had positive effects on kidney function.[3] The EMPA-REG outcome showed that 40% of T2DM patients have CKD, and more than 20% have clinically diagnosed CKD.[4]In patients with CKD stages 1 to 4, the National Kidney Foundation (NKF) advises a blood pressure of less than 130/80mmHg.[5]Dapagliflozin, a SGLT2 inhibitor increases urine glucose excretion by decreasing glucose reabsorption in the proximal convoluted tubule of the kidney. T2DM is the main contributor to CKD, which has a high morbidity and mortality rate. These patients need early detection and early implementation of suitable therapeutic therapies that reduce disease development and avoid negative outcomes since they have a significant risk of developing cardiovascular disease and end-stage kidney disease.[6] SGLT2 inhibitors were initially developed for the treatment of type 2 diabetes because they enhance glycemic control.[7] Regardless of the presence or absence of T2DM,

SGLT2 inhibitors reduce the risk of death and other negative outcomes in patients with chronic heart failure and a reduced ejection fraction (i.e., a left ventricular ejection fraction of 40%) as well as in those with chronic kidney disease. SGLT2 inhibitors were initially developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus.[8] In patients with T2DM and CKD, physicians frequently concentrate on treating modifiable risk factors, such as blood pressure, blood glucose levels, and albuminuria, as well as monitoring kidney function and coordinating care[6] In patients with type 1 diabetes, SGLT-2 has been demonstrated to lower intraglomerular pressure and improve hyper filtration; it has been hypothesised that these benefits may translate into better renal outcomes. However, worries have been expressed that sodium-glucose cotransporter 2 inhibitors can have long-term negative effects on the kidneys.[9] UTIs, increased urination, and female genital mycotic infections are the most often reported side effects with SGLT-2.[10]

Methods:

Study Design: A prospective, observational study was conducted at tertiary care, Dhiraj Hospital, Pipariya Vadodara, Gujarat, India. This study was conducted for 6 months (five month of data collection and one month of analysis). The study included patients of age groups 18 and above and gave consent. This study material comprises of an Informed Consent Form (ICF),a Patient Information Sheet (PIS), a proforma and questionnaires. After obtaining ethics committee authorisation (SVIEC/ON/Phar/BNPG21/Nov/22/17), enrolment of the patient began using inclusion and exclusion criteria. Patients who meet the study requirement for inform about the result and asked to fill a PIS (Annexure A).

Objectives:

Primary Objectives:

- To determine the change in eGFR following the initiation of Dapagliflozin in CKD patients over 6 months.
- To determine the need for hemodialysis/progression of CKD in patients on Dapagliflozin.

Secondary Objectives:

- To evaluate Glomerular Filtration Rate after initiation of Dapagliflozin.
- To check for changes in specific parameters like eGFR, serum creatinine, urine albumin and HbA1C.

Inclusion Criteria:

- Patient from age group- 18 or above.
- Patient with diagnosed CKD with/without hemodialysis
- Patient with CKD and with diabetes
- Patient recently initiated or on treatment with Dapagliflozin.
- Patient diagnosed GFR <60 ml/min / 1.73m2

Exclusion Criteria:

- Patient who does not want to participate in study
- GLP-1 medications with an action mechanism comparable to that of dapagliflozin were not prescribed.
- Patient with end stage renal disorder.

Methodology:

The data was gathered using the lab reports and clinical proforma of the patient who were initiated with the Dapagliflozin. Regular follow-up of patients was taken after one and a half month and 3 months. If in case patient was not available, telephonic communication was carried out. The collected data was assessed appropriately by proper statistical method.

Statistical Analysis: After the data collection, for statistical analysis all gathered data was transcribed into Microsoft Excel. Analysis was carried out using SPSS software using all the quantitative data in percentage (%) and mean standard deviations. all the date was exported to statistical software for statistical analysis. P value frequencies of drug compliance were described.

Result

Patients Sociodemographic Data:

Table 1: Sociodemographic Data

		Mean / %
Age		51.61
	≤30	23
	31 to 40	35
	41 to 50	45.93
	51 to 60	55.73
	≥61	62.12
Gender	Male	40.82%
	Female	59.18%
CKD Duration		8.77
Past History	Present	16.33%

	Absent	83.7 %
Family History	Mother	4.0%
	Father	2.0%
Social history		
Diet	Veg	65.3 %
	Non- Veg	34.7 %
Alcohol	Yes	36.7 %
	No	63.3 %
Smoking	Yes	26.5 %
	No	73.5 %

Patient Distribution on The Basis of eGFR: Out of collected N = 49 patients, mean ± SD for GFR baseline was 34.878±5.8189, mean ± SD for follow up 1 was 40.102±7.1945 and mean ± SD for follow up 2 was 47.286±7.5194. Mean Difference was -12.4082.

Table 2: Distribution of eGFR

		eGFR_Base	eGFR_FU_I	eGFR_FU_II
N	Valid	49	49	49
	Missing	0	0	0
Mean		34.88	40.10	47.29
Median		33.00	40.00	46.00
Std. Deviation		5.82	7.19	7.52
Minimum		24.0	27.0	31.0
Maximum		59.0	64.0	66.0
Friedman's Two-way ANOVA: P: 00001Significant.				

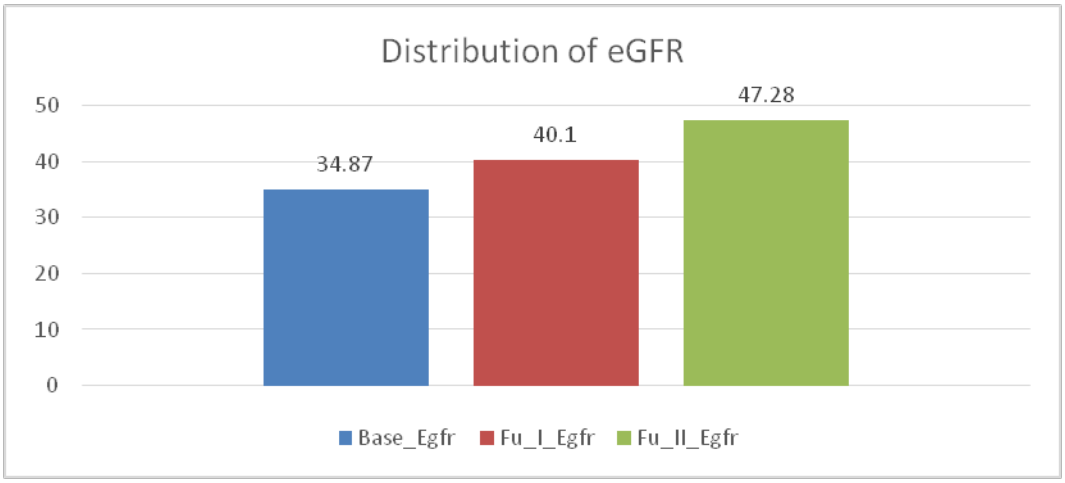

Figure 1: Distribution of eGFR

Patient Distribution on the Basis of Creatinine: Out of collected N = 49 patients, mean ± SD for baseline was 2.0022±0.26028, mean ± SD for follow up 1 was 1.7467±0.26081 and mean ± SD for follow up 2 was 1.4849±0.24872. Mean Difference was 0.517347.

Table 3: Creatinine distribution

		Creat_Base	Creat_FU_I	Creat_FU_II
N	Valid	49	49	49
	Missing	0	0	0
Mean		2.00	1.75	1.48
Median		1.90	1.80	1.50
Std.Deviation		.260	.260	.248
Minimum		1.40	1.10	1.00
Maximum		2.90	2.60	2.30

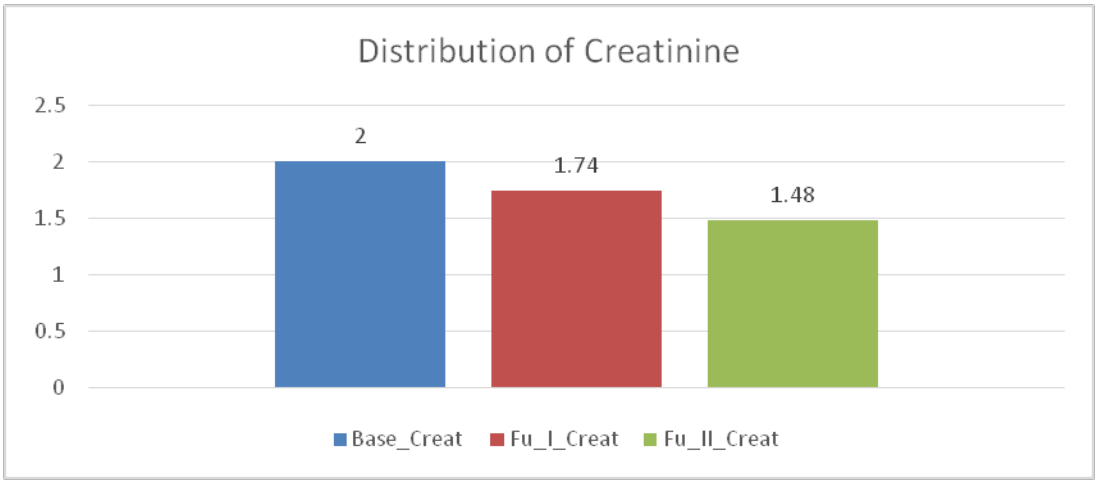

Figure 2: Distribution of Creatinine

Patient Distribution on The Basis of HbA1C: Out of collected N = 49 patients, mean ± SD for baseline was 7.17±0.99, mean ± SD for follow up 1 was 6.98±0.85, and mean ± SD for follow up 2 was 6.75±0.92. Mean difference (Follow Up 2 – Baseline) was 0.42.

Table 4: DistributionofHbA1C

		HbA1C_Base	HbA1C _FU_I	HbA1CFU_II
N	Valid	45	45	45
	Missing	04	04	04
Mean		7.17	6.98	6.75
Median		7.30	7.00	6.70
Std. Deviation		0.99	0.85	0.92
Minimum		5.80	5.80	3.90
Maximum		10.10	9.10	8.50
Friedman's Two-way ANOVA: P: 0.0001Significant.				

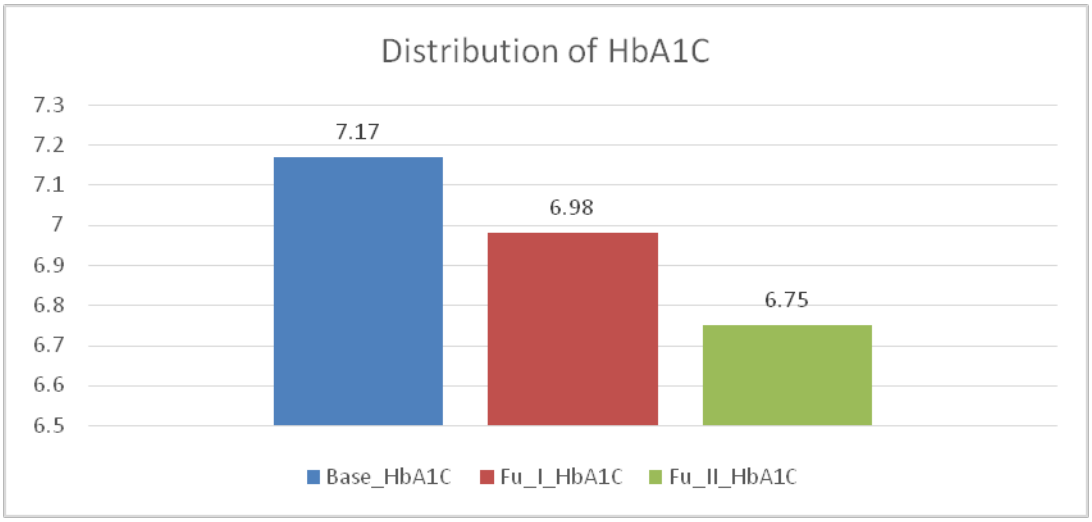

Figure 3: Distribution of HbA1C

Data of CKD Progression According To Stages

Table 5: CKD Progression

Stages	Pre-Stage	Post Stage 1	Post Stage 2
G1	0	0	0
G2	0	1	4
G3a	4	7	27

G3b	44	40	18
G4	1	1	0
G5	0	0	0
Total	49	49	49

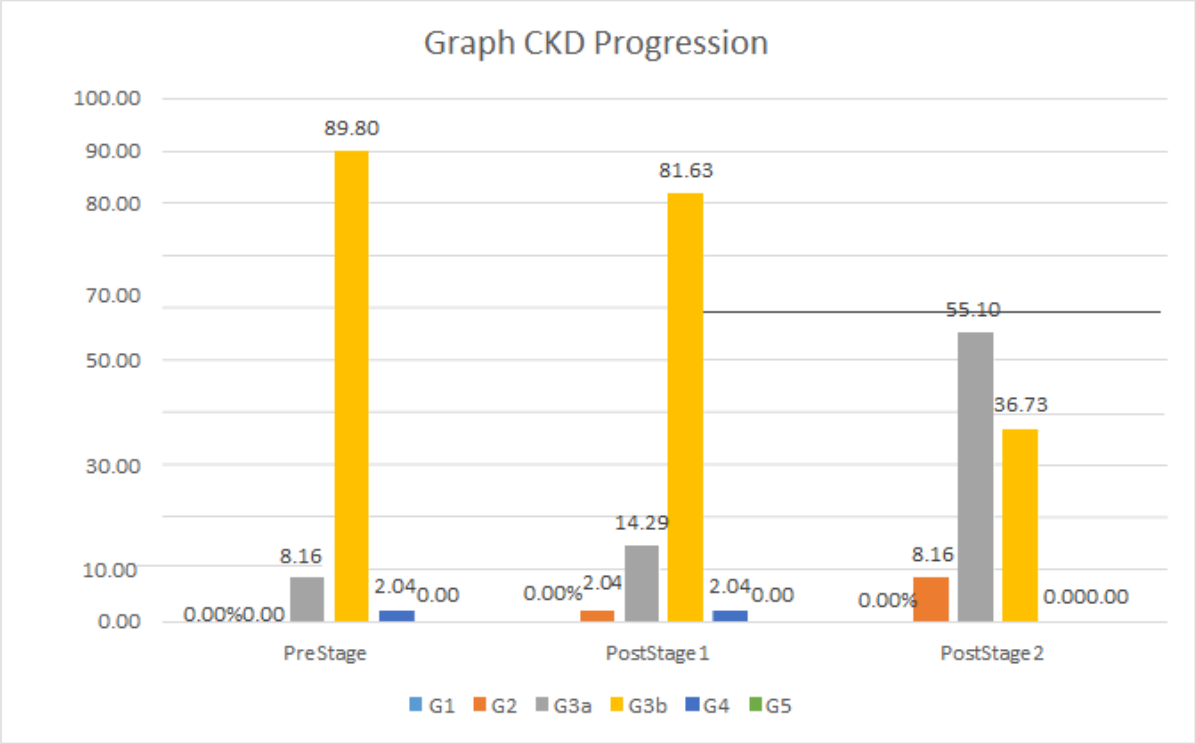

Figure 4: CKD Progression

Table 6: Data According to Mean Difference

variables	Baseline	follow up	mean differ-ence (bl - f1)	follow up 2	mean differ-ence (f1-f2)	mean difference (bl - f2)
Hb	15.02	15.32	-0.29	15.60	-0.28	-0.57
RBC	4.27	4.35	-0.074	4.43	-0.08	-0.16
TC	7993.88	8038.78	-44.90	8140.82	-102.04	-146.94
Neutrophil	63.94	65.05	-1.11	64.65	0.40	-0.71
Lymphocyte	25.87	26.55	-0.69	26.12	0.43	-0.26
Eosinophil	3.22	3.08	0.14	3.06	0.02	0.16
Monocytes	2.67	2.49	0.18	2.57	-0.08	0.10
Platelets	1.92	2	-0.08	2	0	-0.09
Hct	42.29	42.49	-0.20	42.59	-0.10	-0.3
MCV	88.31	88.89	-0.58	88.97	-0.08	-0.66
MCH	29.44	29.73	-0.29	29.76	-0.03	-0.32
MCHC	32.64	32.98	-0.34	33.02	-0.04	-0.38
RDW	16.23	16.14	0.084	16.22	0.20	0.28
Urea	56.53	54.41	2.12	50.86	3.55	5.67
Creatinine	**2**	**1.75**	**0.26**	**1.48**	**0.26**	**0.52**
Uric acid	9.09	7.25	1.84	7.25	0.32	2.16
Na	146.84	145.86	0.98	145	0.86	1.84
K	4.93	4.81	0.12	4.76	0.05	0.17
Ca	104.82	104.02	0.80	102.84	1.18	1.98
Sr Electrolyte	2.96	3.04	-0.08	3.11	-0.07	-0.15
RBS	170.78	168.24	2.53	166.29	1.96	4.49
HbA1C	**7.17**	**6.99**	**0.18**	**6.75**	**0.24**	**0.42**
Sr Fe	64.57	68.30	-3.72	70.15	-1.85	-5.57
Transferrin	20.34	22.14	-1.79	23.52	-1.38	-3.17

TIBC	253.96	264.40	-10.45	264.36	0.04	-10.40
Ferritin	150.80	150.98	-0.17	153.54	-2.57	-2.74
CRP	0.75	0.84	-0.10	0.80	0.039	-0.06
eGFR	**34.88**	**40.10**	**-5.22**	**47.29**	**-7.18**	**-12.41**

Discussion

Our research involved 49 participants, all of whom had CKD and type 2 diabetes from rural as well as urban areas, and were aged 18 or above, with a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m². In the study conducted at Dhiraj Hospital, the participant distribution revealed that 59.18% were females; while 40.82% were males this gender distribution reflects a relatively balanced representation of both sexes. Conversely, in a separate study conducted across 88 centres, out of the 321 patients involved, 56.9% were males, and 43.1% were females, with a mean age of 65.3.[11]The distribution of patients across different age groups shows that the majority of individuals were between 41 to 60 years old.

The biomarkers for chronic kidney disease (CKD) and Diabetes were considered in our assessment of the condition's progression. In this group of patients, which included individuals with estimated GFRs as low as 24 ml per minute per 1.73 m2, dapagliflozin displayed a tolerable safety profile. In our study, the baseline eGFR was 34.87, which improved to 47.28 at follow-up 2, resulting in a significant change of -12.40. The increase in eGFR signifies improved kidney function, as it indicates the kidneys' ability to filter waste products and fluids. A significant improvement in eGFR or a slower decline is observed, it would support the potential use of Dapagliflozin as an adjunct therapy for managing CKD in patients with type 2 diabetes. We noticed a similar outcome in another study involving 4304 patients, where the observed mean eGFR was 43.2±12.3.[3]Additionally, a different study investigating the impact of SGLT2 inhibitors on renal outcomes and diabetes reported a mean eGFR of 56.3±18.2.[12]

Regarding the mean Haemoglobin A1c (HbA1c) in our study, Baseline HbA1C levels were 7.17, and at follow-up 2, they decreased to 6.75, indicating a reduction of 0.42. Lower HbA1C values reflect improved glycemic control, suggesting that dapagliflozin effectively managed blood glucose levels in patients with type 2 diabetes. The decrease in HbA1C levels indicates a reduced risk of diabetic complications, including kidney damage.In another related study exploring SGLT2 inhibitors and their effects on renal outcomes in individuals with Type 2 Diabetes and Nephropathy, the mean HbA1c was found to be 8.3±1.3.The mean creatinine is and in the study with the mean was found to be 6.1±0.8.[12]

The Dapagliflozin study conducted in 386 sites across 21 countries did not mention serum creatinine levels. However, in our study, the baseline mean creatinine level was 2.00, which decreased significantly to 1.48 at follow-up 2, with a change of 0.51. This improvement suggests enhanced kidney function following dapagliflozin treatment. A reduction in creatinine levels indicates a slower decline in renal function and suggests potential renoprotective effects of dapagliflozin.

A study involving 4,304 patients demonstrated a consistent and ongoing decrease in the estimated glomerular filtration rate (GFR) by at least 50%. This finding suggests that the progression of the disease is slower. However, it should be noted that the article did not rule out the possibility of staging the disease.[3]

The study enrolled 49 patients with varying stages of renal function, categorized as G1, G2, G3A, G3B, G4, and G5. None of the patients were initially classified as G1 or G2, with the majority falling into the G3B stage. After a 1.5 month follow-up period, one patient progressed to G2, while the majority remained in G3B. The number of patients in G3A and G4 stages slightly decreased. In the final follow-up, there were no patients in G4 or G5 stages, and a significant decrease was observed in G3A and G3B stages.

At the initial visit, none of the patients were classified as G1 (indicating normal or high eGFR) or G2 (mildly reduced eGFR). The majority of the patients fell into the G3B stage (eGFR between 30-44 ml/min/1.73m²), accounting for 89.80% of the total population. G3A stage (eGFR between 45-59 ml/min/1.73m²) comprised 8.16% of the patients, while G4 (eGFR between 15-29 ml/min/1.73m²) and G5 (eGFR less than 15 ml/min/1.73m²) stages constituted 2.04% and 0% respectively.

After a 1.5-month follow-up period, the distribution of patients across the stages showed some changes. There was still no patient classified as G1. One patient had progressed to G2 stage, while the majority of patients were still in the G3B stage, accounting for 40 out of 49 patients. The number of patients in G3A and G4 stages decreased slightly to 7 and 1 respectively, while G5 stage remained at 0.

Conclusion

Dapagliflozin has demonstrated efficacy in improving glycaemic control and offering renal protection through enhancements in eGFR and creatinine levels. As a result, Dapagliflozin shows promise as a therapeutic solution for addressing the complex

connection between CKD and T2DM. This treatment option provides patients with a viable approach that targets multiple aspects of their conditions. However, this study included caveats like:1) If the study is done with a wider range of population, the result could be generalised in the population. 2) Also, this study did not include ESRD population.

Future Direction for Study

- This study can be done on large scale to get more knowledge on the role of dapagliflozin in CKD patients.
- The scope of study should include the entire spectrum of CKD candidates (CKD G1-G5d) to evaluate the role of SGLT2 inhibitor on the dialysis population as well.
- As the current studies (DAPA-CKD) in non-diabetic populations showed an increase in the eGFR with preservation of residual renal function and improvement in microalbuminuria, future studies can be planned at our centre in the non-diabetic population to evaluate the response.

Abbreviations

- CKD-chronic kidney disease
- CRP- C-reactive protein
- eGFR- estimated Glomerular filtration rate.
- EMPA-REG- Empagliflozin Regimen
- GFR- Glomerular filtration rate
- HbA1C- Haemoglobin A! C
- Hb- Haemoglobin
- MCH- Mean corpuscular haemoglobin
- MCHC-Mean corpuscular haemoglobin concentration.
- MCV-Mean corpuscular volume.
- NKF- National Kidney Foundation
- RBC-Red blood cells
- RBS- Random blood sugar
- RDW-Red cell distribution width
- SGLT2- Sodium Glucose Cotransporter 2
- SPSS- Statistical Package for Social Science
- Sr Fe- Serum Ferritin
- TC- Total Count
- TIBC- Total iron binding capacity
- T2DM- Type 2 Diabetes Mellitus

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