Effect of SGLT2 Inhibitors on anaemia In patients with CKD 3 & 4 secondary to Diabetic Nephropathy.

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ABSTRACT:
Objective: The objective of the study is to evaluate the effect of adding dapagliflozin to standard anaemia care on hemoglobin trajectories in stage 3-4 diabetic chronic kidney disease (CKD).
Methodology: Adults aged 40-80 years with stage 3-4 diabetic CKD, Hb <13.0 g/dL (males) or <12.0 g/dL (females), and MCV 80-100 fL were enrolled (n=86). Participants were randomized (1:1) to Group A (dapagliflozin 10 mg daily plus oral iron, Haemopoietin, insulin, and standard CKD care) or Group B (oral iron, Haemopoietin, insulin, and standard CKD care). Hb and HbA1c were measured at baseline, 1, and 3 months. The primary outcome was Hb improvement at 3 months (≥1 g/dL rise from baseline or normalization to WHO thresholds).
Results: Baseline characteristics were similar between groups. Group A showed larger and earlier Hb increases than Group B. Mean Hb change in Group A was +0.45 g/dL at 1 month and +0.96 g/dL at 3 months (both $p < 0.01$). Group B experienced smaller increases (+0.08 g/dL at 1 month, $p = 0.069$; +0.25 g/dL at 3 months, $p = 0.020$). The linear mixed-effects model demonstrated significant effects of time, treatment group, and their interaction (all $p < 0.001$). The predefined primary outcome at 3 months was met in 33/43 (76.7%) participants in Group A versus 13/43 (30.2%) in Group B ($p < 0.001$).
Conclusions: Adding dapagliflozin to standard anaemia management yields a larger and more sustained rise in haemoglobin.

Keywords: Dapagliflozin, SGLT2 inhibitors, Chronic kidney disease (CKD), Diabetic nephropathy, Anemia.

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Introduction:

Chronic kidney disease (CKD) is a major and growing global health problem. It affects a large share of the global population.[1] About 600-700 million people had CKD in recent estimates, equivalent to roughly 9-10% of the world's population.[2 3] The global burden has risen over the last decades and is increasing in low- and middle-income regions.[3] In Pakistan, community and hospital series report higher rates than global averages.[4] Local studies in high-risk groups report CKD prevalences between about 12% and 30%, and some urban high-risk surveys find roughly one quarter of participants with CKD.[4] Dapagliflozin belongs to the SGLT2 inhibitor class. These drugs lower blood glucose by increasing urinary glucose excretion.[5] They consistently raise haemoglobin and haematocrit in clinical trials.

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The haemoglobin rise appears to reflect true stimulation of erythropoiesis and better iron handling rather than only haemoconcentration.[6] Proposed mechanisms include improved renal cortical oxygenation, reduced renal inflammation, greater erythropoietin production, and altered iron metabolism that supports red-blood-cell production.[7] Clinical studies report modest average increases in haemoglobin (0.5-0.8 g/dL) and higher rates of anaemia correction in treated patients.

Despite these promising observations, data remain limited on the role of SGLT2 inhibition specifically for correcting anaemia in patients with diabetic nephropathy receiving standard anaemia therapies. There is a plausible biological rationale to expect additive benefit when dapagliflozin is combined with iron and erythropoiesis-stimulating strategies.[8] This study therefore evaluated whether adding dapagliflozin to standard care leads to greater and more sustained hemoglobin improvement over three months compared with standard care alone in patients with stage 3 -4 diabetic CKD.

Objective:

The objective of the study is to evaluate the effect of adding dapagliflozin to standard anaemia care on haemoglobin trajectories in stage 3-4 diabetic chronic kidney disease (CKD).

Methodology:

This prospective, randomized, interventional study was conducted in the Department of Nephrology, Sheikh Zayed Hospital, Lahore. The study duration was six months from July 2024 to December 2024 Approval was obtained from the institutional ethical review committee before starting the study (TERC approval letter No. TERC/SC/INT/2025/457). A total of 86 patients were enrolled. There were 43 patients

in each study group. Patients were recruited during the six-month enrolment period, unless the sample size was completed earlier. Each patient was followed for 3 months after enrolment.

The sample size was calculated using the WHO sample size calculator. A 90% confidence level was used. An anticipated population proportion of 52%[1] and an absolute precision of 0.09 were assumed. A non-probability consecutive sampling technique was used. Participants were selected according to feasibility within the study period.

Patients aged 40 to 80 years of either gender were included. All had diabetic nephropathy with stage 3 or 4 chronic kidney disease (CKD). All were already receiving oral iron and erythropoietin therapy. Haemoglobin levels were below 12 g/dL in females and below 13 g/dL in males. Eligible patients also had a mean corpuscular volume (MCV) between 80 and 100 Fl.

Patients with type 1 diabetes were excluded. Patients with polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis were also excluded. Further exclusion criteria were an estimated glomerular filtration rate (eGFR) less than 20 ml/min, transferrin saturation below 20%, serum folate below 4.5 nmol/L, or vitamin B12 levels under 200 pg/ml..

After obtaining informed written consent, patients fulfilling the inclusion criteria were randomly allocated into two groups through a lottery method. Group A (intervention group) received oral iron, Haemopoietin, insulin, and dapagliflozin 10 mg once daily, along with standard diabetic and CKD management aimed at maintaining HbA1c levels below 7%. Group B (control group) received oral iron, Haemopoietin, and insulin with regular dose adjustments based on HbA1c monitoring, targeting HbA1c levels below 7%, along with standard care. Both groups continued to receive comprehensive CKD management, including blood pressure control, dietary counselling, and the use of ACE inhibitors or ARBs when appropriate.

All participants were followed at 1 and 3 months after enrolment. At each follow-up visit hemoglobin and HbA1c levels were measured to monitor status of anemia and glycemic control. The primary outcome was improvement in anemia, defined as an increase in hemoglobin of at least 1 g/dL from baseline or achievement of normal hemoglobin levels according to WHO criteria (≥13.0 g/dL for males and ≥12.0 g/dL for females).

Statistical Analysis:

All statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Data were first checked for completeness. Data were also checked for accuracy. Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Normality of continuous data was assessed using the Shapiro-Wilk test. Histograms were also inspected visually to check normality.

For baseline comparisons between the two treatment groups, different tests were used. The independent-samples t-test was used for continuous variables with normal distribution. The Mann-Whitney U test was used for continuous variables without normal distribution. Categorical variables, such as gender and treatment response, were compared using the Chi-square test. Fisher's exact test was used when cell counts were small.

Within each group, changes in hemoglobin levels from baseline to 1 month and 3 months were analysed using the paired-samples t-test. A Linear Mixed-Effects Model (LMM) was used to assess the overall effect of time, treatment group, and their interaction on hemoglobin levels. This model accounted for the correlation of repeated measurements within the same participant. The model also allowed inclusion of all available data points. Statistical significance was set at a p-value < 0.05 for all analyses.

Graphs and boxplots were created to show trends in hemoglobin levels over time. These also showed differences between groups. Estimated marginal means with 95% confidence intervals were obtained from the LMM. These values showed adjusted mean changes in hemoglobin across visits and between treatment groups.

Results:

A total of eighty-six patients were included in the study, with forty-three patients in each group. In Group A (DAPA + Standard Care), there were twenty-one males (48.8%) and twenty-two females (51.2%). In Group B (Standard Care), there were nineteen males (44.2%) and twenty-four females (55.8%). The gender distribution was almost equal between the two groups, showing no significant difference.

Table 1 presents the summary of baseline and follow-up laboratory characteristics for both treatment groups. The table includes the mean, standard deviation, standard error of the mean, and 95 percent confidence intervals for each variable. Overall, the average age of participants was similar in both groups, indicating that the two treatment populations were comparable in terms of age distribution. The baseline haemoglobin levels were almost identical across the two groups, suggesting that both groups started the study with similar anaemia severity.

Table 2 summarizes the comparison of baseline characteristics between the two study groups: Group A (DAPA + Standard Care) and Group B (Standard Care). The results show that both groups were comparable in all major baseline parameters. There were no statistically significant differences in age, baseline haemoglobin, mean corpuscular volume (MCV), serum vitamin B12, serum folate, transferrin saturation (TSAT), or HbA1c levels. A slight, non-significant trend was noted toward higher TSAT values in Group A, suggesting marginally better iron availability, but this difference did not reach statistical significance.

The only significant difference observed between the groups was in the proportion of patients who showed improvement at the end of the study period. A much higher number of participants in Group A demonstrated hemoglobin improvement compared with those in Group B, and this difference was statistically significant ($p < 0.001$).

In Group A (dapagliflozin + standard care) mean hemoglobin rose markedly from baseline to 1 month and increased further by 3 months. Both increases were highly significant by paired t-test ($p < 0.0001$). In Group B (standard care alone) hemoglobin also rose from baseline, but to a smaller extent: at 1 month the mean increase was 1.25 g/dL and at 3 months 1.37 g/dL; both changes were likewise statistically significant.

These findings using boxplot are shown in fig 1. The left boxplot illustrates Group A, where a clear upward shift in median haemoglobin levels is observed from baseline to 3 months. The boxes become slightly higher and narrower, suggesting both an increase and stabilization of Hb values over time. In contrast, the right boxplot representing Group B shows only mild elevation in median Hb with wider interquartile ranges, indicating slower and more variable improvement among participants.

Table No 1: Comparison of group A (DAPA + Std Care) and group B (Std Care).

	Group A				
Variable	Mean	±SD	Std. Error of Mean	95% CI Lower	95% CI Upper
Age (years)	58.98	10.07	1.536	55.88	62.08
Baseline Hb (g/dL)	9.135	0.426	0.065	9.004	9.266
MCV (fL)	88.28	4.723	0.7202	86.82	89.73
Serum B12 (pg/mL)	376.7	90.86	13.86	348.78	404.71
Serum Folate (nmol/L)	18.54	5.639	0.8599	16.80	20.27
TSAT (%)	31.65	5.096	0.7771	30.08	33.22
HbA1c (%)	7.540	0.5118	0.07805	7.38	7.70
1st month Hb (g/dL)	11.158	0.99	0.1510	10.853	11.463
3rd month Hb (g/dL)	11.667	0.9975	0.1521	11.36	11.974
	Group B				
Age (years)	57.95	8.349	1.273	55.383	60.523
Baseline Hb (g/dL)	9.065	0.408	0.062	8.94	9.191
MCV (FL)	89.02	4.920	0.7502	87.5092	90.5373
Serum B12 (pg/mL)	377.4	80.72	12.31	352.6003	402.2834
Serum Folate (nmol/L)	18.18	6.389	0.9744	16.2104	20.1431
TSAT (%)	29.21	5.526	0.8428	27.5109	30.9124
HbA1c (%)	7.379	0.5837	0.08902	7.1994	7.5587
1st month Hb (g/dL)	10.447	1.170	0.1784	10.0865	10.8066
3rd month Hb (g/dL)	10.658	1.200	0.1829	10.289	11.027

Table No 2: Comparison of Baseline Characteristics Between

Variable	Group A Mean	Group B Mean	P value	Interpretation
Age (years)	58.98 ± 10.07	57.95 ± 8.35	0.54	Insignificant
Baseline Hb (g/dL)	9.135 ± 0.426	9.072 ± 0.4	0.483	Insignificant
MCV (fL)	88.28 ± 4.72	89.02 ± 4.92	0.49	Insignificant
Serum B12 (pg/mL)	376.74 ± 90.86	377.44 ± 80.72	0.97	Identical between groups
Serum Folate (nmol/L)	18.54 ± 5.64	18.18 ± 6.39	0.77	No difference
TSAT (%)	31.65 ± 5.10	29.21 ± 5.53	0.06	Group A slightly higher iron saturation
HbA1c (%)	7.54 ± 0.51	7.38 ± 0.58	0.19	Comparable glycaemic control
Gender (Male: Female)	21: 22	19: 24	0.67	No significant gender difference
Improved at End (Yes : No)	33 : 10	13 : 30	< 0.001	Significantly higher improvement in Group A

The change in haemoglobin levels over three months between the two treatment groups is shown in fig 2. The linear mixed-effects model showed that haemoglobin levels significantly increased over time in both groups ($p < 0.001$). There was also a significant difference between the groups, with Group A (Dapagliflozin+ Standard Care) maintaining consistently higher haemoglobin values than Group B (Standard Care alone) throughout the study period ($p < 0.001$). Moreover, a significant interaction between group and time ($p < 0.001$) indicated that the pattern of haemoglobin improvement differed between the two groups.

Table No 3: Comparing baseline Hb with Hb at 1 and 3 month Hb for group A and B.

Group	Comparison	Mean diff (g/dL)	SD diff	Wilcoxon p
A (DAPA + Std Care)	1st month vs Baseline	2.073	0.879	<0.0001
A (DAPA + Std Care)	3rd month vs Baseline	2.496	0.855	<0.0001
B (Std Care)	1st month vs Baseline	1.253	0.893	<0.0001
B (Std Care)	3rd month vs Baseline	1.370	0.767	<0.0001

Fig No 1: Box plot showing changes in Hb in both groups

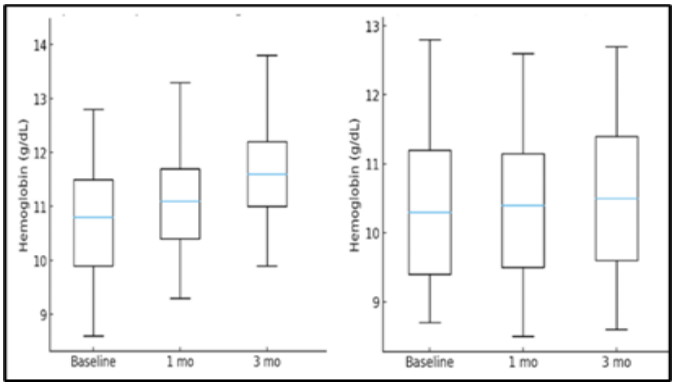
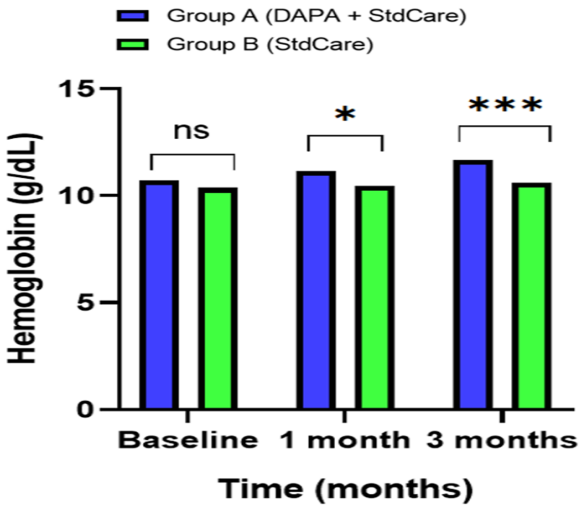


Figure 1: Left Boxplot shows changes in Hb over time for Group A patients whereas right boxplot shows changes in Hb over time for Group B patients.

Fig No 2: Change in Hemoglobin Levels Over Time Between Treatment Groups



At baseline, haemoglobin levels were comparable between Group A and Group B. However, from the first month onward, Group A showed a greater and faster increase in haemoglobin. The difference between the groups widened progressively, reaching more than 1 g/dL by the third months. The estimated marginal means, and their confidence intervals confirmed this consistent upward trend in Group A compared with a slower and less marked rise in Group B. Overall, the figure demonstrates that the addition of dapagliflozin to standard care resulted in a significantly greater improvement in haemoglobin levels over time. The primary outcome (≥1 g/dL rise or normalization) was achieved by 33/43 (76.7%) in Group A versus 13/43 (30.2%) in Group B ($p < 0.001$).

Discussion:

This study shows that adding dapagliflozin to standard care resulted in a larger and steadier rise in hemoglobin than standard care alone over the 3-month follow-up. Hemoglobin increased across all time points (1 and 3 months). The mixed-effects model confirmed significant effects of time, group, and their interaction. A higher proportion of patients in the dapagliflozin arm achieved the predefined improvement threshold by three months. These findings suggest a clinically meaningful hematologic benefit. Improved hemoglobin can lessen fatigue, reduce reliance on high doses of erythropoiesis-stimulating agents, and support better quality of life. The pattern aligns with biological mechanisms proposed for SGLT2 inhibition, including improved renal oxygenation, anti-inflammatory effects, enhanced erythropoietin signalling, and more efficient iron handling.

The results are consistent with several recent studies. In a large CKD trial analysis, dapagliflozin corrected anaemia in 53.3% of patients with baseline anaemia versus 29.4% with placebo, and increased haematocrit by 2.3 percentage points over a median 2.4 years.[10] In heart failure patients, anaemia was corrected at any point during follow-up in 62.2% with dapagliflozin versus 41.1% with placebo, indicating a substantial absolute difference.[11] A target-trial emulation cohort comparing SGLT2 inhibitors with GLP-1 receptor agonists reported a lower risk of composite anaemia outcomes over as long as three years, reflecting a population-level benefit in routine care.[11] Post-hoc analyses from the CREDENCE trial showed canagliflozin reduced incident anaemia from 176.2 to 96.7 events per 1000 person-years (hazard ratio ≈0.51), supporting a class effect on anaemia prevention.[12] Additional work in DAPA-HF documented placebo-corrected increases in haematocrit of about 2.4% by eight months, reinforcing a sustained erythropoietic signal.[13] Taken together, these reports and the present trial show convergent evidence that SGLT2 inhibition improves hemoglobin, increases the chance of anaemia correction, and lowers anaemia incidence over time.

This study has limitations. It was single-centre and modest in size. Follow-up lasted three months, so longer-term durability cannot be confirmed. The design was not blinded, which can introduce performance or detection bias. Mechanistic biomarkers such as erythropoietin, hepcidin, ferritin dynamics, and soluble transferrin receptor were not measured serially. Subgroup analyses by CKD stage, iron status, and glycaemic control were underpowered. These issues limit generalizability and mechanistic inference.[14]

Future research should include multicentre randomized trials with longer follow-up. Studies should incorporate serial erythropoietin and iron metabolism biomarkers to clarify mechanisms. Pragmatic trials should evaluate ESA dose requirements, quality of life, cardiovascular events, and progression to dialysis. Comparative effectiveness work should assess different SGLT2 inhibitors and dosing strategies. Cost-effectiveness analyses are warranted in CKD populations with high anaemia burden.

Conclusion:

By three months, a greater proportion of patients in the dapagliflozin group had made clinically significant improvements. These findings support dapagliflozin's use as an adjuvant to routine anemia therapy in diabetic CKD stages 3-4.

Conflict of Interest : None
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Authors' Contribution	
Palwisha Ameen Muhammad Abdullah Hashmi	Data collection, statistical analysis, interpretation of data.
Mateen Akram M Usman Ashraf	Conceptualization of the study design, critical review, supervision
Shazia Abbas, Huma Najeeb	Literature search, manuscript drafting, proofreading.