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Research Article

NOVEL APPROACHES FOR ANEMIA IN CARDIORENAL SYNDROME: A RANDOMIZED CONTROLLED TRIAL OF HYPOXIA-INDUCIBLE FACTOR PROLYL HYDROXYLASE INHIBITOR VS SGLT2 INHIBITOR

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ABSTRACT

Objectives: The study was designed to compare and discern the effects of desidustat versus dapagliflozin in managing anemia in addition to the standard treatment in cardiorenal syndrome (CRS).

Methods: Patients were randomly allocated into three groups: Group A (standard heart failure therapy+oral hypoglycemics), Group B (standard therapy+dapagliflozin), and Group C (standard therapy+desidustat). At baseline, 12 weeks, and 24 weeks, the hematology, iron-related parameters were estimated. The Kidney Disease Quality of Life questionnaire (KDQOL-36) was used to evaluate the quality of life of these patients.

Results: After 24 weeks, Group C exhibited significant improvements with a rise in hemoglobin (Hb) (p=0.001), other hematology, and iron parameters. Group B showed a modest but significant increase in Hb (p=0.04) alongside improved glycemic parameters. In contrast, KDQOL scores improved in Group C, specifically for the burden of kidney disease (p=0.03), symptoms (p=0.001), and daily life impact (p=0.001). Group B also showed significant changes in the burden of kidney disease (p=0.04), symptoms (p=0.002), and daily life impact (p=0.001). In Group A, significant changes were observed in the burden of kidney disease (p=0.001) and the impact on daily life (p=0.01).

Conclusion: Desidustat demonstrated greater hematopoietic efficacy compared to dapagliflozin and standard therapy alone, hence emerging as a better treatment choice over conventional treatment in managing anemia in CRS.

Keywords: Anemia, Cardiorenal syndrome, Desidustat, Dapagliflozin, Hematological parameters

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INTRODUCTION

Cardiorenal syndrome (CRS) is defined as a cascade of interrelated conditions affecting the heart and kidneys, wherein the deterioration of one organ consequently precipitates the dysfunction in the other. Cardiovascular and renal disorders share robust pathological connections [1], including the effects of inflammation, neurohormonal activation, co-morbid anemia, and many more [2]. Anemia can be defined as when hemoglobin (Hb) levels fall below 12 g/dL in women and 13 g/dL in men [3]. This is a common, yet prevalent comorbidity linked with CRS that can intensify both heart failure (HF) and chronic kidney disease (CKD), escalating the risk of mortality [4]. Anemia prevalence escalated from 21 to 70% in patients with CKD and from 9 to 79% in patients with HF, correlating with the disease progression [5]. Inadequate erythropoietin (EPO) synthesis, iron insufficiency (functional or absolute), hemodilution, chronic inflammation, elevated hepcidin, and occasionally malabsorption can also restrict the iron uptake, reflecting anemia in CRS [6-8]. Persistent anemia can cause fluid overload, thereby impairing cardiac function, inducing left ventricular hypertrophy [9]. Anemia predominantly results in hypoxia, impaired mitochondrial function, and reduced aerobic metabolism, which can interfere with daily physical routines and exercise tolerance. Hence, addressing anemia in CRS is of paramount importance in improving the symptoms and prolonging the quality of life (QoL) [10,11].

Iron and EPO supplementation have served as the cornerstone in managing anemia, tailored according to the patient's requirements. However, Kidney Disease Improving Global Outcomes guidelines have lacked definitive recommendations regarding the optimal treatment regimen for anemia in CRS [6]. Evidence from a few clinical trials, like FIND-CKD, demonstrated that intravenous (IV) iron supplementation exhibited greater efficacy over oral iron supplementation in non-dialysis-related CKD due to impaired gastrointestinal absorption [12,13]. A retrospective study and the IRONOUT-HF trial also indicated improvements in iron indices with oral iron therapy for 16 weeks in HF patients. However, the excess iron supplementation is concurrently linked to detrimental iron overload, oxidative stress, endothelial damage, and resultant cellular injury [14,15]. Erythropoiesis-stimulating agents (ESAs) currently constitute the cornerstone for renal anemia management and stand as an effective intervention for increasing Hb concentration, diminishing the necessity for blood transfusions [16]. The major limitation of endogenous ESAs is the IV mode of administration, which is not patient-friendly and also carries an elevated risk of thrombosis and negative cardiovascular events [17,18].

Renal and cardiovascular diseases are frequently precipitated by the presence of type 2 diabetes mellitus (T2DM), which is a predominant contributor to morbidity [19]. Worldwide, 697 million suffer from CKD, 64 million experience HF, and 537 million individuals are affected by T2DM [20]. These conditions create detrimental pathophysiological cycles, where the existence of one may facilitate the emergence of the others [21]. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) represent a recent advancement in the therapy of T2DM that work by selectively blocking the SGLT2 protein, which reabsorbs glucose from the renal tubules, mitigating hyperglycemia [22]. They also demonstrated a wide range of vascular and metabolic advantages in

HF and CKD [23-25]. The role of SGLT2 inhibitors in anemia remains ambiguous. The proposed mechanism involves a reduction in hepcidin and ferritin levels, stimulated by enhanced gastrointestinal iron absorption, facilitating the release of iron from intracellular storage without necessitating additional iron supplementation, thereby serving as a treatment option for managing co-morbid anemia linked to HF [26].

Novel drug class for treating renal anemia is hypoxia inducible factor prolyl hydroxylase inhibitors (HIF PHDi). HIFs, the main transcription factors, enhance the expression of various genes involved in erythropoiesis, hypoxia adaptation, and angiogenesis. They are structurally composed of three alpha subunits (HIF-1α, HIF-2α, and HIF-3α) and a beta subunit (HIF-β). In normoxia, HIF-1α is hydroxylated first, then binds with VHL, which is ubiquitinated and finally degraded. Conversely, in hypoxia, HIF-α dimerizes with HIF-β and stabilizes, regulating target gene expression, promoting endogenous EPO production, thereby enhancing Hb concentration. Phase 2,3 clinical trials also highlighted HIF-PHDi superiority over conventional ESAs in treating renal anemia [27,28], but there is no evidence of these studies in HF. The role of desidustat in the treatment of anemia in HF remains unexplored. Therefore, this study was designed to address the knowledge gap and evaluate the effects of HIF-PHDi and SGLT2i in the treatment of anemia in CRS.

METHODS

Study oversight

This pilot, prospective, randomized, controlled three-arm study was performed over 6 months in the Cardiology Unit of a tertiary care hospital. The Institutional Human Ethical Committee approved the study's ethical clearance (Ref no: 8522/IEC/2023). The study followed the guidelines proposed in the Declaration of Helsinki. This study was registered with the Clinical Trial Registry of India (CTRI) https://ctri.nic.in (Ref no: CTRI/2024/01/06208). The study followed the CONSORT guidelines.

Inclusion and exclusion criteria

The study enrolled adult male and female patients between 20 and 80 years of age who were diagnosed with T2DM with HbA1c above 48 mmoL/moL. HF of either reduced type (ejection fraction [EF] ≤40%) or preserved type (EF ≥50%) along with renal dysfunction defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 and serum creatinine above 1.5 mg/dL without any recent hospital admissions. Anemia, as defined by the World Health Organization criteria, was a prerequisite, with evidence of iron deficiency with serum ferritin levels between 100 and 299 ng/mL, transferrin concentrations ranging from 200 to 400 mg/dL, and transferrin saturation (TSAT) below 20% [29].

Exclusion criteria were patients with a medical history of severe anemia treated with ESAs, blood transfusion, or therapy with SGLT2i within 1 month before trial commencement. Additional criteria included the presence of comorbidities such as patients with mildly reduced EF type (HFmrEF) (EF-40–50%), dialysis-linked renal dysfunction, hemolytic anemia, thalassemia, or idiopathic thrombocytopenic purpura. Participants were excluded if they had gastrointestinal malabsorption disorders, pre-existing urinary tract infections that would be potentially worsened by SGLT2i, women who were pregnant or lactating, or patients who had undergone major surgery or trauma in the preceding 3–4 months.

Randomization

A total of 105 participants were randomized into three different groups using block randomization in a 1:1:1 ratio, with the sequence generated by the Random Allocation software online tool. The allocation process was handled by a third person who was not involved in the study. Each allocation was sealed in a sequentially numbered, opaque envelope to maintain allocation concealment. Based on the sequence, participants were assigned equally into three groups: Group A (n=35), Group B (n=35), and Group C (n=35). Group A (Control arm) received the standard treatment regimen that included oral hypoglycemic agents such as biguanides or sulfonylureas for T2DM, along with other supportive therapies such as ferrous ascorbate 100 mg/OD, diuretics, angiotensin receptor blockers, beta-blockers, angiotensin-converting enzyme inhibitors, and positive inotropic agents for CRS. Group B (comparator arm) received the same standard treatment along with dapagliflozin 10 mg orally once a day. Group C (intervention arm) received the standard treatment plus desidustat 50 mg taken orally once daily.

Procedure of the study

Initially, 112 CRS patients with anemia were assessed for trial eligibility. Seven participants had been excluded, and 105 patients fulfilled the study's precise criteria and were randomized into three groups of 35 patients in each cohort. Before enrollment, a clear explanation was given about the study procedure, and then, a signed informed consent document was collected from each patient. After inclusion, the baseline parameters were collected. Follow-up assessments were conducted at 12 and 24 weeks, respectively. At the 12-week follow-up, one patient from group A (n=34), two from group B (n=33), and three from group C (n=32) were lost to follow-up. The consort flow chart of the research study is illustrated in Fig. 1.

At each visit, a structured questionnaire was utilized to gather all the demographic details from the patients. Blood pressure (BP) was recorded by a digital BP monitor (Omron HEM 7120). Glycemic parameters, such as postprandial plasma glucose (PPG), HbA1c (glycated Hb), fasting plasma glucose (FPG), hematologic parameters including mean corpuscular volume (MCV), Hb, mean corpuscular Hb concentration (MCHC), packed cell volume (PCV), mean corpuscular Hb (MCH), ferritin, transferrin, serum iron, and TSAT, were measured at each follow-up.

QoL was also measured for all the treatment arms at baseline and the end of 24 weeks of treatment using the KDQOL questionnaire.

Biochemistry

Blood sample of 5 mL was collected in a vacutainer for hematological and iron profile analysis. Complete blood picture was performed using the Sysmex XN-1000 hematology analyzer. Serum iron concentration was measured using a spectrophotometric method. Ferritin and transferrin levels were quantified using an immunoassay analyzer. TSAT was calculated using the Omni Calculator through (TSAT [%] = [Serum Iron/Transferrin] ×70.9).

For glycemic assessments, a 2 mL blood sample was drawn after an overnight fast of 8 h, followed by centrifugation at 3,000–4,000 rpm for 10 min. FPG was estimated using the enzymatic hexokinase method and HbA1c analysis, which was conducted using high-performance liquid chromatography. Another 2 mL blood sample was collected 2 h after food intake for PPG measurement using an enzymatic process.

Statistics

Previous studies have shown the efficacy of desidustat in managing renal anemia. There is no clinical study evaluating the effects of desidustat in CRS. Due to these constraints, we were unable to determine the sample size from earlier research, and so, we conducted a pilot study, ensuring a 95% confidence level was used with a power of 80% (1-β) and frequency of type I error of 0.05. The analyzed parameters were expressed as mean±standard deviation. Statistical interpretation was done by GraphPad Prism software (V8, San Diego, CA) and Statistical Package for the Social Sciences (SPSS) (V24, SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the Chi-square test. Repeated measures analysis of variance (ANOVA) with correction applied for multiple comparisons was used to assess differences in mean changes within treatment groups, while ANOVA was used to compare parameters for between-group analysis. The level of significance was concluded if the p-value was <0.05. QoL parameters were analyzed using a t-test for different time points.

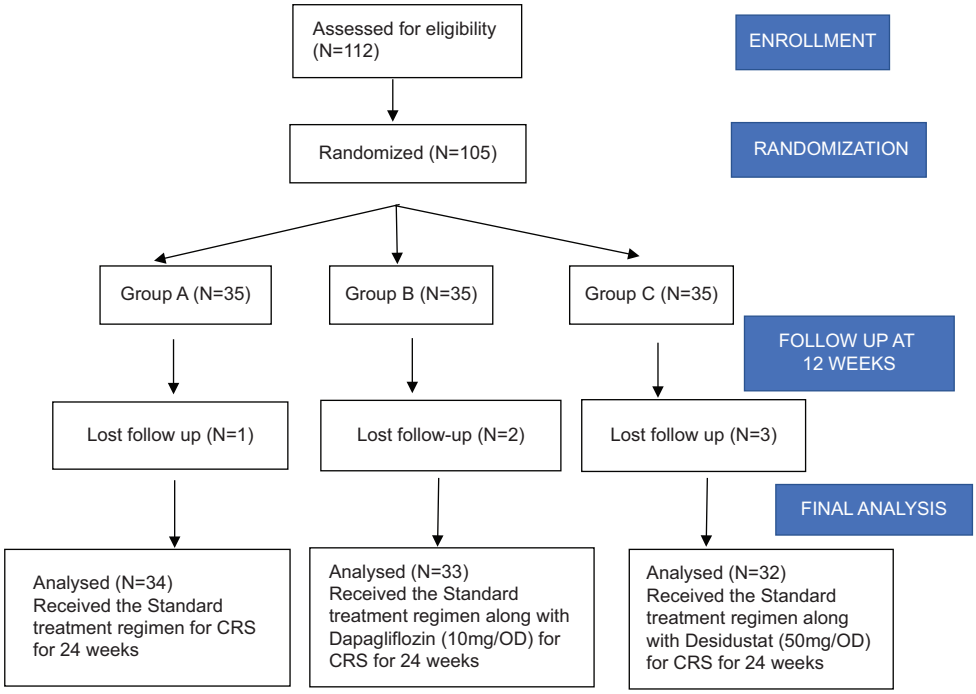

Fig. 1: Consort flow chart of the study

Outcomes

The primary outcomes were the changes in hematologic parameters (Hb, MCV, MCH, MCHC, and PCV), iron indices (serum iron, ferritin, transferrin, and TSAT), and glycemic parameters (FPG, PPG, and HbA1c) measured at each follow-up visit.

The secondary outcomes were improvement and enhancement in QoL assessed using the KDQOL 36 questionnaire. The scoring of each component is based on responses given on a Likert scale, where items are coded. The physical and mental component is based on responses that assess physical functioning, emotional status, and general health, where higher scores indicate better physical and mental health. The burden of kidney disease component relates to the impact of kidney disease, where higher scores mean a lower burden. The symptoms of kidney disease subscale evaluate the frequency of renal symptoms, with higher scores representing less severe symptoms. The effects of kidney disease subscale show much the disease interferes with daily life, where higher values indicate a better QoL.

Assessment of safety profile

Patients were asked to report any unintended drug effects faced during the treatment period, and during each visit, a direct patient interaction was initiated to enquire, especially about any untoward events faced during treatment.

RESULTS

Sociodemographic attributes of the patients

Most participants in all the treatment groups were aged between 41 and 60 years, with no significant difference in age distribution (p=0.89). The proportion of men to women was similar across groups (p=0.8). Co-morbid medical conditions such as hypertension, dyslipidemia, and coronary artery disease were observed, and no significant variation was noted (p=0.6). In terms of HF, the majority of patients were classified under NYHA Class II and III, which was statistically similar across the groups (p=0.9) (Table 1).

Baseline characteristics of the patients

The baseline characteristics of the patients were evaluated, revealing no significant differences between the treatment groups (Table 2).

Table 1: Sociodemographics of the patients in the study

Parameters	Group A (n=34)	Group B (n=33)	Group C (n=32)	p-value
Age-wise distribution				
20–40	2 (5.9)	4 (12.1)	3 (9.4)	0.89
41–60	24 (70.6)	20 (60.6)	23 (71.9)	
61–80	8 (23.5)	9 (27.3)	8 (25)	
Gender				
Male	18 (52.9)	19 (57.6)	19 (59.4)	0.8
Female	16 (47.1)	14 (42.4)	15 (46.9)	
Medical history				
Hypertension	07 (20.6)	10 (30.3)	09 (28.1)	0.6
Dyslipidemia	08 (23.5)	13 (39.4)	12 (37.5)	
Coronary artery disease	05 (14.7)	02 (6.1)	04 (12.5)	
Others	03 (8.8)	03 (9.1)	02 (6.2)	
NYHA class				
Class I	01 (2.9)	02 (6.1)	01 (3.1)	0.9
Class II	16 (47.1)	15 (45.5)	17 (53.1)	
Class III	17 (50)	16 (48.5)	15 (46.9)	
Class IV	0	0	0	

The parameters were expressed as n (%). p<0.05* was considered to reflect statistical significance

Data analysis

Changes in the parameters within the study groups

The mean changes in hematologic, iron, and glycemic parameters within the treatment group A were demonstrated (Table 3).

The mean changes in hematologic, iron, and glycemic parameters within the treatment group B were demonstrated (Table 4).

The mean changes in hematologic, iron, and glycemic parameters within the treatment group C were demonstrated (Table 5).

Between-group analysis

The mean changes in Hb (Fig. 2), hematology indices, iron, and glycemic parameters between the treatment groups were demonstrated (Table 6).

Table 2: Comparison of baseline clinical parameters among the study population

Parameters	Group A (n=34)	Group B (n=33)	Group C (n=32)	p-value
BP				
Systolic blood pressure (mmHg)	132.2±12.3	130.4±17.5	131.4±16.1	0.42
Diastolic blood pressure (mmHg)	84.5±6.3	84.2±5.9	84.2±6.2	0.06
Ejection fraction (%)	42.3±2.3	42.6±2.5	41.3±3.0	0.08
eGFR (mL/min/1.73 m^2)	48±1.2	49±1.6	47±1.9	0.06
Serum creatinine (mg/dL)	1.9±0.25	1.84±0.33	1.87±0.28	0.07
Blood glucose parameters				
FPG (mg/dL)	244.4±24.1	230.6±23.3	231.6±32.6	0.09
PPG (mg/dL)	300±33.2	304±23.4	304±25.3	0.79
HbA1c (mmoL/moL)	71.8±13.2	69.5±12.2	70.5±12.5	0.46
Hematology profile				
Hb (g/dL)	10.6±1.1	10.2±1.2	10.2±1.7	0.1
MCV (fL)	77.1±4.3	76.1±2.3	77.2±2.3	0.7
MCH (pg)	21.6±5.1	21.3±4.1	22.9±4.3	0.22
MCHC (g/dL)	28±1.7	30.1±1.2	29±1.2	0.06
PCV (%)	31.9±2.2	31.3±2.9	31.4±3.4	0.08
Transferrin (mg/dL)	297.4±10.8	300.3±15.9	301.2±14.4	0.09
Serum ferritin (ng/mL)	118.6±19.2	116.9±16.2	116.3±16.3	0.43
Serum iron (mcg/dL)	85.7±6.8	84.2±4.8	83.9±4.8	0.07
TSAT (%)	19.2±2.3	19.8±3.2	18.9±3.2	0.74

The represented values were expressed as mean±SD changes. The p-values were calculated based on ANOVA. BP: Blood pressure, eGFR: Estimated glomerular filtration rate, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular Hb concentration, MCH: Mean corpuscular Hb, PCV: Packed cell volume, TSAT: Transferrin saturation, SD: Standard deviation, ANOVA: Analysis of variance

Table 3: Changes in the parameters within the study "group A"

Parameter	Baseline visit	12 weeks	24 weeks	p-value
Hematological parameters				
Hb (g/dL)	10.6±1.1	10.1±0.6	10±0.7	0.06
MCV (fl)	77.1±4.3	79.8±3.44	75.9±3.1	0.17
MCH (pg)	21.6±5.1	21.2±3.97	23.9±2.8	0.52
MCHC (g/dL)	28±1.7	27±1.49	28.5±1.65	0.06
PCV (%)	31.9±2.2	30±3.24	31.9±2.9	0.09
Transferrin (mg/dL)	297.4±10.8	299±6.8	308.2±9.8	0.08
Serum ferritin (ng/mL)	118.6±19.2	122.4±12.9	120±13.3	0.24
Serum iron (mcg/dL)	85.7±6.8	83±5.1	84.8±7.8	0.11
TSAT (%)	19.2±2.3	20.1±2.3	20.9±2.1	0.35
Glycemic parameters				
FPG (mg/dL)	244.4±24.1	222.1±23.5	204.4±22.3	0.01*
PPG (mg/dL)	300±33.2	290±32.1	283.3±22.9	0.52
HbA1c (mmol/mol)	71.8±13.2	69.2±20.6	67.8±13.1	0.54

The represented values were expressed as mean±SD changes. The p-values were calculated based on repeated measures ANOVA. Hb: Hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular Hb concentration, MCH: Mean corpuscular Hb, PCV: Packed cell volume, TSAT: Transferrin saturation, SD: Standard deviation, ANOVA: Analysis of variance, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin. *$p < 0.05$ were considered statistically significant

Table 4: Changes in hematologic parameters within the study "group B"

Parameter	Baseline visit	12 weeks	24 weeks	p-value
Hematological parameters				
Hb (g/dL)	10.2±1.2	10.4±0.3	10.7±0.2	0.04*
MCV (fL)	76.1±2.3	77.8±3.32	78.9±3.2	0.03*
MCH (pg)	21.3±4.1	21.8±3.6	22.9±2.1	0.46
MCHC (g/dL)	30.1±1.2	33.2±1.4	35±1.75	0.01*
PCV (%)	31.3±2.9	30.6±2.4	33.9±2.3	0.03*
Transferrin (mg/dL)	300.3±15.9	293±5.4	306.4±9.2	0.08
Serum ferritin (ng/mL)	116.9±16.2	121.5±12.9	111.4±16.3	0.09
Serum iron (mcg/dL)	84.2±4.8	84±5.1	82.3±7.8	0.10
TSAT (%)	19.8±3.2	21.4±1.9	21.9±2.5	0.07
Glycemic parameters				
FPG (mg/dL)	230.6±23.3	202.1±11.3	188.7±13.5	0.001**
PPG (mg/dL)	304±23.4	287.3±21.7	267.3±12.4	0.002*
HbA1c (mmoL/moL)	69.5±12.2	60.3±23.3	58.2±30.2	0.001**

The represented values were expressed as mean±SD changes. The p-values were calculated based on repeated measures ANOVA. Hb: Hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular Hb concentration, MCH: Mean corpuscular Hb, PCV: Packed cell volume, TSAT: Transferrin saturation, SD: Standard deviation, ANOVA: Analysis of variance, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin. *$p < 0.05$; **$p < 0.01$ were considered statistically significant

Table 5: Changes in hematologic parameters within the study "group C"

Parameter	Baseline visit	12 weeks	24 weeks	p-value
Hematological parameters				
Hb (g/dL)	10.2±1.7	10.9±1.9	11.8±1.7	0.001**
MCV (fL)	77.2±2.3	78.6±2.1	80.2±2	0.02*
MCH (pg)	22.9±4.3	23.9±3.5	25.1±3.2	0.02*
MCHC (g/dL)	29±1.2	30.2±1.1	32±2.2	0.03*
PCV (%)	31.4±3.4	32.3±2.4	34.3±2.4	0.04*
Transferrin (mg/dL)	301.2±14.4	310±11.2	321±12.4	0.001**
Serum ferritin (ng/mL)	116.3±16.3	110.3±11.4	102.3±12.4	0.07
Serum iron (mcg/dL)	83.9±4.8	84.4±4.2	86.9±3.7	0.04*
TSAT (%)	18.9±3.2	18.5±2.4	17.1±2.9	0.03*
Glycemic parameters				
FPG (mg/dL)	231.6±32.6	226.6±16.2	201.6±18.9	0.01*
PPG (mg/dL)	304±25.3	299±33.5	287.3±33.2	0.06
HbA1c (mmoL/moL)	70.5±12.5	67.4±18.9	66.4±20.4	0.05

#The represented values were expressed as mean±SD changes. The p-values were calculated based on repeated measures ANOVA. Hb: Hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular Hb concentration, MCH: Mean corpuscular Hb, PCV: Packed cell volume, TSAT: Transferrin saturation, SD: Standard deviation, ANOVA: Analysis of variance, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin. *p < 0.05; **p < 0.01 were considered statistically significant

Table 6: Changes in hematologic parameters between groups A, B, and C

Hematology profile at 12 weeks					Hematology profile at 24 weeks			
Analytical parameters	**Group A**	**Group B**	**Group C**	**p-value**	**Group A**	**Group B**	**Group C**	**p-value**
Hb (g/dL)	10.1±0.6	10.4±0.3	10.9±1.9	0.01*	10±0.7	10.7±0.2	11.8±1.7	0.001**
MCV (fL)	79.8±3.44	77.8±3.32	78.6±2.1	0.02*	75.9±3.1	78.9±3.2	80.2±2	0.01*
MCH (pg)	21.2±3.97	21.8±3.6	23.9±3.5	0.06	23.9±2.8	22.9±2.1	25.1±3.2	0.01*
MCHC (g/dL)	27±1.49	33.2±1.4	30.2±1.1	0.05	28.5±1.65	35±1.75	32±2.2	0.02*
PCV (%)	30±3.24	30.6±2.4	32.3±2.4	0.06	31.9±2.9	33.9±2.3	34.3±2.4	0.02*
Transferrin (mg/dL)	299±6.8	293±5.4	310±11.2	0.03*	308.2±9.8	306.4±9.2	321±12.4	0.01*
Serum ferritin (ng/mL)	122.4±12.9	121.5±12.9	110.3±11.4	0.03*	120±13.3	111.4±16.3	102.3±12.4	0.01*
Serum iron (mcg/dL)	83±5.1	84±5.1	84.4±4.2	0.02*	84.8±7.8	82.3±7.8	86.9±3.7	0.03*
TSAT (%)	20.1±2.3	21.4±1.9	18.5±2.4	0.05	20.9±2.1	21.9±2.5	17.1±2.9	0.01*
Glycemic profile at 12 weeks					**Glycemic profile at 24 weeks**			
FPG (mg/dL)	222.1±23.5	202.1±11.3	226.6±16.2	0.04*	204.4±22.3	188.7±13.5	201.6±18.9	0.01*
PPG (mg/dL)	290±32.1	287.3±21.7	299±33.5	0.03*	283.3±22.9	267.3±12.4	287.3±33.2	0.01*
HbA1c (mmoL/moL)	69.2±20.6	60.3±23.3	67.4±18.9	0.04*	67.8±13.1	58.2±30.2	66.4±20.4	0.04*

#The represented values were expressed as mean±SD changes. The p-values were calculated based on ANOVA. Hb: Hemoglobin, MCV: Mean corpuscular volume, MCHC: Mean corpuscular Hb concentration, MCH: Mean corpuscular Hb, PCV: Packed cell volume, TSAT: Transferrin saturation, SD: Standard deviation, ANOVA: Analysis of variance, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, HbA1c: Hemoglobin. *p < 0.05; **p < 0.01 were considered statistically significant

Adverse effects noted in the study groups

The adverse effects noted in the study were mild, and there were no dropouts in the study because of adverse clinical effects. All the patients experiencing adverse events were closely monitored, and appropriate medical support was provided. The higher incidence of UTIs observed in the dapagliflozin group may be attributed to glycosuria, which provides a favorable environment for bacterial growth in the urinary tract, which was corrected with appropriate antibiotic therapy as per the physician (Table 7).

The QoL was determined using different domains (Table 8).

Table 7: Comparison of adverse effects noted in the study groups

Adverse event	Group A (n=34) (%)	Group B (n=33) (%)	Group C (n=32) (%)
Palpitations	5 (14.7)	1 (3.0)	1 (3.1)
Edema	5 (14.7)	4 (12.1)	4 (12.5)
Constipation	4 (11.8)	3 (9.1)	2 (6.2)
Nausea and vomiting	4 (11.8)	3 (9.1)	3 (9.4)
Abdominal discomfort	3 (8.8)	2 (6.1)	2 (6.2)
Pyrexia	2 (5.9)	3 (9.1)	3 (9.4)
Headache	1 (2.9)	1 (3.0)	2 (6.2)
Urinary tract infection	1 (2.9)	6 (18.2)	2 (6.2)

DISCUSSION

CRS represents a strong intersection of cardiovascular and renal dysfunctions, often aggravated by anemia, particularly in patients with comorbid T2DM. Anemia in CRS is multifactorial, commonly arising from impaired EPO production and resistance, chronic inflammation, and altered iron metabolism. Current treatment approaches, such as iron and EPO supplementation, can promptly increase Hb concentrations, yet raising the concern for iron overload and CV toxicity [14,18]. Therefore, the current study was designed to explore the novel and patient-centric therapeutic approaches in the management of CRS, addressing the adverse effects associated with conventional treatment.

In group C, desidustat significantly improved hematological and iron parameters, including a 1.6 g/dL rise in Hb after 24 weeks. In addition, serum iron levels rose by 3 mcg/dL, presenting a 3.6% improvement. Transferrin levels increased by 19.8 mg/dL, reflecting a 6.5% enhancement in iron transport. Ferritin levels decreased by 12%, and TSAT dropped by 9.5%, indicating a greater mobilization and utilization of stored iron, as shown in Table 5. These findings align with the research by Agrawal *et al*. This suggests that HIF-PHD inhibition may serve as a promising alternative in CRS by enhancing endogenous EPO production and improving iron metabolism without the risks associated with iron supplements or ESA use.

In Group B, dapagliflozin showed moderate improvements in hematology profile with a rise of 0.5 g/dL in Hb after 24 weeks; however, the iron parameters remained non-significant as represented in Table 4. A rise in Hb was due to possible mechanisms such as hemoconcentration due to volume reduction, improved iron mobilization, and hepcidin reduction, supported by studies conducted by Docherty *et al*. and Ghanim *et al.* [23,26,30]. Standard treatment group A did not show any progress in the hematology or iron parameters after 24 weeks, as shown in Table 3.

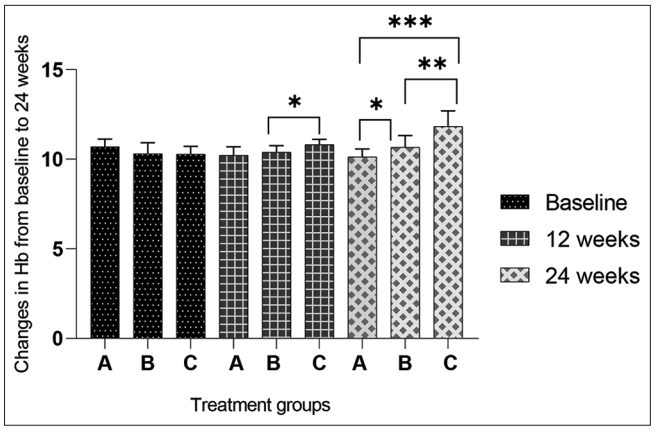

Fig. 2: Comparison of hemoglobin between the groups at various time points

Moreover, dapagliflozin demonstrated superior glycemic control due to glycosuria that lowers plasma glucose levels and HbA1c in T2DM patients according to Henry *et al*. [31]. Aligning with these findings, the current study observed a significant improvement in glycemic parameters such as FPG (p=0.001), PPG (p=0.002), and HbA1c (p=0.001) noted by the 24-week follow-up in group B compared to other groups, as shown in Table 4.

In contrast, standard treatment in T2DM and group C had a significant improvement in FPG (p=0.01) and no significant change in PPG and HbA1c, as shown in Tables 3 and 5.

According to Hoshino *et al*., both low Hb (<10 g/dL) and inactivity were independently linked to increased chances of CKD worsening and risk of death [32]. QoL was assessed between the groups. There was an improvement in QoL in the intervention and comparator arms. The QoL

Table 8: Determination of QOL (KDQOL) questionnaire

Parameters	Group A			Group B			Group C		
	Baseline	24 weeks	p-value	Baseline	24 weeks	p-value	Baseline	24 weeks	p-value
SF-12 physical and mental function	42±3.86	38.3±4.3	0.2	40.01±2.04	43.3±2.36	0.09	41.7±3.8	46.1±2.8	0.06
Burden of kidney disease	18±3.1	12.3±2.3	0.001*	19±2.2	13.7±2.2	0.04*	17±2.2	10.4±1.8	0.03*
Symptoms	43.52±1.9	41.7±2.6	0.08	42±2.56	33.2±2.17	0.002*	41.86±4.5	28.5±4.87	0.001**
Effects of kidney disease on daily life	21.3±4.2	18.3±3.8	0.01*	21.9±2.3	19±2.1	0.001*	22.3±5.3	17.2±3.4	0.001**

The represented values were expressed as mean±S.D changes. The p-values were calculated based on ANOVA. SD: Standard deviation, ANOVA: Analysis of variance. '*p < 0.05; **p < 0.01 were considered statistically significant

S. no	Reviewer's query	Response to the query
1.	A major and highly concerning issue is present in Table 5 and subsequently in Table 6. The hemoglobin (Hb) value for Group C at 24 weeks is reported as 11.8±10.7 g/dL. The standard deviation (10.7) is larger than the mean (11.8), which is biologically and statistically implausible for this parameter. It suggests either a severe outlier, a data entry error, or a calculation error. This invalidates the primary conclusion regarding the superiority of desidustat for improving Hb. The authors must urgently re-check, verify, and correct this data point and all subsequent analyses and conclusions that depend on it, including the p values in Tables 5 and 6, and Figure 2. The manuscript cannot be evaluated fairly until this critical error is resolved.	Typo error. It was 11.8±1.7 but was mistakenly typed as 11.8±10.7. This was corrected in the manuscript.
2.	The management of iron deficiency is a cornerstone of anemia treatment. The inclusion criteria required evidence of iron deficiency, yet the manuscript does not specify whether patients received concomitant iron supplementation during the trial. This is a major confounding factor. If iron was given, the protocol must be described in the Methodology. If it was not given, this represents a significant deviation from standard of care and must be explicitly stated and justified, as it could lead to an underestimation of the treatment effects. Clearly state in the Methodology whether iron supplementation was administered to all participants as part of the "standard treatment" or if it was prohibited, as this is essential for interpreting the results.	The standard treatment also included ferrous ascorbate supplementation (100 mg/OD). This was corrected accordingly in the methodology part of the manuscript.
3.	The safety profile is mentioned, but the reporting is insufficient. The term "burning micturition" is non-specific; it should be clarified if these were confirmed urinary tract infections or genitourinary symptoms. A more rigorous analysis should be performed and reported to properly compare adverse event rates between groups. Reclassify adverse events using standard medical terminology and perform and report statistical comparisons of key adverse events between the three groups.	This term "burning micturition" has been reclassified as urinary tract infection (UTI). All these patients with UTI received appropriate antibiotic therapy as per the physician's guidance until the complete resolution of symptoms. All the patients experiencing adverse events were closely monitored, and appropriate medical support was provided whenever required. To ensure clarity, the adverse events were tabulated and expressed as n (%) in each group.

parameters were physical and mental functioning, burden of kidney disease, symptom experience, daily life interference with disease, and overall QoL, based on responses from the KDQOL-36 questionnaire. The scores aligned with the findings evaluated by Zimbudzi *et al*. in patients with co-morbid CKD [33] and Yang *et al*., where roxadustat significantly improved the QoL in uremic patients as shown by higher SF-36 scores across physical, emotional, and social domains compared to EPO [34].

Limitations of the study

Our study has certain limitations. Patients classified under NYHA class IV and dialysis-dependent kidney failure, and HFmrEF were excluded; hence, the drug effect in this population needs further investigation. Moreover, the majority of the trial participants were between the ages of 41 and 60 and predominantly exhibited the "warm-wet" phenotype. Older patients, particularly those over 75 years, with the "cold-dry" phenotype as described by Sonaglioni *et al.* [35], were not included, which should be prioritized in future studies. A relatively small sample size in our pilot study limits the statistical power for subgroup analysis. Multicenter and larger studies are required for additional analysis. In the study, QoL was evaluated just with the KDQOL questionnaire. Future assessments should include more validated questionnaires to address both cardiovascular and renal perspectives, such as the Minnesota Living with HF Questionnaire or the SF-36, to offer a clear perspective. Although randomization was performed, potential confounding factors such as gender, differences in concomitant medications, glycemic control, age, comorbidities, dietary habits, and treatment adherence cannot be fully controlled and might have influenced the outcomes.

CONCLUSION

The findings of this study contribute to the growing evidence supporting the combination of desidustat with standard treatment for CRS, resulting in a substantial rise in hematological indices, along with improved QoL. Although dapagliflozin showed a mild improvement in anemia status, the effects were minimal. Despite these outcomes, larger multicenter studies are still required to validate our research findings.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest in the present study.

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APPROPRIATE USE OF AI TOOLS

AI-based tools (Grammarly/QuillBot) were used only for assistance in writing/summarizing or refining the manuscript.

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