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General Medicine

SGLT2 INHIBITOR THERAPY IS ASSOCIATED WITH ENHANCED ERYTHROPOIESIS AND ADAPTIVE IRON REDISTRIBUTION IN CONGESTIVE HEART FAILURE: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background Congestive heart failure (CHF) is frequently complicated by anaemia and disordered iron metabolism, both of which contribute to impaired functional capacity and adverse clinical outcomes. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have emerged as foundational therapy for heart failure, conferring substantial reductions in hospitalization and mortality independent of diabetic status. Beyond their cardiometabolic effects, these agents consistently increase haemoglobin and haematocrit, suggesting modulation of erythropoiesis and iron homeostasis. However, real-world data delineating the pattern of changes in red blood cell indices and iron parameters among CHF patients receiving SGLT2 inhibitors remain limited. **Methods** In this prospective observational study conducted at GMC Srinagar, 157 adults with clinically diagnosed CHF receiving SGLT2 inhibitor therapy were evaluated over an 18-month period. Clinico-demographic characteristics were recorded, and serial measurements of haemoglobin and iron indices—including serum ferritin, serum iron, transferrin saturation, transferrin concentration, and total iron-binding capacity (TIBC)—were obtained at baseline and following therapy. Paired statistical analyses were performed to assess longitudinal changes. **Results** The cohort had a mean age of 61 ± 12.2 years and was predominantly male (73.2%), with hypertension and diabetes as the most common comorbidities. SGLT2 inhibitor therapy was associated with a significant rise in haemoglobin levels (10.98 ± 1.91 g/dL to 11.69 ±1.63 g/dL; $p < 0.001$), indicating enhanced erythropoiesis. Concurrently, serum ferritin and serum iron levels declined significantly, whereas transferrin concentration and TIBC increased significantly. Transferrin saturation showed a nonsignificant downward trend.This constellation of changes is consistent with mobilization and utilization of iron stores rather than depletion, suggesting improved iron availability for erythropoiesis. **Conclusion** In patients with congestive heart failure, SGLT2 inhibitor therapy is associated with a distinct hematologic profile characterized by increased haemoglobin and adaptive alterations in iron metabolism. The observed reduction in ferritin and serum iron, coupled with increased transferrin and TIBC, likely reflects enhanced erythropoietic activity and iron redistribution rather than worsening iron deficiency. Recognition of this pattern is clinically important to prevent misinterpretation of iron studies and unnecessary supplementation. These findings provide real-world evidence supporting a mechanistic link between SGLT2 inhibition, erythropoiesis, and iron handling in heart failure.

KEYWORDS : Heart failure; SGLT2 inhibitors; erythropoiesis; iron metabolism; anaemia; ferritin; transferrin.

INTRODUCTION

Congestive heart failure (CHF) represents a major public health challenge worldwide, with increasing prevalence driven by population aging, improved survival following myocardial infarction, and the rising burden of diabetes mellitus, hypertension and chronic kidney disease. Anaemia and iron deficiency are among the most prevalent comorbidities in patients with chronic heart failure. In the recent past, sodium-glucose cotransporter, 2 (SGLT2) inhibitors have become the mainstay of heart failure treatment. One of the most consistent findings across clinical trials of SGLT2 inhibitors is a sustained increase in haemoglobin concentration, haematocrit, and red blood cell mass. This effect was initially attributed to haemoconcentration secondary to osmotic diuresis and plasma volume contraction. However, subsequent analyses demonstrated that the rise in red blood cell indices is progressive and sustained, suggesting stimulation of true erythropoiesis rather than simple haemo-concentration. Therefore, the present study is focused on evaluating changes in red blood cell indices as well as iron profile parameters after starting therapy with SGLT2 inhibitors.

AIMS AND OBJECTIVES

1. The aim of my study is to estimate the prevalence of changes in RBC indices and iron profile in congestive heart failure patients on SGLT inhibitors therapy.
2. The objective is to study the clinical, etiological, demographic profile, the admitting reason, changes in RBC indices, iron profile and the final outcome of such patients.

MATERIALS AND METHODS

Prospective observational study conducted over a period of 4 months with 75 patients of either sex, aged > 18 years presenting to the medical department and associated Hospital of GMC Srinagar, J&K with congestive heart failure were enrolled in the study after proper informed consent.

Inclusion Criteria: Age >18 years, diagnosed CHF, consented. **Exclusion Criteria:** Non-cardiac iron deficiency, ESRD, malignancy.

Baseline and follow-up hemogram and iron profile assessed. Statistical analysis performed using SPSS v29. Paired t-test applied; $p<0.05$ significant.

RESULTS

Table 1- compares baseline haemoglobin levels with post–SGLT inhibitor haemoglobin levels. The mean haemoglobin level increased significantly from 10.98 ± 1.91 g/dL at baseline to 11.69 ± 1.63 g/dL. This change was statistically significant ($t = -8.412$, $p < 0.001$), with a 95% confidence interval for the mean difference ranging from −0.878 to −0.544.

Table 1: Comparison of Baseline and Post–SGLT Inhibitor Haemoglobin Levels in the Study Group (n=75)

Hb (Mean ± SD)	Post SGLT Hb (Mean ± SD)	Std. Error of Diff. of Mean	95% Confidence Interval of the Difference		t-value	P-value
			Lower	Upper		
10.98±1.91	11.69±1.63	0.0846	-0.878	-0.544	-8.412	<0.001

Table 2- compares baseline serum ferritin levels with post–SGLT inhibitor ferritin levels. The mean serum ferritin level decreased significantly from 262.65 ± 322.54 ng/mL to 217.21 ± 228.09 ng/mL. This reduction was statistically significant ($t = 5.049$, $p < 0.001$), with a 95% confidence interval of 27.664 to 63.212.

Table 2: Comparison of Baseline and Post–SGLT Inhibitor Serum Ferritin Levels in the Study Group (n=75)

Ferritin (Mean ± SD)	Post SGLT Ferritin (Mean ± SD)	Std. Error of Diff. of Mean	95% Confidence Interval of the Difference		t-value	P-value
			Lower	Upper		
262.65±322.54	217.21±228.09	8.998	27.664	63.212	5.049	<0.001

Table 3- compares baseline serum iron levels with post–SGLT inhibitor serum iron levels. The mean serum iron level decreased significantly from 61.87 ± 35.25 µg/dL at baseline to 55.25 ± 23.59 µg/dL after therapy. This change was statistically significant ($t = 4.102$, $p < 0.001$), with a 95% confidence interval ranging from 3.431 to 9.804.

Table 3: Comparison of Baseline and Post–SGLT Inhibitor Serum Iron Levels in the Study Group (n=75)

Iron (Mean ± SD)	Post SGLT Ferritin (Mean ± SD)	Std. Error of Diff. of Mean	95% Confidence Interval of the Difference		t-value	P-value
			Lower	Upper		
61.87±35.25	55.25±23.59	1.613	3.431	9.804	4.102	<0.001

Table 4- compares baseline transferrin saturation with post–SGLT inhibitor transferrin saturation. Although there was a reduction in mean transferrin saturation from 37.08 ± 40.18% to 32.5 ± 23.96%, this difference was not statistically significant (t = 1.2904, p = 0.199).

Table 4: Comparison of Baseline and Post–SGLT Inhibitor Transferrin Saturation (%) in the study group (n=75)

Trans Satu (Mean ± SD)	Post SGLT Trans saturation (Mean ± SD)	Std. Error of Diff. of Mean	95% Confidence Interval of the Difference		t-value	P-value
			Lower	Upper		
37.08±40.18	32.5±23.96	3.503	-2.399	11.441	1.2904	0.199

Table 5- compares baseline transferrin levels with post–SGLT inhibitor transferrin levels. The mean transferrin level increased significantly from 259.57 ± 81.47 mg/dL to 296.47 ± 89.65 mg/dL after therapy. This increase was statistically significant (t = −10.2262, p < 0.001), with a 95% confidence interval ranging from −44.017 to −29.765.

Table 5: Comparison of Baseline and Post–SGLT Inhibitor Transferrin (TRF) Levels in the Study Group (n=75)

TRF (Mean ± SD)	Post SGLT TRF (Mean ± SD)	Std. Error of Diff. of Mean	95% Confidence Interval of the Difference		t-value	P-value
			Lower	Upper		
259.57±81.47	296.47±89.65	-36.891	-44.017	-29.765	-10.2262	<0.001

Table 6- compares baseline TIBC with post–SGLT inhibitor TIBC. The mean TIBC increased significantly from 220.95 ± 120.24 µg/dL to 249.19 ± 140.11 µg/dL following therapy. This increase was statistically significant (t = −2.545, p = 0.012), with a 95% confidence interval of −50.147 to −6.323.

Table 6: Comparison of Baseline and Post–SGLT Inhibitor Total Iron Binding Capacity (TIBC) in the study group (n=75)

TIBC (Mean ± SD)	Post SGLT TIBC (Mean ± SD)	Std. Error of Diff. of Mean	95% Confidence Interval of the Difference		t-value	P-value
			Lower	Upper		
220.95±120.24	249.19±140.11	11.09315	-50.147	-6.323	-2.545	0.012

DISCUSSION

The study evaluated the changes in RBC indices and iron profile of CHF patients on SGLT inhibitor therapy. The findings demonstrate significant alterations in erythropoietic indices and iron biomarkers following SGLT2 inhibitor use. Mechanistically, SGLT2 inhibitors are believed to stimulate erythropoietin production by improving renal cortical oxygenation and reducing tubular workload. This hypothesis is supported by findings from **Sano et al. (2016)** and **Kato et al. (2019)**, who demonstrated increased erythropoietin levels shortly after initiation of SGLT2 inhibitors, followed by sustained increases in red blood cell mass. Reduction in ferritin likely reflects improved iron mobilization rather than true depletion. Findings align with mechanistic data supporting suppression of hepcidin and improved iron availability. Studies by **Bonnet et al. (2018)** and **Dekkers et al. (2018)** have shown that SGLT2 inhibition reduces inflammatory markers, which may contribute to lower ferritin concentrations. The increase in transferrin and TIBC observed in this study supports the hypothesis that SGLT2 inhibitors promote a physiological state favouring erythropoiesis through enhanced iron handling rather than iron accumulation. **Tziastoudi et al. (2023)** also highlighted that SGLT2 inhibitors consistently increase transferrin concentrations by reducing hepcidin levels, thereby improving iron mobilization and transport.The collective changes observed namely increased haemoglobin, reduced ferritin, increased transferrin and TIBC, and stable transferrin saturation suggest that SGLT2 inhibitors improve erythropoiesis by optimizing iron utilization. . Observational studies by **Inzucchi et al. (2018)** and **Neuen et al. (2019)** have shown that improvement in haemoglobin levels with SGLT2 inhibitors is associated with better cardiovascular and renal outcomes.

CONCLUSION

The present study demonstrates that SGLT2 inhibitor therapy is associated with a significant increase in haemoglobin levels in patients, suggesting improved erythropoiesis. Significant reductions in serum ferritin levels alongside increases in transferrin and total iron binding capacity indicate enhanced mobilization and utilization of stored iron rather than depletion of iron reserves. The absence of a significant change in transferrin saturation further supports the presence of functional iron redistribution. These findings highlight the modulatory effect of SGLT2 inhibitors on iron metabolism in addition to their glycaemic benefits. Overall, SGLT2 inhibitor therapy may offer added clinical advantage in patients with anaemia or functional iron deficiency.

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