

Cardiovascular, Renal, and Metabolic Effects of SGLT-2 Inhibitors in Type 2 Diabetes Mellitus: A Prospective Cohort Study

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Abstract

Background

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors provide cardiovascular and renal benefits in patients with type 2 diabetes mellitus (T2DM), but prospective real-world evidence regarding their effects on echocardiographic parameters, pulmonary hemodynamics, and inflammatory status remains limited. This study evaluated changes in metabolic, cardiorenal, and inflammatory parameters observed during SGLT-2 inhibitor therapy in patients with T2DM.

Methods

This prospective, uncontrolled single-center cohort study included 51 patients with T2DM who initiated empagliflozin (10 mg/day) or dapagliflozin (10 mg/day) and were followed for six months. Clinical, biochemical, renal, and echocardiographic parameters, including left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), and Doppler-derived indices, were assessed at baseline and at 6-month follow-up and compared using paired statistical tests.

Results

After six months, significant reductions were observed in body mass index, systolic blood pressure, heart rate, HbA1c, urinary albumin, urinary creatinine, albumin-to-creatinine ratio, inflammatory markers, and ferritin, along with improvement in lipid profile. LVEF remained stable and TAPSE was unchanged, whereas pulmonary and aortic velocity time integrals and mitral E-wave velocity increased significantly; PASP increased modestly but remained within the normal physiological range.

Conclusions

SGLT-2 inhibitor therapy was associated with favorable changes in metabolic control, renal biomarkers, lipid profile, and inflammatory status, without evidence of decline in left ventricular systolic function, and with favorable changes in selected echocardiographic parameters in patients with T2DM. Given the observational, uncontrolled design of this study, these findings should be regarded as hypothesis-generating rather than confirmatory; larger controlled studies are needed to confirm these associations and clarify the effects of SGLT-2 inhibitors on pulmonary hemodynamics.

Background

Type 2 diabetes mellitus (T2DM) affects more than 530 million adults worldwide and is associated with a broad spectrum of macrovascular and microvascular complications [1–3]. Diabetic nephropathy, a

major microvascular complication characterized by progressive impairment of renal function, contributes substantially to end-stage renal disease, morbidity, and mortality. Chronic glycemic variability and hypertension remain the most critical risk factors for its development and progression [2, 4, 5].

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have been shown to reduce HbA1c, systolic blood pressure, and body weight in individuals with T2DM. They also mitigate renal hyperfiltration and intraglomerular hypertension. Because reductions in HbA1c, systolic blood pressure, body mass index, and intraglomerular pressure are associated with antialbuminuric effects, SGLT-2 inhibitors are expected to lower the urinary albumin-to-creatinine ratio (UACR) [3]. Findings from major phase III randomized controlled trials, including EMPA-REG, CANVAS, DECLARE-TIMI, and DAPA-CKD, have demonstrated that long-term treatment with empagliflozin, canagliflozin, and dapagliflozin results in significant and sustained reductions in albuminuria [6–9].

Emerging evidence suggests that SGLT-2 inhibitors may exert favorable effects on resting heart rate and potentially reduce the incidence of atrial fibrillation (AF); however, conflicting data have also indicated a possible increase in arrhythmic events associated with these agents [10–13]. These inconsistencies highlight the need for further large-scale, well-designed randomized controlled trials to better elucidate the impact of SGLT-2 inhibitors on arrhythmogenesis and heart rate modulation.

Beyond cardiometabolic effects, SGLT-2 inhibitors have been investigated for their impact on pulmonary artery pressure, cardiac function, diabetic target-organ injury, and inflammatory biomarkers in recent studies [1, 14, 15].

Despite these advances, the potential influence of diabetes on the pulmonary vascular system remains insufficiently characterized. Pulmonary arterial hypertension (PAH), defined by persistent elevation of pulmonary arterial pressure and progressive pulmonary vascular remodeling, ultimately leads to right heart failure and increased mortality [16].

Gliflozins may also provide therapeutic benefits in conditions such as obesity, atherosclerosis, and non-alcoholic steatohepatitis through their anti-inflammatory properties [17–19].

Although inflammation initially serves as a protective response, chronic inflammation promotes tissue injury. In various experimental models, SGLT-2 inhibitors have been shown to attenuate inflammatory processes, improve cellular energy metabolism, and reduce oxidative stress [18, 20].

The hematologic effects of SGLT-2 inhibitors have been attributed to two primary mechanisms. One involves hemoconcentration secondary to their mild diuretic action. The other relates to increased erythropoietin (EPO) production mediated by hypoxia-inducible factor-2 α (HIF-2 α) activation under hypoxic conditions, along with hepcidin-regulated modulation of iron metabolism [4].

In this study, we sought to comprehensively evaluate the effects of SGLT-2 inhibitors on pulmonary artery pressure (PAP), left ventricular ejection fraction (LVEF), renal parameters (proteinuria), inflammatory

markers (C-reactive protein and erythrocyte sedimentation rate), lipid profile, and hematologic indices in patients with T2DM, and to characterize the associated patterns of target-organ involvement.

Materials and Methods

Study Design and Participants

This prospective cohort study was conducted at a tertiary care center. Patients with T2DM were consecutively enrolled between April and November 2024, and outcome assessments were completed by May 2025, six months after enrollment of the last participant.

A total of 51 patients aged between 18 and 80 years who newly initiated SGLT-2 inhibitor therapy (empagliflozin 10 mg/day or dapagliflozin 10 mg/day) were included in the study. Eligibility criteria included HbA1c $\geq$ 6.5%, fasting plasma glucose $\geq$ 126 mg/dL, or random plasma glucose $\geq$ 200 mg/dL on at least two occasions [24].

Each participant was followed for a fixed duration of 6 months after initiation of SGLT-2 inhibitor therapy. All included patients completed the 6-month follow-up period, and no patient was lost to follow-up.

Exclusion criteria included New York Heart Association (NYHA) class III–IV heart failure, baseline pulmonary artery systolic pressure (PASP) $>$ 30 mmHg, recent acute coronary syndrome or stroke, estimated glomerular filtration rate (eGFR) $<$ 30 mL/min/1.73 m², type 1 diabetes mellitus, significant hepatic impairment, pregnancy, and use of investigational drugs.

The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2024-05-03), and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Data Collection

Demographic data and medical histories of the patients included in the study were recorded. Transthoracic echocardiography was performed in the supine position by a single blinded cardiologist to minimize interobserver variability. Standard measurements included left ventricular ejection fraction (LVEF, Simpson biplane method), tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery pressures (systolic, mean, and diastolic; derived from the tricuspid regurgitation jet). Additional parameters, such as left ventricular end-diastolic pressure, were also evaluated when feasible.

Spot urine albumin-to-creatinine ratio (UACR), serum creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lipid profile (HDL, LDL, total cholesterol, triglycerides), complete blood count (Hb, Hct, WBC), and metabolic parameters (HbA1c) were assessed at baseline and 6 months after initiation of SGLT-2 inhibitor therapy. Three patients were excluded due to newly detected cardiac dysfunction during echocardiographic screening.

All transthoracic echocardiographic examinations were performed using the same imaging system at the cardiology outpatient clinic of the study center to ensure consistency. Laboratory analyses, including blood and urine tests, were conducted in the central laboratory of the study center using standardized automated analyzers.

The aforementioned parameters were statistically compared between baseline and 6-month follow-up values in patients who initiated SGLT-2 inhibitor therapy.

Statistical Analysis

Data were analyzed using SPSS version 18.0 (IBM Corp., Armonk, NY, USA). Normally distributed variables were expressed as mean $\pm$ standard deviation (SD), whereas non-normally distributed variables were presented as median [interquartile range, IQR]. For continuous variables, the paired Student's t-test or the Wilcoxon signed-rank test was applied as appropriate. Categorical variables were compared using the chi-square test. A two-sided p value < 0.05 was considered statistically significant.

Results

A total of 54 patients were screened for eligibility. Three patients were excluded after echocardiographic evaluation revealed previously unrecognized left ventricular dysfunction. Subsequent coronary angiography demonstrated significant coronary artery disease requiring percutaneous coronary intervention with stent implantation. To avoid potential confounding effects on study outcomes, these patients were excluded. Consequently, 51 patients were included in the final analysis (Fig. 1). The mean age was 53.5 ± 10.5 years, with 52.9% female and 47.1% male. Empagliflozin was prescribed in 37.3% of patients, while 62.7% received dapagliflozin. Comorbidities included hypertension (21.6%), hyperlipidemia (17.6%), and coronary artery disease (7.8%). Baseline patient characteristics are summarized in Table 1.

Table 1
Baseline
Patient
Characteristics

Category	Characteristic	Value
Demographics	Age (years)	53.5 ± 10.5 (32–77)
	Female, %	52.9
	Male, %	47.1
Medications	Empagliflozin, %	37.3
	Dapagliflozin, %	62.7
	Metformin use, %	39.2
	DPP-4 inhibitor use, %	19.6
	Sulfonylurea use, %	3.9
	Insulin use, %	0
Comorbidities	Hypertension, %	21.6
	Hyperlipidemia, %	17.6
	Coronary artery disease, %	7.8

DPP-4: dipeptidyl peptidase-4. Continuous variables presented as mean ± standard deviation; categorical variables presented as percentages.

Over the 6-month follow-up period, significant improvements were observed in clinical and cardiac parameters. Body mass index decreased from 32.0 ± 5.3 to 30.0 ± 4.7 kg/m² ($p < 0.001$). Systolic blood pressure showed a modest but statistically significant reduction (123.13 ± 11.31 mmHg vs. 119.51 ± 7.69 mmHg, $p = 0.03$), whereas diastolic blood pressure remained unchanged. Heart rate also declined significantly, from 78 ± 9 to 75 ± 7 beats/min ($p = 0.004$) (Fig. 2).

In echocardiographic assessments, right ventricular function measured by TAPSE did not change significantly. However, pulmonary artery systolic pressure increased slightly but significantly (19.88 ± 6.34 vs. 21.96 ± 5.98 mmHg, $p = 0.02$). Left ventricular ejection fraction remained stable, while posterior wall thickness increased (9.81 ± 1.75 vs. 10.19 ± 1.57 mm, $p = 0.005$). Hemodynamic indices, including pulmonary VTI ($p = 0.02$), E wave velocity ($p = 0.02$), and aortic VTI ($p = 0.007$), improved significantly.

With respect to urinary parameters, spot urine protein levels did not change significantly. In contrast, spot urine albumin ($p = 0.005$), creatinine ($p = 0.002$), and the albumin-to-creatinine ratio ($p = 0.001$) all decreased significantly after 6 months of treatment (Fig. 3). These findings are summarized in Table 2.

Table 2
Metabolic and
Hemodynamic
Changes from
Baseline to 6-
Month Follow-
up

Category	Parameter	Baseline	6-Month Follow-up	p-value
General parameters	BMI (kg/m ²)	32.03 ± 5.35	30.08 ± 4.76	< 0.001
	Systolic BP (mmHg)	123.13 ± 11.31	119.51 ± 7.69	0.03
	Diastolic BP (mmHg)	73.92 ± 8.51	73.21 ± 7.05	0.64
	Heart rate (beats/min)	78.04 ± 9.18	75.37 ± 7.62	0.004
Cardiac parameters	TAPSE (mm)	23.04 ± 4.27	22.02 ± 3.79	0.10
	PASP max (mmHg)	19.88 ± 6.34	21.96 ± 5.98	0.02
	EF (%)	61.27 ± 6.62	62.35 ± 3.51	0.14
	Posterior wall thickness (mm)	9.81 ± 1.75	10.19 ± 1.57	0.005
	Pulmonary VTI (cm)	20.67 ± 4.36	22.12 ± 4.07	0.02
	E wave (cm/s)	68.63 ± 20.23	73.91 ± 21.64	0.02
	Aortic VTI (cm)	24.68 ± 6.39	26.91 ± 5.21	0.007
Urinary parameters	Spot urine protein (mg/dL)	76.5 (43.2–125)	70 (37.9–125)	0.19
	Spot urine albumin (mg/L)	21 (11.8–47.5)	15 (10–30)	0.005
	Spot urine creatinine (mg/dL)	78.1 (50–100)	61.5 (41–74)	0.002
	Spot urine albumin/creatinine (mg/g)	34 (21–70.5)	24 (14–46)	0.001

BMI: body mass index; BP: blood pressure; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary artery systolic pressure; EF: ejection fraction; VTI: velocity time integral. Normally distributed continuous variables are presented as mean ± standard deviation; non-normally distributed variables are presented as median (interquartile range).

Similarly, significant changes were observed in hematological, lipid, and inflammatory parameters. White blood cell and neutrophil counts decreased significantly (both p = 0.001), while red blood cell count

increased modestly but significantly ($p = 0.02$). Favorable changes in the lipid profile were also noted, with a significant rise in HDL cholesterol ($p = 0.03$), a reduction in LDL cholesterol ($p = 0.02$), and a marked decrease in triglyceride levels ($p < 0.001$).

Regarding inflammatory markers, ferritin levels declined significantly ($p = 0.001$), along with HbA1c values ($p < 0.001$), ESR ($p = 0.02$), and CRP concentrations ($p = 0.007$). These results are summarized in Table 3.

Table 3
Hematological, Lipid, and Inflammatory Parameters from Baseline to 6-Month Follow-up

Parameter	Baseline	6-Month Follow-up	p-value
WBC ($10^3/\mu\text{L}$)	8.65 ± 2.89	7.49 ± 1.56	0.001
Neutrophils ($10^3/\mu\text{L}$)	4.97 ± 1.51	4.57 ± 1.36	0.001
RBC ($10^6/\mu\text{L}$)	4.79 ± 0.56	4.89 ± 0.51	0.02
HDL cholesterol (mg/dL)	44.38 ± 11.36	49.27 ± 18.33	0.03
LDL cholesterol (mg/dL)	117.41 ± 39.72	105.97 ± 33.89	0.02
Triglycerides (mg/dL)	206.84 ± 98.53	164.67 ± 71.81	< 0.001
Ferritin ($\mu\text{g/L}$)	68.86 ± 25.56	45.08 ± 22.13	0.001
HbA1c (%)	7.79 ± 1.32	6.85 ± 0.71	< 0.001
ESR (mm/h)	11.91 ± 6.68	8.21 ± 5.81	0.02
CRP (mg/L)	7.03 ± 4.21	4.25 ± 2.35	0.007

WBC: white blood cell; RBC: red blood cell; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: hemoglobin A1c; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein. All values are presented as mean $\pm$ standard deviation.

Discussion

In this prospective, uncontrolled cohort study of 51 patients with type 2 diabetes mellitus (T2DM), initiation of SGLT-2 inhibitor therapy was followed by significant favorable changes in metabolic, renal, inflammatory, and hematological parameters over a 6-month follow-up period, with no significant decline in left ventricular systolic function. To our knowledge, this is among the few prospective studies to simultaneously evaluate echocardiographic, renal, inflammatory, and hematological outcomes in a relatively treatment-naïve T2DM cohort, with no insulin use and minimal exposure to sulfonylureas or other potent glucose-lowering agents, thereby allowing a more direct, though still observational, assessment of changes occurring during SGLT-2 inhibitor therapy.

Renal parameters improved significantly, with reductions in spot urine albumin ($p = 0.005$) and albumin-to-creatinine ratio (ACR; $p = 0.001$). The magnitude of ACR reduction ($\sim 30\%$) is broadly consistent with findings from the CREDENCE and DAPA-CKD trials, despite those studies having enrolled populations with more advanced renal impairment [1]. Mechanistically, these effects are attributed to restoration of tubuloglomerular feedback and reduction of intraglomerular pressure mediated by decreased proximal tubular sodium–glucose reabsorption [21]. Notably, spot urine total protein did not change significantly, whereas albumin decreased. This dissociation is of interest: it suggests that the renoprotective effect of SGLT-2 inhibitors in our cohort was primarily reflected in reduced glomerular albumin permeability rather than a global reduction in proteinuria. One possible explanation is that, in a population with relatively preserved renal function and low baseline proteinuria, the sensitivity of total protein measurement may be insufficient to detect changes that are more readily captured by the albumin-specific assay.

Significant reductions in C-reactive protein (CRP; $p = 0.007$) and erythrocyte sedimentation rate (ESR; $p = 0.02$) were observed, supporting the anti-inflammatory properties of SGLT-2 inhibitors. Proposed mechanisms include attenuation of NLRP3 inflammasome activation, ketone body–mediated suppression of inflammatory signaling, and indirect anti-inflammatory effects secondary to weight loss and reduced adipose tissue inflammation [20]. Previous studies have similarly reported reductions in high-sensitivity CRP with SGLT-2 inhibitor therapy [22, 23]. However, other studies and meta-analyses have demonstrated variable or non-significant effects on inflammatory biomarkers, likely reflecting differences in study design, sample size, baseline inflammatory burden, and follow-up duration [24]. In contrast, the neutrophil-to-lymphocyte ratio (NLR) did not change significantly. Similar findings have been reported in studies evaluating inflammatory biomarkers during SGLT-2 inhibitor therapy, in which reductions in CRP and other inflammatory mediators were observed despite inconsistent changes in leukocyte-derived indices [24]. The discordance between NLR stability and CRP/ESR reduction may indicate that SGLT-2 inhibitors primarily modulate hepatic acute-phase responses and systemic inflammatory signaling rather than altering the balance of circulating leukocyte subpopulations. Whether NLR is an adequately sensitive marker for the type of anti-inflammatory effect exerted by SGLT-2 inhibitors remains uncertain and warrants further investigation [25].

Although hemoglobin and hematocrit did not change significantly, red blood cell count increased modestly ($p = 0.02$). This pattern may reflect early stimulation of erythropoiesis—likely mediated through hypoxia-inducible factor-2 α (HIF-2 α)–driven erythropoietin production—that has not yet translated into a measurable rise in hemoglobin concentration [26]. The concurrent decline in ferritin ($68.86 \rightarrow 45.08$ $\mu\text{g/L}$; $p = 0.001$) is consistent with increased iron utilization for new red blood cell synthesis, potentially through hepcidin suppression and enhanced iron mobilization from stores [4]. Taken together, these findings suggest that SGLT-2 inhibitors stimulate erythropoiesis with consequent depletion of iron stores, a mechanism that has been proposed to contribute to the cardioprotective effects of these agents through improved myocardial oxygen delivery [18].

The significant reductions in white blood cell and neutrophil counts (both $p = 0.001$) are less frequently reported and may reflect the anti-inflammatory milieu discussed above, or a direct effect on

myelopoiesis. This finding merits confirmation in larger studies.

Favorable changes in lipid parameters were observed, including increased HDL cholesterol ($p = 0.03$), decreased LDL cholesterol ($p = 0.02$), and a marked reduction in triglycerides ($p < 0.001$). The effects of SGLT-2 inhibitors on lipid metabolism remain heterogeneous across the literature; some studies have reported paradoxical increases in LDL cholesterol, possibly related to reduced LDL receptor-mediated clearance, while others have demonstrated improvements in triglycerides attributed to enhanced fatty acid oxidation and reduced hepatic lipogenesis [27]. The favorable lipid profile observed in our cohort may partly reflect the concomitant weight loss and improved insulin sensitivity.

Left ventricular ejection fraction remained stable, and right ventricular systolic function as assessed by TAPSE did not change significantly; these findings indicate that no significant decline in biventricular systolic function was detected over the follow-up period, though the absence of a control group and complementary diastolic indices (E/A ratio, tissue Doppler e' , E/e' , left atrial volume) limits our ability to conclude that function was actively preserved by SGLT-2 inhibitor therapy specifically. The significant increases in pulmonary velocity time integral (VTI), aortic VTI, and E wave velocity are compatible with enhanced forward flow, but on their own do not establish improved diastolic filling; this interpretation would require the complementary diastolic parameters noted above, and remains speculative in the absence of a comparator group, which may partly reflect reduced preload and afterload in the setting of volume contraction and blood pressure lowering.

The modest increase in posterior wall thickness ($9.81 \rightarrow 10.19$ mm; $p = 0.005$) was unexpected. While this could theoretically suggest concentric remodeling, the magnitude of change is small and may fall within intra- and interobserver measurement variability. It is also possible that hemoconcentration secondary to the diuretic effect altered acoustic tissue properties. This finding should be interpreted cautiously and confirmed in studies with more sensitive imaging modalities such as cardiac MRI.

Perhaps the most intriguing finding of this study is the modest but statistically significant increase in pulmonary artery systolic pressure. This contrasts with the EMBRACE-HF trial, in which empagliflozin reduced pulmonary artery systolic and mean pressure in heart failure patients with implanted hemodynamic monitors [15]. Similarly, in a meta-analysis of SGLT-2 inhibitor use in patients with left ventricular assist devices, no significant change in mean pulmonary artery pressure was observed [28], while small cohort studies have shown variable results [14]. Several hypotheses may explain this finding. First, SGLT-2 inhibitors cause hemoconcentration through natriuresis and osmotic diuresis, which increases hematocrit. Higher blood viscosity in the low-pressure pulmonary circuit could plausibly elevate PASP, even in the absence of true pulmonary vascular remodeling. Second, if left ventricular filling pressures decrease while systemic venous return is relatively maintained, the right heart may transiently face a proportionally increased load, manifesting as mildly elevated PASP. Third, SGLT-2 inhibitor-mediated stimulation of erythropoiesis could increase pulmonary vascular resistance through elevated red cell mass.

However, it is equally important to consider the possibility that this finding represents measurement artifact. Baseline PASP in our cohort was well within the normal range, and the absolute increase of approximately 2 mmHg is small relative to the inherent variability of echocardiographic PASP estimation, which depends on the quality and angle of the tricuspid regurgitation jet. The clinical significance of this change is therefore uncertain. Regardless of mechanism, this observation merits attention. Most existing studies of SGLT-2 inhibitors and pulmonary pressures were conducted in heart failure populations with elevated baseline pressures, where the therapeutic effect of volume unloading is expected to be more pronounced. Our finding raises the question of whether the hemodynamic response differs in normotensive pulmonary circulations and underscores the need for serial invasive hemodynamic assessments or cardiac MRI-based studies to clarify this issue.

In our study, transthoracic echocardiographic screening identified asymptomatic cardiac dysfunction in three patients, who subsequently underwent coronary angiography and percutaneous coronary intervention with stent placement. Although limited in number, this finding underscores the potential value of systematic cardiac evaluation in patients with diabetes who initiate SGLT-2 inhibitor therapy.

This study has several limitations that should be considered when interpreting these findings. It was a single-center study with a relatively small sample size, and no formal sample size or power calculation was performed prior to enrollment; several observed differences had p values in the 0.02–0.03 range and should therefore be interpreted with caution, as they may not withstand correction for multiple comparisons. No adjustment was made for multiple testing across the large number of metabolic, renal, echocardiographic, hematological, lipid, and inflammatory parameters assessed, and the study did not report effect sizes or 95% confidence intervals alongside p values, which limits the ability to judge the clinical magnitude and precision of the observed changes. Most critically, this was an uncontrolled, single-arm, before-after design without a concurrent comparator group; this restricts the generalizability of the findings, precludes causal inference, and limits the ability to establish causal relationships—observed changes may partly reflect natural disease progression, regression to the mean, concurrent lifestyle modifications, or other unmeasured factors rather than a specific effect of SGLT-2 inhibitor therapy. Longitudinal data were limited to two time points (baseline and 6 months); a repeated-measures or mixed-model approach using additional intermediate assessments, had they been available, would have allowed a more complete characterization of the trajectory of change over time. Empagliflozin and dapagliflozin users were analyzed as a single pooled group, and the analysis was not adjusted for concomitant medications, baseline HbA1c, obesity, hypertension, baseline renal function, diabetes duration, or other clinical covariates that could confound the observed associations. The exclusion of patients with advanced heart failure, markedly elevated pulmonary pressures, severe renal impairment, and recent cardiovascular events resulted in a relatively stable and selected cohort, which may limit generalizability to broader, less-selected populations of patients with T2DM. PASP was estimated echocardiographically rather than measured invasively, introducing measurement imprecision; the small absolute increase observed may lie within the range of measurement variability rather than reflecting a true hemodynamic change. Given these limitations, the findings of this study should be regarded as

exploratory and hypothesis-generating rather than confirmatory, and they should be interpreted as associations observed during SGLT-2 inhibitor therapy rather than as established treatment effects.

Despite these limitations, this prospective study has notable strengths. It provides real-world clinical data and includes a comprehensive assessment of metabolic, renal, inflammatory, and echocardiographic parameters. Consistency was ensured by having all echocardiographic examinations performed by a single operator. Additionally, the exclusion of insulin-treated patients and minimal use of sulfonylureas—agents with strong glucose-lowering effects—allowed for a more objective evaluation of the independent effects of SGLT-2 inhibitors. Furthermore, the exclusion of patients with advanced heart failure or markedly elevated pulmonary pressures enhanced the homogeneity of the study population.

In conclusion, in this exploratory, uncontrolled prospective cohort study, initiation of SGLT-2 inhibitor therapy was associated with favorable changes in metabolic, renal, inflammatory, and hematological parameters in patients with T2DM and minimal concomitant antidiabetic therapy. No significant decline in left ventricular systolic function was observed, and several hemodynamic indices changed favorably, although these observations cannot be attributed with certainty to SGLT-2 inhibitor therapy given the absence of a control group. The modest increase in PASP, though of uncertain clinical significance, warrants further investigation in studies with invasive hemodynamic monitoring or advanced imaging. Because of the uncontrolled, single-arm design, the absence of adjustment for multiple comparisons, and the lack of confounder adjustment, these findings should be regarded as hypothesis-generating rather than confirmatory. Controlled, adequately powered studies are needed to determine whether the associations observed here reflect true treatment effects of SGLT-2 inhibitors, and to further evaluate their pulmonary vascular effects (Graphical Abstract).

Abbreviations

T2DM

type 2 diabetes mellitus

SGLT-2

sodium-glucose cotransporter-2

LVEF

left ventricular ejection fraction

TAPSE

tricuspid annular plane systolic excursion

PASP

pulmonary artery systolic pressure

VTI

velocity time integral

UACR

urinary albumin-to-creatinine ratio

CRP

C-reactive protein
ESR
erythrocyte sedimentation rate
HDL
high-density lipoprotein
LDL
low-density lipoprotein
eGFR
estimated glomerular filtration rate
NYHA
New York Heart Association
HbA1c
hemoglobin A1c
WBC
white blood cell
RBC
red blood cell
BMI
body mass index
BP
blood pressure
SD
standard deviation
IQR
interquartile range
NLR
neutrophil-to-lymphocyte ratio
HIF-2 α
hypoxia-inducible factor-2 alpha.

Declarations

Ethics approval and consent to participate:

The present work was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2024-05-03). Written informed consent to participate was obtained from all participants.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author Contribution

O.K. and A.E.A. conceptualized and supervised the study. O.K. collected the data. O.K. drafted the manuscript. O.K. and A.E.A. performed patient evaluation and critically reviewed the manuscript for important intellectual content. C.G. and İ.Ş. contributed to manuscript writing and editing. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1. Patient Flow Diagram

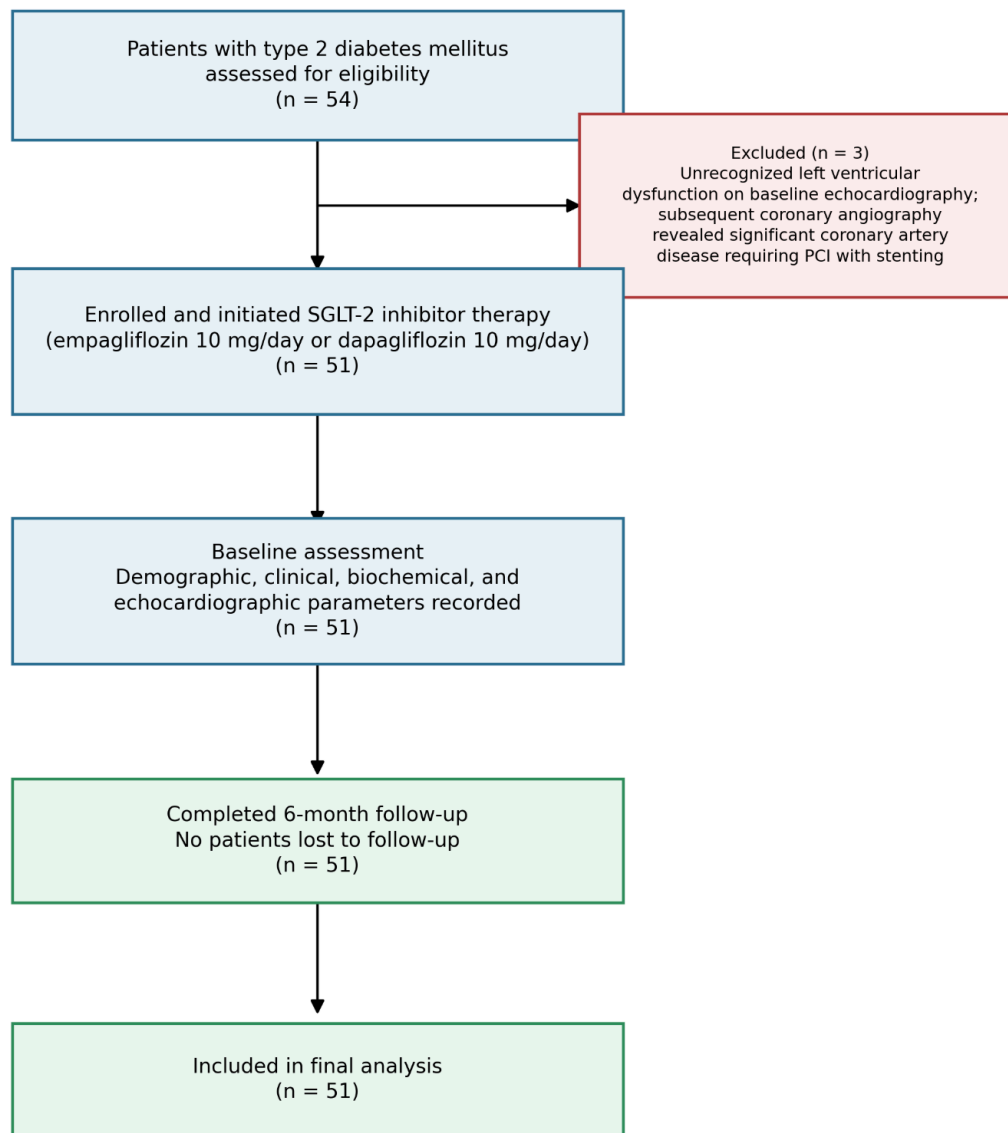


Figure 1. Patient flow diagram. Of 54 patients with type 2 diabetes mellitus screened for eligibility, 3 were excluded after baseline echocardiography revealed previously unrecognized left ventricular dysfunction, which on subsequent coronary angiography was attributed to significant coronary artery disease requiring percutaneous coronary intervention (PCI) with stenting. The remaining 51 patients were enrolled, completed the 6-month follow-up with no losses, and were included in the final analysis.

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Patient flow diagram. Of 54 patients with type 2 diabetes mellitus screened for eligibility, 3 were excluded after baseline echocardiography revealed previously unrecognized left ventricular dysfunction, which on subsequent coronary angiography was attributed to significant coronary artery disease requiring percutaneous coronary intervention (PCI) with stenting. The remaining 51 patients were enrolled, completed the 6-month follow-up with no losses, and were included in the final analysis.

Figure 2. Clinical and Metabolic Parameters at Baseline and 6-Month Follow-up

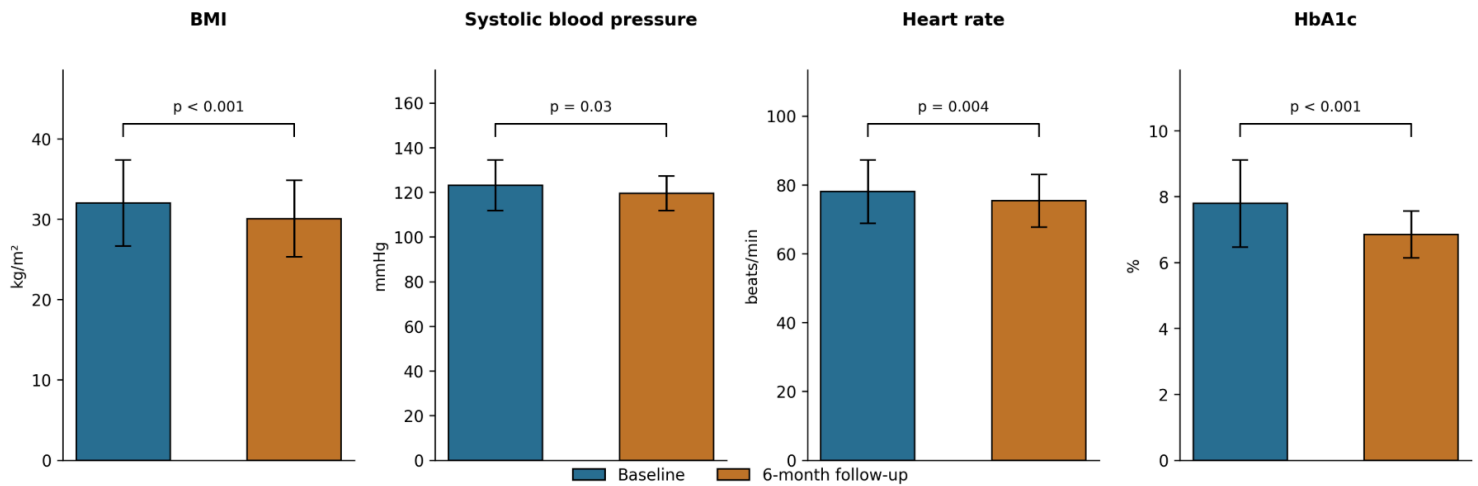


Figure 2. Clinical and metabolic parameters at baseline and 6-month follow-up. Bars represent mean values; error bars indicate standard deviation. BMI: body mass index.

Figure 2

Clinical and metabolic parameters at baseline and 6-month follow-up. Bars represent mean values; error bars indicate standard deviation. BMI: body mass index.

Figure 3. Renal parameters at baseline and 6-month follow-up

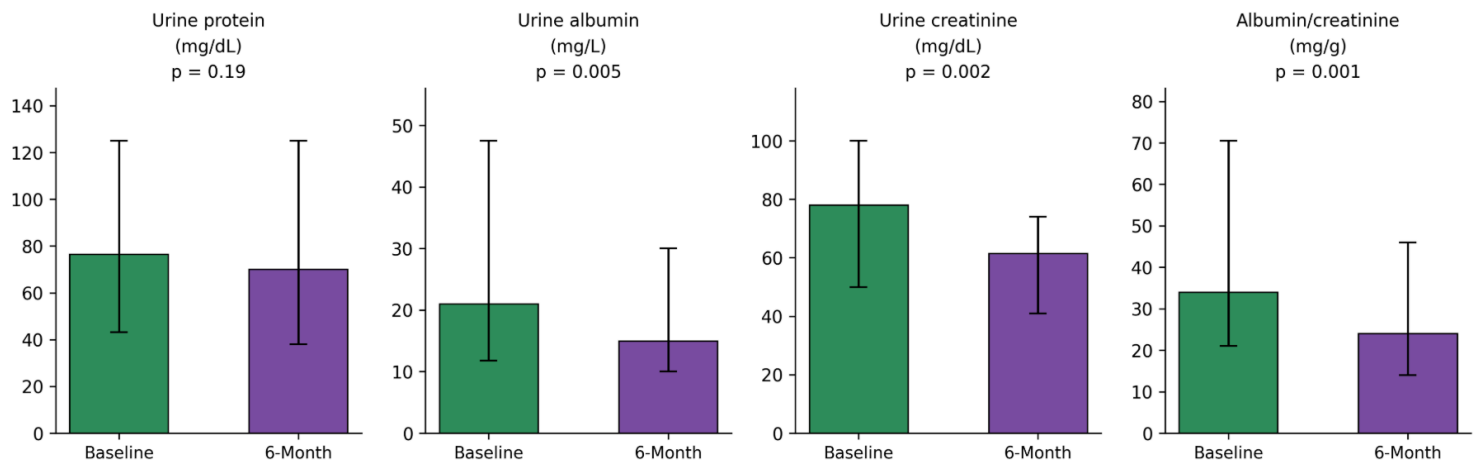


Figure 3. Renal parameters at baseline and 6-month follow-up. Bars represent median values; error bars indicate interquartile range.

Figure 3

Renal parameters at baseline and 6-month follow-up. Bars represent median values; error bars indicate interquartile range.

Supplementary Files

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