Patient Preference and Adherence

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Glucosuria as a Biomarker of Adherence to Sodium-Glucose Co-Transporter Protein Type 2 Inhibitors

José Escribano-Serrano[1,2], Enrique Jiménez-Varo[1,3], María Escribano-Cobalea[1,4], Cristina Casto-Jarillo[1,3], Ana López-Ceres[1,3], Emilio Campos-Dávila[1,5], Antonio Hormigo-Pozo[1,6], Josep Franch-Nadal[7,8], Alfredo Michán-Doña[1]

[1]Grupo CARTEIA, Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Cádiz, España; [2]Unidad de Investigación e Innovación, AGS Campo de Gibraltar Este, Cádiz, España; [3]UGC Laboratorio Análisis Clínicos, Hospital de La Línea de la Concepción, Cádiz, España; [4]UGC Obstetricia y Ginecología, Hospital Universitario Punta de Europa de Algeciras, Cádiz, España; [5]UGC Farmacia, Hospital Universitario de La Línea de la Concepción, Cádiz, España; [6]UGC San Andrés-Torcal, AGS Málaga Guadalhorce, Málaga, España; [7]Centre de Salut Raval Sud, Institut Català de la Salut, Barcelona, España; [8]Grup DAP_CAT, Fundació IDIAP Jordi Gol, Barcelona, España

Correspondence: José Escribano-Serrano, Grupo CARTEIA, Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Cádiz, España, Email jescribano19@gmail.com; investigaunidad@gmail.com

Purpose: Adherence to treatment with sodium-glucose co-transporter protein type 2 inhibitors (SGLT2i) is essential for the successful treatment of type 2 diabetes. As SGLT2i induce glucosuria, the main study objective was to assess the potential relationship between glucosuria level and adherence to SGLT2i.

Patients and Methods: The study used electronic health records of patients aged ≥45 years old that had urinalysis data. Glucosuria was classified as absent/normal (0 mg/dL), intermediate (1–1000 mg/dL), and evident (>1000 mg/dL). Renal function, expressed by estimated glomerular filtration rate and stage of chronic kidney disease (CKD), was also assessed. Adherence to SGLT2i was measured with the proportion of days covered in 6 months.

Results: Only 9.2% of samples showed evident glucosuria; of these, 87.5% belonged to patients treated with SGLT2i. Among these patients, glucosuria was mostly evident (78.9%). Absent glucosuria was more common in patients with CKD and in advanced KDIGO stages; therefore, in these patients glucosuria as adherence marker should be interpreted with caution.In patients treated with SGLT2i, absent glucosuria was detected in 4.5% of samples from patients with good adherence, 18.5% of samples from patients with intermediate adherence, and up to 38.5% of samples from patients with poor adherence ($p < 0.01$). Absent glucosuria was also associated with higher blood uric acid level and lower hemoglobin and hematocrit. Absent glucosuria was more common in women and older patients.

Conclusion: Absent glucosuria could be an easy biomarker of poor adherence in patients treated with SGLT2i in clinical practice.

Plain Language Summary: Adherence to treatment is the degree to which a patient takes their medication as prescribed. As poor adherence is associated with reduced efficacy of treatment,early detection of low adherence is important, especially in chronic diseases such as diabetes. However, measuring adherence in clinical practice can be difficult. The objective of the study was to assess glucose (sugar) in urine as a marker of poor adherence in patients with diabetes treated with SGLT2i, a class of antidiabetic drugs characterized by increasing glucose in urine. Examples of SGLT2i are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. Using electronic health records with urine analysis data, the researchers classified glucose in urine as absent (0 mg/dL), intermediate (1-1000 mg/dL), and evident (higher than 1000 mg/dL). Glucose was evident in 78.9% of urine samples, as expected because of the effect of SGLT2i of increasing glucose in urine. However, glucose was absent in a significant 9% of urine samples. Regarding the relationship between glucose in urine and adherence, glucose was absent in almost 40% of samples from patients with poor adherence. Furthermore, absent glucose in urine was more common in advanced stages of chronic kidney disease and therefore its value as an adherence marker should be interpreted with caution in these cases. Absent glucose in urine was also related to higher blood uric acid level and lower hemoglobin and hematocrit. The researchers concluded that glucose in urine could be an easy way to evaluate adherence in patients treated with SGLT2i in clinical practice.

https://doi.org/10.2147/PPA.S576212
Received: 23 October 2025
Accepted: 5 February 2026
Published: 19 February 2026

Keywords: diabetes mellitus, type 2 diabetes, glucosuria, adherence, sodium-glucose co-transporter protein type 2 inhibitors

Introduction

Diabetes mellitus (DM) is a global health challenge and its prevalence is steadily increasing worldwide.[1] More than 90% of cases are type 2 diabetes (T2D), which affected around 530 million people in 2024 and it is estimated that over 767 million people will have T2D in 2050.[1] Prevalence increases with age and is highest (24.8% in 2024) among men and women aged between 75 and 79 years.[1] T2D can affect virtually any organ and system of the human body, but cardiovascular complications represent the main cause of death.[2]

Drug therapy of T2D was strengthened with the release of the sodium-glucose co-transporter protein type 2 inhibitors (SGLT2i). These agents selectively and reversibly inhibit the SGLT2 receptor, blocking the reabsorption of glucose in the renal proximal tubule and thus enhancing glucose excretion by the kidneys and reducing glycemia.[3] To date, the European Medicines Agency has authorized four SGLT2i (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin), alone or combined with the classic antidiabetic metformin, for the treatment of T2D.[4] However, SGLT2i agents not only reduce glycemia, but they also have cardiorenal protection effects, which appear to be larger than could be expected according to their hypoglycemic effect.[5] They could even be the first endothelial-protector for diabetic nephropathy,[6] as they inhibit SGLT2 not only in the renal proximal tubule, but also in stressed endothelial cells.[6] Furthermore, cardiorenal effects of SGLT2i agents occur in patients without DM.[5] Thus, dapagliflozin and empagliflozin are also indicated for the treatment of symptomatic chronic heart failure and chronic kidney disease (CKD) in adults. Canagliflozin is also indicated for the treatment of CKD but only in adults with T2D. Besides, SGLT2i agents have holistic effects such as an increase of hematocrit or a reduction of uric acid levels and they could have other effects that are still undergoing investigation.[7]

Clinical outcomes in T2D patients treated with SGLT2i are affected by therapeutic adherence. In a real-world study in 2252 patients with T2D treated with SGLT2i, adherent patients showed a lower incidence of the primary outcome, a composite of insulin initiation, hospitalization for micro- and macrovascular complications and all-cause mortality after the first year of drug treatment (HR: 0.69, 95% CI 0.55–0.87).[8] However, according to the results of a systematic review and meta-analysis of 22 real-world studies, adherence to SGLT2i is poor.[9] Therefore, it is important to assess adherence to SGLT2i. Measures of adherence are either direct, such as examination of blood, urine or other body fluids for the presence of the drug or a metabolite, or indirect. Indirect methods can be subjective, such as self-reports from patients, or objective, such as pill counts, prescription reordering, pharmacy refill records, and electronic medicine monitoring. There is no agreement on the preferred method to assess adherence to medication in patients with DM,[10] and it is recommended to choose a method according to each study and the available resources.[10]

SGLT2i increase the renal excretion of glucose.[11] They are the only class of antidiabetic drugs with this inherent and distinctive characteristic, which can allow direct measurement of the drug effect. In exploratory studies, 86% of patients treated with SGLT2i had evident glucosuria, defined as a urine glucose level ≥1000 mg/dL.[12] However, this high percentage implied that 14% of patients treated with SGLT2i did not have evident glucosuria, possibly due to a lack of adherence to SGLT2i. Measuring glucosuria is not a validated method to assess adherence to antidiabetic treatment. However, due to the effect of SGLT2i on glucosuria, the main objective of the current study was to assess glucosuria as a marker of adherence to SGLT2i. Secondary objectives included differentiating evident glucosuria in patients with and without DM; describing the relationship between glucosuria levels and impaired renal function, and assessing the relationship between glucosuria and other parameters of SGLT2i effectiveness such as blood uric acid level or hematocrit.

Materials and Methods

Study Design and Population

This was an observational retrospective study of electronic health records (EHR) from patients treated between July 2022 and June 2023 in the Campo de Gibraltar Este Healthcare Area (Cádiz, Spain), which is part of the Andalusian Public Healthcare System (SSPA).

Inclusion criteria were individuals aged ≥45 years and with available glucosuria and fasting plasma glucose (FPG) data obtained at the same timepoint as part of routine analysis. Exclusion criteria comprised individuals aged younger than 45 years, familial glucosuria in patients without DM or SGLT2i treatment, patients that initiated SGLT2i treatment in 2023, and patients with missing data.

The study was composed of a first phase, which included all patients that met the inclusion criteria (phase 1), and a second phase, conducted in patients treated with SGLT2i (phase 2).

Phase 1: Glucosuria in the General Population

Samples were stratified into three groups. The first group was composed of samples from patients without DM. Another group comprised samples from patients with DM but without SGLT2i treatment during the period 2022–2023. These patients were treated with other code A10 drugs (insulin and analogues, blood glucose lowering drugs excluding insulin, and other drugs used in DM) according to the Anatomical Therapeutic Chemical (ATC) Classification System.[13] The third group included patients with DM that were treated with SGLT2i during the period 2022–2023. It is important to note that, in the 2022–2023 period, SGLT2i were approved for the treatment of T2D as well as for heart failure with reduced ejection fraction (HFrEF). In this first phase, glucosuria and FPG results were recorded for the whole study population, whether with or without DM. The aim was to try to show that evident glucosuria had a weak relationship with DM under treatment, but a very strong relationship with glycosuric drugs (SGLT2i).

Phase 2: Glucosuria in the SGLT2i Population

In a second phase, the analysis was focused on glucosuria measurements performed in patients treated with SGLT2i in 2022–2023. The aim in this phase was to assess the intensity of glucosuria and its relationship with other parameters of adherence, such as the proportion of days covered (PDC).[14]

Patients' data were obtained from SIDICAM (corresponding to the initials, in Spanish, of State of Diabetes in the Campo de Gibraltar Area),[15] a database that includes pseudonymized data from laboratory determinations (blood biochemistry and hematology tests and urine test) and use of drugs (therapeutic groups ATC A10 [drugs used in DM], C08 [calcium channel blockers], and C09 [agents acting on the renin-angiotensin system]) in the population of the cited healthcare area during the period 2019–2023.

Study Variables

Glucosuria was analyzed with a standard semi quantitative method using reflectance photometry (UNAMAX®, A. Menarini Diagnostics, Badalona, Spain). According to the results, glucosuria was categorized as absent or normal (0 mg/dL), intermediate (1–1000 mg/dL) and evident (>1000 mg/dL). The main variable of the study was evident glucosuria.

DM was identified by means of a validated algorithm that considers an individual to be positive if treated with any ATC A10 drug (except for guar gum) financed by the SSPA during the study period.[16] Therefore, all patients with samples included in the second phase had DM. However, this algorithm cannot distinguish between type 1 diabetes and T2D. For this reason, only individuals aged ≥45 years were included in an attempt to focus on individuals with T2D. Furthermore, study calculations were performed separately by biological sex and age group (45–59 years, 60–74 years and ≥75 years).

Relationships between glucosuria and several factors were assessed in patients treated with SGLT2i. These factors were hyperglycemia, defined as a FPG ≥200 mg/dL, which is the traditionally accepted threshold for glucosuria in DM patients (≥180 mg/dL for people without DM); CKD, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2

and/or albuminuria >30 mg/g for more than 3 months;[17] stage of CKD, from G1 (normal, ≥90 mL/min/1.73 m^2) to G5 (kidney failure, <15 mL/min/1.73 m^2).[17] Both CKD and its stages were assessed according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline.[17] In addition, the relationship between glucosuria and drug class (only SGLT2i, fixed-dose combination of SGLT2i plus an oral antidiabetic, and SGLT2i plus A10 drugs) was assessed.

Adherence was measured between January and June 2023 by the PDC method.[14] Patients were stratified into three groups by PDC during 6 months: <40% (group 1, poor adherence), 40–79% (group 2, intermediate adherence), and ≥80% (group 3, good adherence). Subsequently, the correlation between glucosuria and adherence was analyzed, as well as the potential impact of factors such as age and biological sex.

Finally, correlations of glucosuria and other described effects of SGLT2i drugs were also analyzed. To that end, the study used blood count, including hemoglobin and hematocrit, and renal function (eGFR, albuminuria and blood uric acid level) data for each patient's EHR.

Statistical Analysis

A data matrix was created and processed statistically using the MedCalc® Statistical Software version 22.021 statistical package (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024). Statistical significance was established at 95% ($\alpha = 0.05$).

Data obtained for qualitative variables were represented descriptively, using frequency and percentage, while quantitative variables were expressed by mean and standard deviation or by median and 95% confidence interval (95% CI).

Ethical Statement

The study was approved by the provincial Clinical Research Ethics Committee of Cadiz, Spain (SICEIA-2024-002554 code). Informed consent was not required because of the retrospective design, the use of administrative registries previously pseudonymized and the high number of studied determinations. Furthermore, the study was conducted in accordance with the Declaration of Helsinki.

Results

Phase I Results

Glucosuria by Groups of Patients

A total of 28742 glucosuria determinations, corresponding to 21377 individuals aged ≥45 years, were performed from January to June 2023. Patients were mainly women (n = 12,128; 57%) and showed differences in age by groups. Patients with DM, including those treated with SGLT2i, were older than patients without DM (Table 1).

Glucosuria was absent in 25138 samples (87.5%), intermediate in 964 (3.4%), and evident in 2640 (9.2%) ($p<0.0001$). By age groups, absent glucosuria was more common in samples from patients aged between 45 and 59 years (91.8%) than in samples from patients aged between 60 and 74 years (84.8%) or older than 75 years (84.5%) ($p<0.01$). By biological sex, absent glucosuria was more frequent in samples from women (90.4%) than from men (83.7%) ($p<0.01$).

Regarding samples with evident glucosuria, 2308 (87.5%) belonged to patients with DM treated with SGLT2i ($p < 0.01$), while only 244 (10.2%) corresponded to patients with DM treated with antidiabetic drugs other than SGLT2i and 88 (2.3%) were from patients without DM.

In the 2925 samples from 1868 patients treated with SGLT2i, 78.9% of glucosuria was evident and 12.1% was intermediate, with 264 samples (9%) negative for glucosuria (Figure 1). These samples were analyzed to assess potential correlations of glucosuria with other variables.

Factors Potentially Related to Glucosuria

To assess a potential relationship between hyperglycemia and glucosuria, samples from patients with DM and with or without SGLT2i treatment were stratified in two groups according to FPG lower than <200 mg/dL (2574 samples; 87.8%)

Table 1 Study Groups According to the Presence of Diabetes Mellitus and Treatment with SGLT2i

Variable			No DM or SGLT2i Treatment	With DM, Without SGLT2i	With DM and SGLT2i	Total
Total samples, n			21 076	4741	2925	28 742
Total patients, n			16 213	3296	1868	21 377
Gender: woman, n (%)		Samples	12 399 (61)	2463 (52)	1603 (55)	16 465 (59)
		Patients	9605 (59)	1684 (51)	839 (45)	12 128 (57)
Age: years, median (IQR)			61 (53–72)	71 (61–79)	69 (61–77)	64 (54–74)
Age groups, n (%)	**45-59 years**	Samples	9465 (46)	998 (21)	656 (22)	11 119 (40)
		Patients	7797 (48)	722 (22)	440 (24)	8959 (42)
	60-74 years	Samples	7148 (33.9)	1925 (40.6)	1351 (46.2)	10 424 (36)
		Patients	5465 (34)	1374 (42)	878 (47)	7717 (36)
	≥75 years	Samples	4078 (20)	1826 (39)	928 (32)	6832 (24)
		Patients	2951 (18)	1200 (36)	550 (29)	4701 (20)

Abbreviations: DM, diabetes mellitus; IQR, interquartile range; SGLT2i, sodium-glucose transporter protein 2 inhibitors.

and ≥200 mg/dL (351 samples; 12.2%). The presence of evident glucosuria was similar in both groups, around 80% (Figure 2A). Moreover, when samples from patients with SGLT2i were classified according to FPG <130 mg/dL, 130–180 mg/dL and >180 mg/dL, evident glucosuria was consistently frequent in the three groups (Figure 2B).

However, in samples from patients with DM treated with A10 drugs other than SGLT2i, the proportion of patients with FPG ≥200 mg/dL was lower. Evident glucosuria in patients with DM and treatment with any A10 other than SGLT2i was related to high plasma glucose, measured as FPG (Figures 2A and B). On the contrary, this relationship did not exist for SGLT2i-treated patients, for which evident glucosuria is associated with SGLT2i intake.

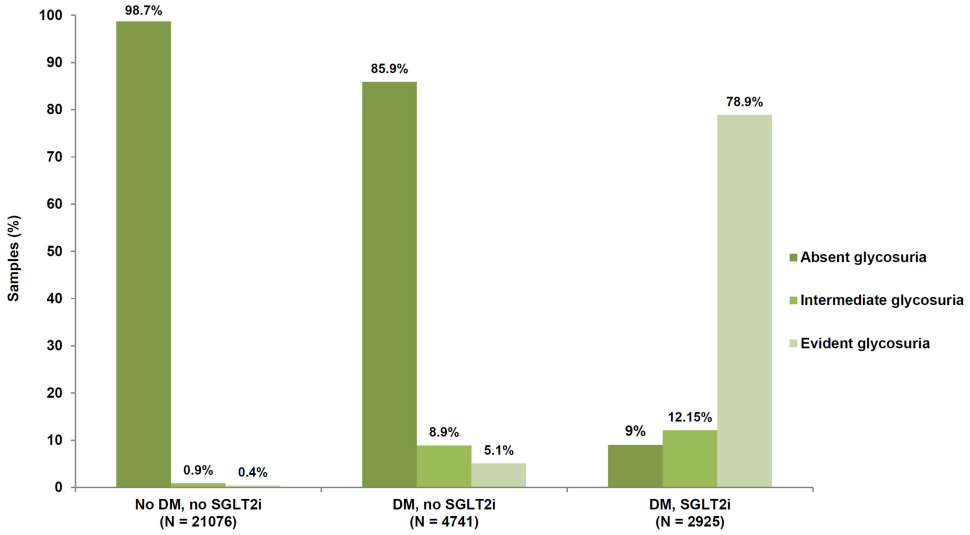

Figure 1 Glucosuria according to the presence of diabetes mellitus and treatment with SGLT2i. Evident glucosuria was more frequent in samples from patients with DM treated with SGLT2i.
Note: Absent glucosuria, 0 mg/dL; intermediate glucosuria, 1–1000 mg/dL; evident glucosuria, >1000 mg/dL.
Abbreviations: DM, diabetes mellitus. SGLT2i, sodium-glucose co-transporter protein 2 inhibitors.

https://doi.org/10.2147/PPA.S576212

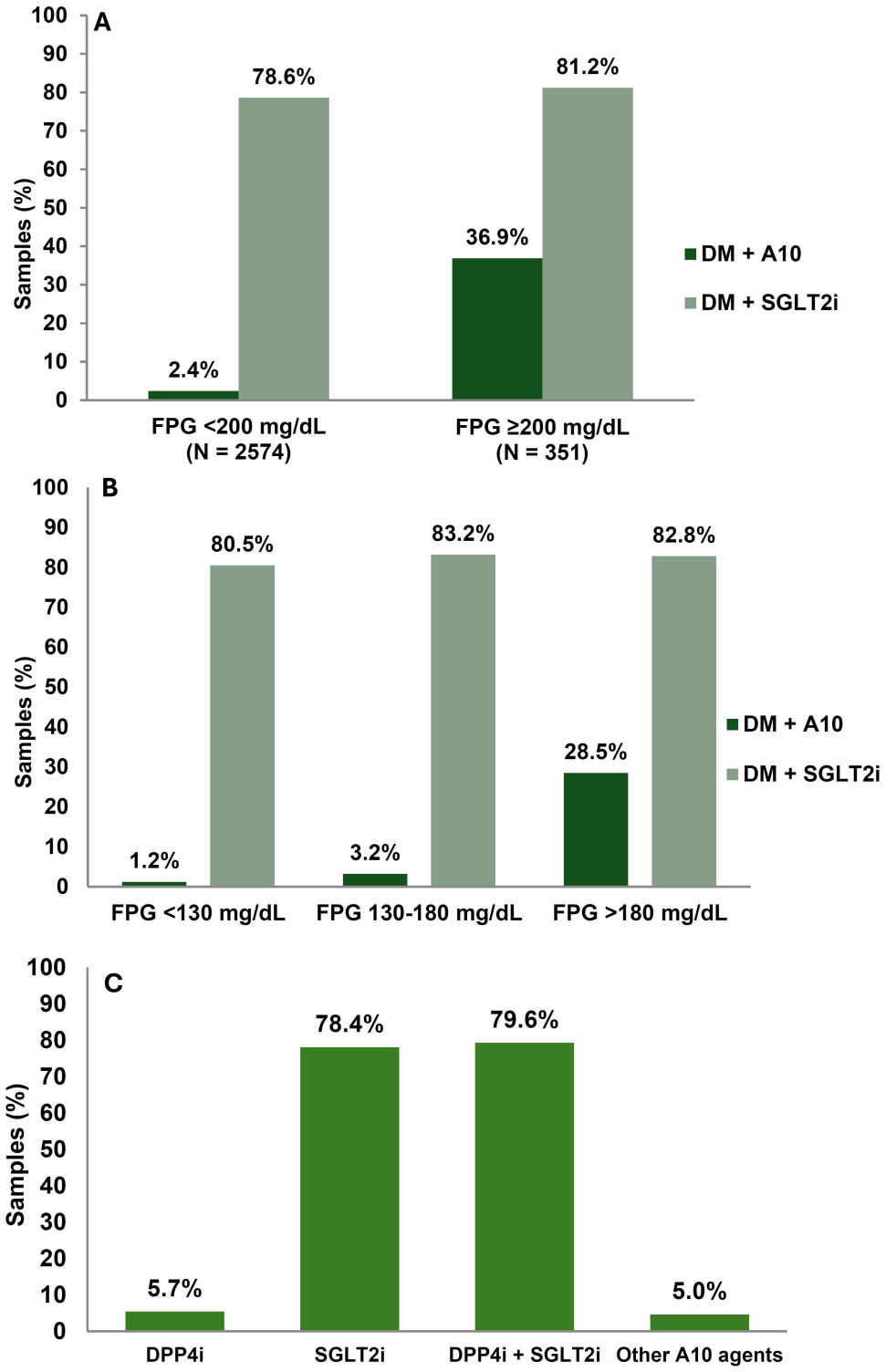

Figure 2 Evident glucosuria in patients with diabetes mellitus treated with SGLT2i or other A10 drugs. (**A**) Evident glucosuria according to fasting plasma glucose (FPG) in patients with DM treated with A10 drugs (other than SGLT2i) or with SGLT2i. Evident glucosuria was related to FPG only in patients treated with other A10 drugs, while in patients treated with SGLT2i it was related to SGLT2i intake. (**B**) Evident glucosuria according to level of FPG in patients with DM treated with A10 drugs (other than SGLT2i) or with SGLT2i. Again, evident glucosuria in patients treated with SGLT2i was not related to FPG, but to SGLT2i intake. (**C**) Evident glucosuria in 8119 samples from patients with diabetes mellitus according to the antidiabetic treatment. Evident glucosuria was clearly more frequent in samples from patients treated with SGLT2i alone or in combination.

Note: Evident glucosuria: >1000 mg/dL.

Abbreviations: FPG, fasting plasma glucose, DM, diabetes mellitus. SGLT2i, sodium-glucose co-transporter protein 2 inhibitors. DPP4i, dipeptidyl peptidase 4 inhibitors.

https://doi.org/10.2147/PPA.S576212

There were also differences in evident glucosuria according to the type of antidiabetic treatment. Evident glucosuria was more common in samples from patients treated with SGLT2i alone or in combination with dipeptidyl peptidase 4 inhibitors (DPP4i) (almost 80% in both groups) than in samples from patients treated with DPP4i alone or other A10 agents (less than 6% in both groups) (Figure 2C).

Regarding CKD, 1566 samples (53.5%) were from patients without CKD (CKD-) and 1359 samples (46.5%) were from patients with CKD (CKD+). Evident glucosuria was more frequent in CKD- samples (n = 1381; 88.2%) than in CKD+ samples (n = 927; 68.2%) ($p<0.0001$). Regarding the relationship between glucosuria and KDIGO stages, evident glucosuria was more frequent in samples from patients in KDIGO stages G1 and G2a (89.4% and 89%, respectively). The frequency of evident glucosuria decreased gradually with increased KDIGO stage to 13.7% in G5 stage ($p < 0.0001$) (Figure 3). Conversely, absent glucosuria increased from 6.1% at G1 up to 32% at G5 stage.

Furthermore, evident glucosuria was more common in samples from patients treated with a fixed-dose combination (87.1%) or with SGLT2i plus A10 (76.4%) than with SGLT2i as a single-agent pharmaceutical form (56.7%) ($p < 0.0001$). Absent glucosuria was more frequent in patients treated only with SGLT2i (18.5%) than in patients treated with a fixed-dose combination or SGLT2i plus A10 (5.1% and 10.6%, respectively).

Phase 2 Results

Glucosuria and Adherence

The potential relationships between glucosuria and adherence were analyzed in SGLT2i-treated patients. Data for tablets were available for all patients included in the second phase of the study, allowing the estimation of PDC. There was a relationship between absent glucosuria and lack of adherence (Figure 4).

Furthermore, absent glucosuria increased with kidney disease (according to KDIGO stages) and with reduced adherence. In samples from patients with poor adherence, absent glucosuria was seen in 100% of samples from patients with KDIGO G5 stage (n = 22), but also in 35.2% of samples from patients with KDIGO G1 stage (n = 804). Evident glucosuria was found in 57.4% of samples from patients with KDIGO G1 stage, diminishing to 0% of samples from patients with KDIGO G5 stage (p=0.1168). However, in samples from patients with good adherence, absent glucosuria was rare, ranging from <5% for patients in G1 stage to 15% for patients in G5 stage. On the contrary, evident glucosuria

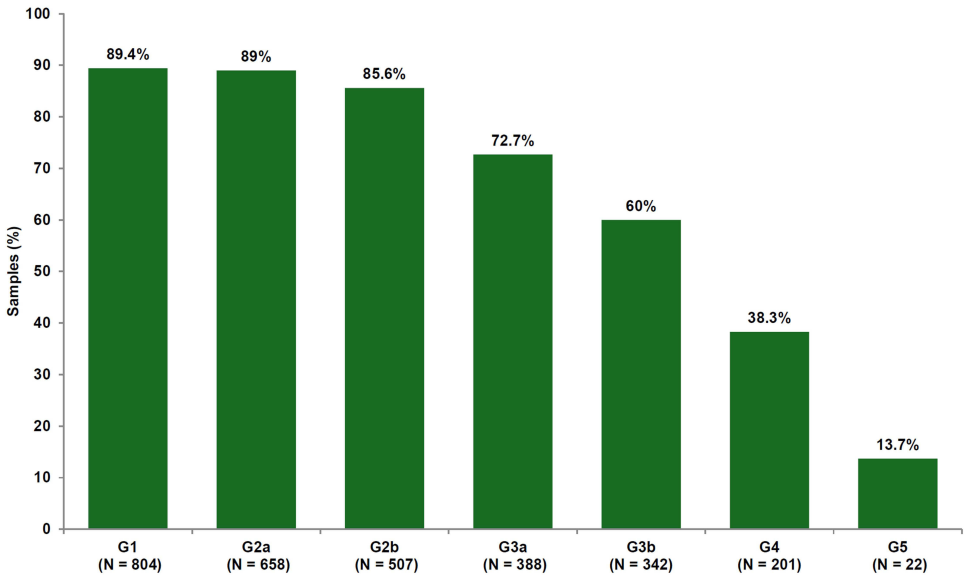

Figure 3 Frequency of evident glucosuria by KDIGO modified stages of eGFR in 2922 samples from patients with diabetes mellitus and SGLT2i treatment. Evident glucosuria was less frequent as severity of chronic kidney disease increased.

Abbreviations: KDIGO, Kidney Disease: Improving Global Outcomes. eGFR, estimated glomerular filtration rate. SGLT2i, sodium-glucose co-transporter protein 2 inhibitors.

https://doi.org/10.2147/PPA.S576212

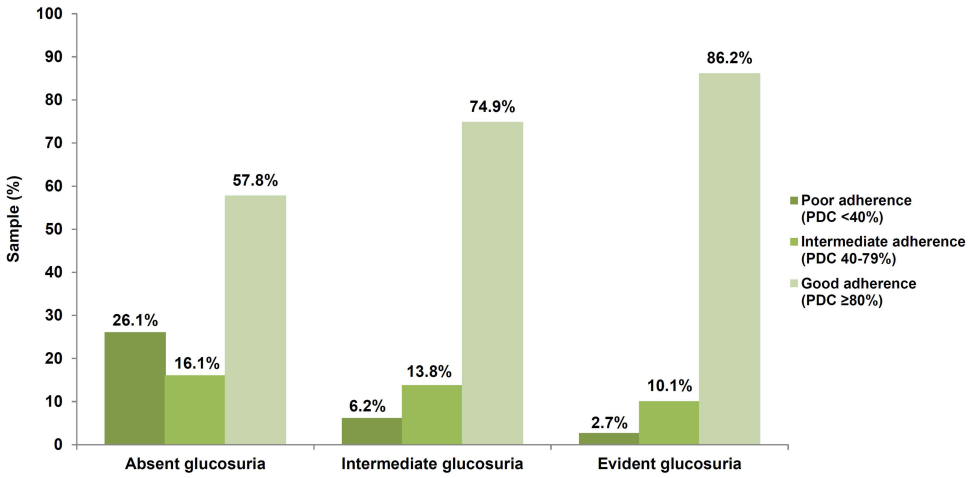

Figure 4 Glucosuria in samples according to groups of patients by adherence to SGLT2i. Absent glucosuria increased with reduced adherence measured by PDC.Absent glucosuria, 0 mg/dL; intermediate glucosuria, 1–1000 mg/dL; evident glucosuria, >1000 mg/dL.
Abbreviations: SGLT2i, sodium-glucose co-transporter protein 2 inhibitors. PDC, proportion of days covered.

was common, ranging from 94.3% and 94.1% in samples from patients with KDIGO G1 and G2 stages, respectively, to 15.4% in samples from patients with KDIGO G5 stage ($p<0.0001$).

Holistic Effects of Glucosuria-Related Drugs

Also in SGLT2i-treated patients, blood uric acid level was higher in patients whose samples had absent glucosuria ($p < 0.01$). Furthermore, hemoglobin and hematocrit were lower in patients, both men and women, with absent glucosuria in urine samples ($p<0.05$ for both variables) (Figure 5).

Discussion

Poor adherence to antidiabetic treatment should be able to be easily recognized in clinical practice, so that healthcare providers can investigate the causes and implement appropriate measures. Adherence to SGLT2i agents has not been studied widely.[18–22] However, the results of these studies suggested that good adherence was associated with higher HbA1c reduction, better glycemic control and reduced need for additional drugs.[18–22] We considered that glucosuria induced by this group of antidiabetic drugs could be a useful biomarker of adherence. Glucosuria is determined routinely in all urinanalyses and therefore, it would be easy to check within any clinical setting, from primary care to hospital and emergency room. To our knowledge, the current study is the first to use glucosuria for evaluating adherence in patients treated with SGLT2i.

Because we used urine samples, there could be more than one sample for each patient. However, we considered that samples represented each patient at different time points (each analysis), and that they could be adherent at a time point and non-adherent at another time point. Therefore, we assessed adherence by glucosuria in each visit, not measured by the patient.

Due to the algorithm we used to identify DM, all patients included in the second phase of the study had DM. This algorithm considered that individuals had diabetes if they were treated with any ATC A10 drug covered by the Andalusian Healthcare system during the study period;[16] as all patients included in the second phase were treated with SGLT2i, all of them were considered as having diabetes. It should be mentioned that SGLT2i are approved in Spain for heart failure since 2021 and for chronic kidney disease since 2021 (dapagliflozin) and 2023 (empagliflozin), under some limitations and requiring a health inspection visa. Despite this, in our study, SGLT2i use in a patient without diabetes could be equivalent to a patient with a good diabetes control; therefore, it should not be considered different in our results of glucosuria or FPG.

Regarding samples with evident glucosuria, almost 90% corresponded to patients with DM treated with SGLT2i. Evident glucosuria was also found in more than 9% of patients with DM treated with other A10 agents. In these latter

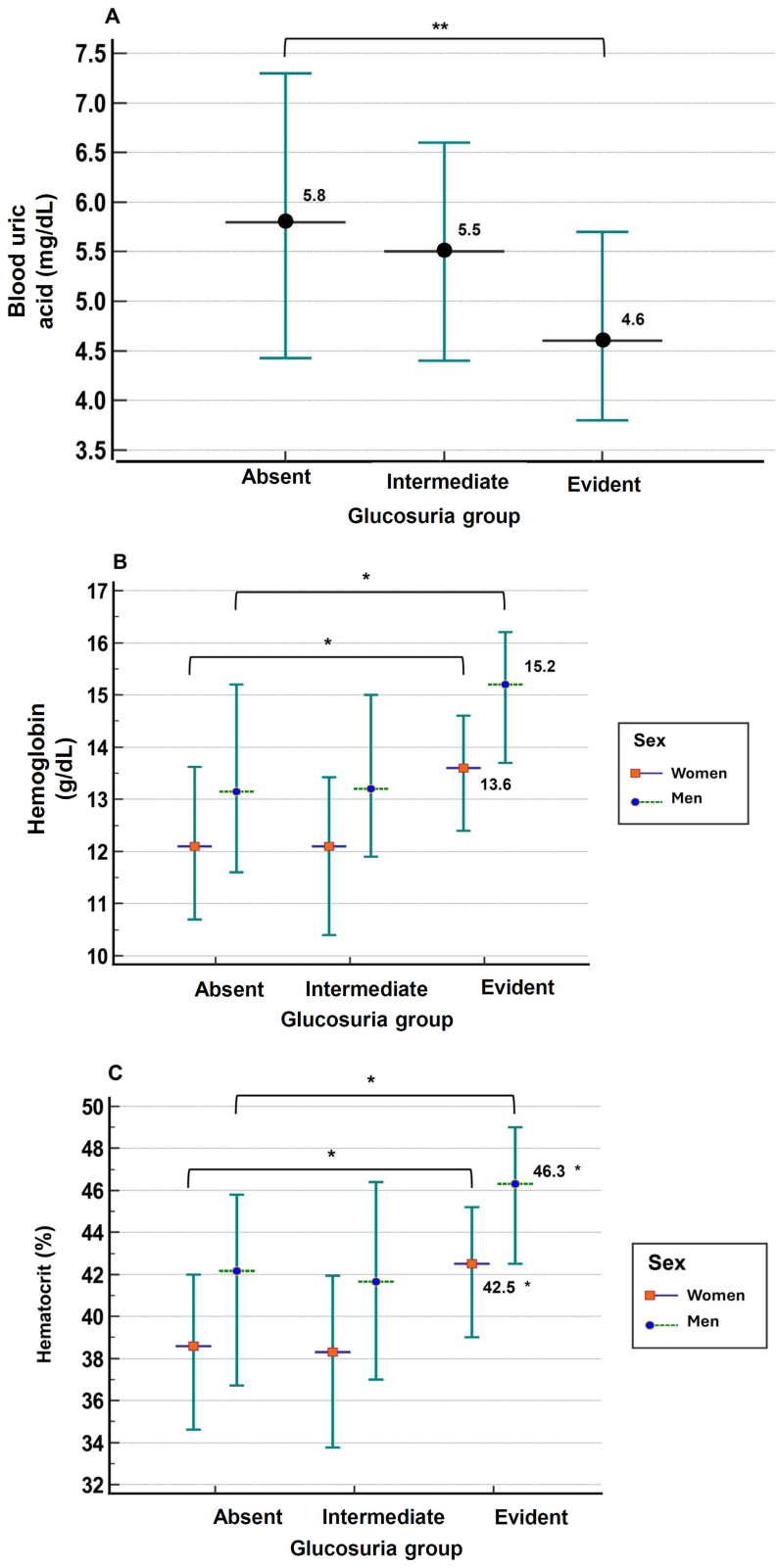

Figure 5 Holistic effects of glucosuria-related drugs. (**A**) Blood uric acid by glucosuria group. (**B**) Hemoglobin by glucosuria group. (**C**) Hematocrit by glucosuria group.
Notes: *p<0.05, **p<0.01Absent glucosuria, 0 mg/dL; intermediate glucosuria, 1–1000 mg/dL; evident glucosuria, >1000 mg/dL.

https://doi.org/10.2147/PPA.S576212

patients, evident glucosuria is likely related to hyperglycemia, because increased urine glucose was much more common in patients with FPG ≥200 mg/dL. On the contrary, in patients with DM treated with SGLT2i, almost 90% of patients with evident glucosuria had FPG <200 mg/dL. In addition, there were 60 samples (2.3%) with glucosuria obtained from patients without DM; these samples were probably from patients with familial renal glucosuria, but no confirmatory diagnostic test was performed.

Also in samples from patients with DM treated with SGLT2i, almost 80% of glucosurias were evident. However, 9% of glucosurias were absent glucosurias. This is an anomaly and the only explanation for absent glucosuria in patients treated with SGLT2i is poor adherence.

On the contrary, in patients without SGLT2i treatment, absent glucosurias were the most common, reaching 99% of samples from patients without DM. Furthermore, in patients with DM treated with A10 agents, 68% of them had FPG higher than 200 mg/dL, suggesting that glucosuria was induced by high plasma glucose. In contrast, in patients with DM treated with SGLT2i, the proportion of patients with high FPG was only 12%, confirming the glycosuric effect of SGLT2i. In a study in 770 patients treated with SGLT2i,[12] 86% of patients had evident glucosuria and no relationship was found between FPG and glucosuria or HbA1c.

When analyzing glucosuria in patients treated with SGLT2i, hyperglycemia did not have any effect. However, in those patients with CKD, evident glucosuria was less common. It should be pointed out that in patients with CKD, glucosuria induced by SGLT2i agents (and their effect on hyperglycemia) declines almost parallel to eGFR reduction.[23] The hypoglycemic effect of SGLT2i is reduced when eGFR <45 mL/min/1.73 m^2,[24] and is minimal when eGFR is <30 mL/min/1.73 m^2,[25] but cardiorenal benefits are maintained.[26] This reduced glucosuria in patients with low eGFR should be taken into account when assessing glucosuria as a biomarker for adherence to SGLT2i, because up to 40% of patients with DM develop CKD.[27] In the present study, evident glucosuria diminished as eGFR was lower, from eGFR < 60 mL/min/1.73 m^2, and intermediate glucosuria increased. However, we also considered the increase in absent glucosuria as an anomaly that could be associated with a lack of adherence and should be further studied.

With regard to the type of drug, the best relationship between evident and absent glucosuria was found with fixed combinations of an SGLT2i and metformin. The poor relationship between evident and absent glucosuria in patients treated with SGLT2i alone was surprising, with more than 18% of absent glucosuria. A possible reason could be that adherence can be lower in polymedicated patients.[28]

Although therapeutic adherence to SGLT2i is essential for effective treatment, its accurate and objective measurement is complicated. Adherence can be assessed by direct and indirect methods. Direct methods, such as measuring levels of drug or its metabolites, are more accurate but also more complex and expensive and show inter-individual differences.[29] Indirect methods are used more commonly in research and include the use of EHR or administrative data, pill count, electronic monitoring devices and self-reported measures such as the eight- and four-item Morisky Medication Adherence Scales (MMAS-8 and MMAS-4).[18,29] In a systematic review of studies on adherence to oral antidiabetic drugs in T2D,[18] the most common methods for assessing adherence were those using administrative data, mainly counting of dispensed packaging in pharmacy offices through the PDC or the Medication Possession Ratio (MPR).[18]

Adherence to SGLT2i has been assessed in other studies using traditional methods. In a meta-analysis of studies where adherence was measured using mainly the PDC method, pooled adherence to SGLT2i was 49% at 1 year.[9] However, in another meta-analysis of studies where adherence to SGLT2i was measured using MPR, up to 54% of patients continued treatment after 1 year, although there were differences according to the specific SGLT2i,[30] from 64% for empagliflozin[19] to 94.9% for an unspecified agent.[31] We did not assess drug-specific differences in glucosuria induced by SGLT2i because the study objective was not to find differences between SGLT2i, but the value of glucosuria as biomarker of adherence. Our results showed 82.9% and 40.2% of good adherence for patients with samples with evident glucosuria and absent glucosuria, respectively. But when we looked at poor adherence, we found 3.9% and 29.5% for patients with samples with evident and absent glucosuria, respectively.

Regarding glucosuria and adherence in SGLT2i-treated patients, absent glucosuria showed a direct and statistically significant relationship with poor adherence. There was also lack of holistic effects of SGLT2i in case of absent or intermediate glucosuria. Furthermore, absent glucosuria was more common in women and at advanced age. On the contrary, evident glucosuria was associated with lower serum uric acid level and increases in

hemoglobin and hematocrit. These improvements, considered to be holistic effects of SGLT2i, have already been seen in clinical trials such as the EMPEROR trials with empagliflozin.[32,33] These holistic effects of SGLT2i are related to renal and cardiovascular benefits of SGLT2i.[34,35] Findings of the present study add real-world evidence to clinical trial results.

Our findings confirm the results of a preliminary study conducted in the same healthcare area. The relationship between glucosuria and adherence was assessed using EHR data from 133 patients with T2D treated with SGLT2i.[36] A total of 124 patients (87%) had evident glucosuria, but there were 9 patients (6.5%) with intermediate glucosuria and 9 patients with absent glucosuria (6.5%), thus suggesting poor adherence in these 18 patients (18%).[36]

Furthermore, our results might modify current clinical practice. Urine glucose testing can be performed using easily paper test strips in primary care clinics and even at home.[37] However, it is not an accurate method to estimate glycemic control[38] and the American Diabetes Association does not currently recommend routine urine glucose testing for patients with DM.[37] However, due to the relationship between glucosuria and adherence to SGLT2i evidenced in our study, urine glucose testing could be considered as a routine analysis in patients treated with SGLT2i.

Strengths and limitations of this study come from the design and data origin. Being based on a wide registry, we were able to gather a large number of samples from a heterogeneous population in a real-world framework. However, as data were collected during clinical practice, registries may be incomplete, due to a lack of assessments or recording, or by misclassification of data,[39] and this could reduce the validity of conclusions. However, most of the variables in the current study are used frequently during real clinical practice to manage these patients. Furthermore, study groups were heterogeneous at baseline, causing a potential bias in results. To avoid this, we could have analyzed data with a propensity score matching test.

In addition, the inclusion algorithm considered that all included patients treated with A10 drugs had DM. This algorithm is out of date, but is the one used in our database since 2014. Furthermore, in 2022–2023 SGLT2i were already indicated in patients without DM, but only in those with HFrEF. However, our protocol did not allow differentiation between patients with and without DM treated with SGLT2i. It was to be expected that in the first semester of 2023 few patients would be treated with SGLT2i if they did not have DM. Therefore, we defined patients as having DM but not T2D despite the fact that SGLT2i are indicated for the treatment of non-insulin dependent DM.

Our results opened new lines of investigation of glucosuria as biomarker of adherence in patients treated with SGLT2i, mainly measuring it quantitatively and exploring its reduction in the subgroup of patients with chronic kidney disease.

Conclusions

Our results suggest that glucosuria could be a biomarker of adherence to SGLT2i. In patients with DM treated with SGLT2i, the presence of evident glucosuria increased as adherence improved. However, interpretation of results should be cautious in patients with CKD and using a semi-quantitative method to measure glucosuria could affect accuracy of results. Despite these limitations, which will be further studied, absent glucosuria might be an easy biomarker of poor adherence in patients treated with SGLT2i in all clinical settings.

Abbreviations

CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EHR, electronic health records; HFrEF, heart failure with reduced ejection fraction; KDIGO, Kidney Disease: Improving Global Outcomes; MPR, Medication Possession Ratio; PDC, Proportion of Days Covered; SGLT2i, sodium-glucose co-transporter protein type 2 inhibitors; SIDICAM, State of Diabetes in the Campo de Gibraltar Area; SSPA, Andalusian Public Healthcare System; T2D, type 2 diabetes mellitus.

Acknowledgments

The authors wish to thank Content Ed Net S.L. and Carmen Acuña-Condal for their help in writing and editing this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The Grupo de Investigación CARTEIA – Fundación para la gestión de la investigación biomédica de Cádiz has supported and funded the publication of this article through an unrestricted grant from Boehringer Ingelheim (BI) Spain. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. BI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations in relation to potential mention of BI substances.

Disclosure

The authors did not receive payment related to the development of the article and declared no conflicts of interest.

References

1. International Diabetes Federation. Diabetes Atlas 15th edition. 2025. Available from: http://www.diabetesatlas.org. Accessed April 20, 2025.
2. Farmaki P, Damaskos C, Garmpis N, Garmpi A, Savvanis S, Diamantis E. Complications of the type 2 diabetes mellitus. *Curr Cardiol Rev*. 2020;16(4):249–251. doi:10.2174/1573403X1604201229115531
3. Morillas C. Positioning of sodium-glucose cotransporter-2 inhibitors in national and international guidelines. *Med Clin*. 2016;147(S1):49–53. doi:10.1016/S0025-7753(17)30626-7
4. European Medicines Agency (EMA). SGLT2 inhibitors - referral. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/sglt2-inhibitors. Accessed April 20, 2025.
5. Herrington WG, Savarese G, Haynes R, et al. Cardiac, renal, and metabolic effects of sodium-glucose co-transporter 2 inhibitors: a position paper from the European Society of Cardiology ad-hoc task force on sodium-glucose co-transporter 2 inhibitors. *Eur J Heart Fail*. 2021;23(8):1260–1275. doi:10.1002/EJHF.2286
6. Viggiano D, Joshi R, Borriello G, et al. SGLT2 inhibitors: the first endothelial-protector for diabetic nephropathy. *J Clin Med*. 2025;14(4):1241. doi:10.3390/JCM14041241
7. Tao S, Guo S, Tong N. Update on the clinical applications of SGLTis: insight to benefits beyond hypoglycemic and cardiorenal protection. *Pharmacotherapy*. 2024;44(8):642–657. doi:10.1002/PHAR.2952
8. Ciardullo S, Savaré L, Rea F, Perseghin G, Corrao G. Adherence to GLP1-RA and SGLT2-I affects clinical outcomes and costs in patients with type 2 diabetes. *Diabetes Metab Res Rev*. 2024;40(4):e3791. doi:10.1002/DMRR.3791
9. Ofori-Asenso R, Sahle BW, Chin KL, et al. Poor adherence and persistence to sodium glucose co-transporter 2 inhibitors in real-world settings: evidence from a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2021;37(1):e3350. doi:10.1002/DMRR.3350
10. Clifford S, Perez-Nieves M, Skalicky AM, Reaney M, Coyne KS. A systematic literature review of methodologies used to assess medication adherence in patients with diabetes. *Curr Med Res Opin*. 2014;30(6):1071–1085. doi:10.1185/03007995.2014.884491
11. Misra M. SGLT2 inhibitors: a promising new therapeutic option for treatment of type 2 diabetes mellitus. *J Pharm Pharmacol*. 2013;65(3):317–327. doi:10.1111/J.2042-7158.2012.01574.X
12. Alonso Fernández M, Crespo Cañete M, Domínguez Fernández L, et al. [P-089. Glycosuria as a measurement of medication adherence in patients treated with SGLT2i]. *Endocrinol Diabetes Nutr*. 2018;65:134.
13. Norwegian Institute of Public Health. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD) Index 2025. Available from: https://atcddd.fhi.no/atc_ddd_index/. Accessed April 9, 2025.
14. Loucks J, Zuckerman AD, Berni A, Saulles A, Thomas G, Alonzo A. Proportion of days covered as a measure of medication adherence. *Am J Heal Pharm*. 2022;79(6):492–496. doi:10.1093/AJHP/ZXAB392
15. Michán-Doña A, Jiménez-Varo E, Escribano-Cobalea M, et al. Prevalencia y características de la anemia en personas con diabetes mellitus de 50 años o más en un área sanitaria de Cádiz (España). *Revista Clínica Española*. 2024;224(7):457–465. doi:10.1016/j.rce.2024.05.007
16. Escribano Serrano J, Méndez-Esteban MI, García-Bonilla A, et al. Prevalencia de diabetes, utilización de antidiabéticos y grado de control glucémico en la provincia de Cádiz (2014-2016): un estudio de base poblacional. *Rev Clin Esp*. 2019;219(4):177–183. doi:10.1016/j.rce.2018.10.005
17. Disease K. Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3(1):1–150. doi:10.1038/kisup.2012.73
18. Piragine E, Petri D, Martelli A, Calderone V, Lucenteforte E. Adherence to oral antidiabetic drugs in patients with type 2 diabetes: systematic review and meta-analysis. *J Clin Med*. 2023;12(5):1981. doi:10.3390/JCM12051981
19. Vlacho B, Mata-Cases M, Mundet-Tudurí X, et al. Analysis of the adherence and safety of second oral glucose-lowering therapy in routine practice from the Mediterranean area: a retrospective cohort study. *Front Endocrinol*. 2021;12:708372. doi:10.3389/FENDO.2021.708372
20. Cai J, Divino V, Burudpakdee C. Adherence and persistence in patients with type 2 diabetes mellitus newly initiating canagliflozin, dapagliflozin, dpp-4s, or glp-1s in the United States. *Curr Med Res Opin*. 2017;33(7):1317–1328. doi:10.1080/03007995.2017.1320277

21. Buysman EK, Anderson A, Bacchus S, Ingham M. Retrospective study on the impact of adherence in achieving glycemic goals in type 2 diabetes mellitus patients receiving canagliflozin. *Adv Ther*. 2017;34(4):937–953. doi:10.1007/S12325-017-0500-4
22. Ofori-Asenso R, Liew D, Lalic S, et al. Adherence, persistence, and switching among people prescribed sodium glucose co-transporter 2 inhibitors: a nationwide retrospective cohort study. *Adv Ther*. 2019;36(11):3265–3278. doi:10.1007/S12325-019-01077-3
23. Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. *Curr Diab Rep*. 2022;22(1):39–52. doi:10.1007/S11892-021-01442-Z/FIGURES/3
24. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2(5):369–384. doi:10.1016/S2213-8587(13)70208-0
25. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int*. 2018;93(1):231–244. doi:10.1016/J.KINT.2017.06.017
26. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. *Kidney Int Reports*. 2022;7(7):1463. doi:10.1016/J.EKIR.2022.04.094
27. Pavkov ME, Miyamoto Y. International Diabetes Federation. IDF atlas reports. Diabetes and Kidney disease. 2023. Diabetes and Kidney disease: https://diabetesatlas.org/resources/idf-diabetes-atlas-reports/diabetes-and-kidney-disease/. Accessed April 20, 2025.
28. García-Pérez LE, Álvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to therapies in patients with type 2 diabetes. *Diabetes Ther*. 2013;4(2):175–194. doi:10.1007/S13300-013-0034-Y
29. Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. *Med Pharm Reports*. 2019;92(2):117–122. doi:10.15386/MPR-1201
30. Holdt-Caspersen NS, Dethlefsen C, Vestergaard P, Hejlesen O, Hangaard S, Jensen MH. Adherence to newer second-line oral antidiabetic drugs among people with type 2 diabetes-A systematic review. *Pharmacol Res Perspect*. 2024;12(2):e1185. doi:10.1002/PRP2.1185
31. Strain WD, Tsang C, Hurst M, et al. What next after metformin in type 2 diabetes? Selecting the right drug for the right patient. *Diabetes Ther*. 2020;11(6):1381–1395. doi:10.1007/S13300-020-00834-W
32. Doehner W, Anker SD, Butler J, et al. Uric acid and SGLT2 inhibition with empagliflozin in heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. *JACC Heart Failure*. 2024;12(12):2057–2070. doi:10.1016/J.JCHF.2024.08.020
33. Ferreira JP, Anker SD, Butler J, et al. Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. *Eur J Heart Fail*. 2022;24(4):708–715. doi:10.1002/EJHF.2409
34. Wanner C, Nangaku M, Kraus BJ, et al. How do SGLT2 inhibitors protect the kidney? A mediation analysis of the EMPA-REG OUTCOME trial. *Nephrol Dial Transplant*. 2024;39(9):1504–1513. doi:10.1093/NDT/GFAE032
35. Inzucchi SE, Zinman B, Fitchett D, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41(2):356–363. doi:10.2337/DC17-1096
36. Crespo Cañete M, Fernández Domínguez M, Escribano Serrano J, Méndez Esteban M, Castro Jarillo C, Berruguilla Pérez E. 242/4286 - GLU_17_1. *Semergen*. 2017;43:1507.
37. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem*. 2023;69(8):808–868. doi:10.1093/CLINCHEM/HVAD080
38. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. *Diabetes Care*. 2004;27(7):1761–1773. doi:10.2337/DIACARE.27.7.1761
39. Galluccio F, Walker UA, Nihtyanova S, et al. Registries in systemic sclerosis: a worldwide experience. *Rheumatology*. 2011;50(1):60–68. doi:10.1093/RHEUMATOLOGY/KEQ355