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FIELD: MEDICINE

DOCTORAL THESIS

SUMMARY

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THE IMPACT OF SODIUM-GLUCOSE COTRANSPORTER II INHIBITOR THERAPY ON KIDNEY DAMAGE IN TYPE 2 DIABETES MELLITUS

PHD THESIS ABSTRACT

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I am deeply grateful to Prof. Alexandu Ciocâlteu for having accepted to supervise this work. His competent and timely guidance was particularly helpful in the elaboration of each chapter of the work.

Preface

The impact of this work will be proven after sufficient time has passed in order to study the favourable effects, but also the possible side effects of the new iSGLT2. The interest in this new class of drugs stems from the fact that in Romania, the evidence for the mechanism of glucose reabsorption from primary urine at the level of the PCT (proximal convoluted tubule) by a "carrier" mechanism was first reported in 1963 in the book "Clinical Nephrology", authored by C. C. Dumitriu and V. Beroniade.

The research on this "carrier" has continued and has led to the exact mechanism of the Na-glucose cotransporter being pinpointed and the appearance of Forxiga on the pharmaceutical market 10 years ago. Penetrating this "universe" of carbohydrate metabolism seems extremely delicate and with multiple side effects, the most important of which is hypoglycaemia in patients receiving sulfonylureas and/or insulin. Like many other drugs it seemed that Forxiga is the "panacea" for diabetes mellitus and heart failure, and even CKD (chronic kidney disease), delaying progression to end-stage CKD and dialysis.

There is a trend today to recommend cutting glucose and salt from the diet. Additionally, another trend relates to antioxidant medication, as if forgetting that we, however, could not survive without oxygen. To not report side effects of an otherwise beneficial, new medication would be dishonest on my part. Let's take the example of a kidney disease's progression to CKD. Numerous conferences recommend the prescription of an ACE-inhibitor in hypertension and in CKD to decrease the atherosclerotic effect of high blood pressure values. It is forgotten that these patients will quite quickly show increases in urea and creatinine values and this will indirectly lead to cardiac repercussions, with secondary increase in blood volume. It is a foolhardy endeavour to fathom the immediate and distant effects of a new class of iSGLT2.

This paper is the debut of future work on either a favourable class effects or effects that could alter the management of iSGLT2 therapy.

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List of published scientific papers

Original articles:

1. "Use of sodium glucose cotransporter type 2 inhibitors in the context of type 2 diabetes mellitus"

published in Acta Medica Transilvanica, Vol. 3/2023

Data from this article can be found in Research Study IV, page 143.

2. "Inhibitors of the sodium-glucose cotransporter type 2 in the treatment of diabetes mellitus" published in Medicine in Evolution, vol. XXIX, no. 3, 2023

Data from this article can be found in Research Study III, page 134.

List of abbreviations and symbols

AKI: Acute kidney injury

ASCVD: Atherosclerotic cardiovascular disease

CI: Confidence interval

CKD: Chronic kidney disease

CV: Cardiovascular

CVD: Cardiovascular diseases

CVOT: Cardiovascular outcome trials

DKD: diabetic kidney disease

DPP-4: dipeptidyl peptidase-4

DM: diabetes mellitus

eGFR: estimated glomerular filtration rate

GFR: glomerular filtration rate

GPL-1: glucagon-like peptide-1

ESKD: end-stage kidney disease

ESRF: end-stage renal failure

GFR: glomerular filtration rate

GLP-1 RA: glucagon-like peptide-1 receptor agonist

MI: myocardial infarction

NAFLD - non-alcoholic fatty liver disease

NEFA - non-esterified fatty acid

NNT: number needed to treat

RRT: renal replacement therapy

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

TDF: Theoretical Domain Framework

UACR: urinary albumin:creatinine ratio

ADM: average distance from mean

Introduction

The objective of this work is to describe the impact and role of sodium-glucose cotransporter 2 (SGLT2) inhibitor on renal impairment in type 2 diabetes mellitus.

The paper is structured in two chapters as follows:

- a general part, presenting theoretical aspects;
- Part two, which highlights personal contributions, focusing on four research studies.

The paper concludes with the chapter "Conclusions and personal contributions".

1. General considerations

1.1 Kidney disease in diabetic patients: from pathophysiology to pharmacological aspects with a focus on therapeutic inertia

Diabetes mellitus is a growing concern for both the public economy and global health. In fact, it can lead to insidious macrovascular and microvascular complications, with a negative impact on patients' quality of life.

Diabetic patients often have diabetic kidney disease (DKD).

The clinical impact of DKD is dangerous not only for the risk of progression to end-stage renal disease and therefore for renal replacement therapies, but also because of the associated increase in cardiovascular events.

Early recognition of risk factors for DKD progression can be decisive in decreasing morbidity and mortality. DKD presents patient, clinician and systemic problems. All of these problems translate into therapeutic inertia, which is defined as failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines.

The avoidance of therapeutic inertia is also mentioned in the "Guidelines for the management of diabetes mellitus - Romania; Evaluation of patients with type 2 diabetes mellitus" published in the Official Monitor of Romania Part 1 No 997bis/19.10.2021. In this guideline, T2DM therapeutic goals are to prevent or delay complications and maintain quality of life. The following are required: glycaemic control, management of cardiovascular risk factors, regular follow-up, avoidance of therapeutic inertia.

There needs to be a patient-centred approach to personalize therapy and increase patient involvement in self-care activities.

Based on established vascular complications and comorbidities, treatment targets need to be identified.

1.2. Pharmacologic management of DKD - New insights and old confirmations

Diabetes mellitus has a multifactorial pathogenesis. The "bad octet" includes β-cell damage with impaired insulin secretion, α-cell damage with increased glucagon secretion, increased hepatic glucose production, dysfunction of brain neurotransmitters, decreased muscle glucose uptake, increased renal glucose reabsorption, increased lipolysis, decreased incretin effect.

There are different treatments, intervening on different pathogenetic mechanisms. Metformin,

sulfonylureas and glinides, DPP4 inhibitors, SGLT2 inhibitors, GLP1 receptor agonists, thiazolidinediones, insulin are used. But how effective are these treatments in preventing and treating complications? The history of diabetes treatment begins 100 years ago with the discovery of insulin.

The UKPDS, DCCT, Kumamoto studies are the triumph of the gluco-centric theory. The ACCORD, ADVANCE, VADT studies raise the question of cardiovascular safety.

In 2008 the individualized approach emerged. The STENO-2 study supported the multifactorial approach.

The studies following EMPA-REG, DECLARE, CANVAS, LEADER, SUSTAIN-6, HARMONY, REWIND represented a multifactorial approach to treatment. One drug interferes with several pathogenetic mechanisms.

Today we're talking about the cardio-reno-metabolic revolution.

DKD is an essential injury in patients affected by DM because it poses a risk of progression of CRB to ESRD and increased CV morbidity and mortality.

DKD treatment addresses both problems with first-line renin-angiotensin system (RAS) blocking drugs, including angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs).

Due to reduced renal excretion, many antidiabetic drugs (excreted substantially through the kidneys) are contraindicated or require dose adjustments in patients with DKD to prevent hypoglycaemia.

The most recent KDIGO guidelines recommend the use of metformin together with inhibitors of sodium-glucose co-transporter-2 (iSGLT2) as first-line therapy, due to their cardioprotective effects and preventive effects on the progression of CRB progression in patients with GFR ≥30 ml/min/ 1.73 m2.

Elevated levels of triglycerides and low-density lipoprotein-cholesterol (LDL-c) are associated with an increased risk of CV and CKD progression in patients with DKD. Thus, an assessment of the lipid profile is indicated and an appropriate pharmacologic approach is needed in patients with DKD. Antiplatelet agents are widely used in the secondary prevention of CV disease.

1.3. Critical DKD management issues

Glycaemic control in patients with DKD is recommended not only for cardiovascular prevention, but also to prevent DKD progression.

Glycaemic management in patients with DKD is challenging due to several factors such as: therapeutic inertia, difficulties in monitoring; complexity in the use of available treatments.

One of the main problems in glycaemic control in patients with DKD is that the risk of hypoglycaemia increases with decreasing GFR, mainly due to altered pharmacodynamic and pharmacokinetic profiles of antidiabetic drugs and reduced renal mass.

Barriers to treatment intensification can be categorized into three levels:

- Patient level: the difficulty to change lifestyle and take the medication is common and contributes significantly to the challenge of reaching glycaemic targets;
- at clinician level: several provider-related factors can lead to therapeutic inertia: overestimation of quality of care, lack of materials, etc;
- System level: several problems at health system level can also lead to difficulties in achieving the goals of therapy.

1.4. Sodium-glucose cotransporter 2 (iSGLT2) inhibitors: benefit versus risk

This sub-chapter reviews the literature, highlighting the positive and negative impact of iSGLT2 on six key organs and systems in the body. These systems include nervous, cardiovascular, pulmonary, pancreatic, hepatic and renal.

Sodium-glucose cotransporter 2 (SGLT2) is widely found in different regions of the brain, such as the hippocampus, cerebellum and blood-brain barrier (BBB).

Industry regulatory agencies have issued a request on cardiovascular risk in diabetes. U.S. Food and Drug Administration (FDA): "To establish the safety of antidiabetic therapy in patients with type 2 diabetes, companies must demonstrate that the treatment does not result in an unacceptable increase in cardiovascular risk [...] over a period of at least 2 years." (Guidance for Industry Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies To Treat Type 2 Diabetes). European Medicines Agency (EMA): "For the medicinal products to be developed it is anticipated that the development program will provide sufficient information to support the lack of

excess cardiovascular risk induced by the drug [...] with a minimum follow-up period of 18-24 months." (EMA Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus).

Mechanisms that could explain the cardiorenal protection with SGLT2 inhibitors are:

- Improvement of myocardial energy metabolism at the mitochondrial level.
- Reduction of preload, afterload and left ventricular wall stress in the heart with improved filling.
- In the circulation, decreases in intravascular volume and extracellular fluid lead to increased haematocrit and decreased arterial pressure.
- At the renal level, SGLT2 inhibitors produce constriction of the afferent arteriole with decreased intraglomerular pressure and improved renal function. Inhibition of SGLT2 and blockade of the renin-angiotensin-aldosterone system (RAAS) reduce glomerular hyperfiltration. SGLT2 inhibitors cause constriction of the afferent arterioles due to increased sodium supply to the macula densa. This results in decreased glomerular pressure and reduced albuminuria. RAAS blockade also causes vasodilation of the efferent arteriole, with the same result on glomerular pressure and albuminuria.

SGLT2 inhibitors reduce interstitial volume more than intravascular volume, unlike loop diuretics. Interstitial oedema is evident in patients with congestive heart failure. SGLT2 inhibitors selectively decrease interstitial volume with minimal change in vascular volume, whereas loop diuretics reduce both interstitial and intravascular volume. This volume regulation produced by SGLT2 inhibitors (interstitial > intravascular) limits the aberrant neurohormonal reflex that is triggered when intravascular depletion occurs. The hemodynamic improvement is only partly the result of osmotic diuresis. There is a reduction in cardiac pressor pressure, which is important in patients with diastolic dysfunction.

Other effects of SGLT2 inhibitors are:

- Decreased arterial stiffness;
- Decreased sympathetic nervous system activity;
- Decreased albumin;
- Lower insulin levels;

• Decreased uric acid;

• Decreased oxidative stress;

• Decreased body weight;

• Decreased visceral adiposity;

• Lower triglycerides, increased HDL-cholesterol and LDL-cholesterol.

The EMPA-REG study showed that in the group treated with empagliflozin there was a significant decrease in:

- Cardiovascular deaths (3.7% vs 5.9% in the placebo group);
- Hospitalizations for heart failure (2.7% vs 4.1% in the placebo group);
- Deaths from any cause (5.7% vs 8.3% in the placebo group).

Empagliflozin resulted in small reductions in body weight, abdominal circumference, uric acid concentration, systolic and diastolic blood pressure without an increase in heart rate. Empagliflozin resulted in small increases in LDL and HDL-cholesterol concentration. There were no semi-significant between-group differences in the rate of myocardial infarction or stroke (myocardial infarction 4.8% vs 5.4% in the placebo group; stroke 3.5% vs 3% in the placebo group). Losses of urinary electrolytes other than sodium (potassium, chloride, calcium, magnesium) have not been reported in the literature.

1.5 Renoprotective effects of SGLT2 inhibitors

Dapagliflozin, empagliflozin, and in other countries canagliflozin are SGLT2 inhibitors used in clinical practice. These molecules were developed to lower blood glucose, but are now a key recommendation in guidelines for the prevention and treatment of CKD (chronic kidney disease) and renal failure.

The mechanism by which SGLT2 inhibitors decrease glycemia is through inhibition of glucose reabsorption in the proximal convoluted tubule, leading to the development or increase in glycosuria. In addition, in clinical trials, this class of drugs has been shown to improve major renal impairment-related endpoints by 30-40% over 2-3 years in people with CKD, with or without diabetes mellitus. The primary mechanism of renal protection is the ability of SGLT2 inhibitors to activate tubuloglomerular feedback and ameliorate hyperfiltration-mediated renal injury.

Recent studies have revealed other mechanisms besides influencing tubuloglomerular feedback.

Thus, SGLT2 inhibitors may protect the kidneys through indirect mechanisms: optimizing kidney energy substrate utilization and delivery; regulating autophagy and maintaining cellular homeostasis; attenuating sympathetic hyperactivity; improving vascular health and microvascular function. In addition to their beneficial role on CKD, SGLT2 inhibitors may also decrease the risk of AKI (acute kidney injury). The reduction in the risk of AKI varies between different classes of SGLT2 inhibitors. Clinical studies show a favourable benefit on AKI with empagliflozin and dapagliflozin, but not with canagliflozin. Similarly, empagliflozin but not canagliflozin reduces histologic markers of tubular injury and AKI biomarkers in rat models of AKI. The mechanisms underlying these differences may involve variations in the effects and selectivity of SGLT2 inhibitors.

In clinical trials, glucose lowering with SGLT2 inhibitors was modest. Therefore, it has been deduced that SGLT2 inhibitors decrease intraglomerular pressure by activating tubuloglomerular feedback (TGF). Other transporters and receptors are also involved in TGF feedback. The NaKCl cotransporter (NKCC2) is found in the kidneys where it extracts sodium, potassium and chloride from the urine so that they can be reabsorbed into the blood. NKCC proteins are membrane transport proteins that transport Na, K and chloride ions across the cell membrane. NKCC2 is specifically found in cells of the ascending arm of the loop of Henle's loop and in the macula densa in nephrons. In these cells NKCC2 is located in the apical membrane surrounded by the lumen of the nephron, which is the empty space containing urine. This transporter serves in both sodium uptake and tubuloglomerular feedback.

Purinergic P2 receptors are activated by extracellular ATP. They may be involved in the progression of chronic kidney disease. Activation of TGF feedback is the direct mechanism by which SGLT2 inhibitors protect the kidneys.

Tubuloglomerular feedback is an adaptive mechanism that regulates single-nephron GFR (SNGFR) in response to tubular fluid salt concentration in the macula densa. The macula densa releases ATP from the basolateral membrane in proportion to the luminal solute concentration sensed by apical Na+ K+ 2Cl- cotransporters (NKCC2). ATP binds to P2 purinergic receptors on afferent arterioles or undergoes cleavage to release adenosine. The action of ATP on P2 purinergic receptors and the action of adenosine on adenosine A1 receptors

causes vasoconstriction in the afferent arterioles. In addition, adenosine-mediated effects on juxtaglomerular cells decrease renin secretion and reduce vasoconstriction in the efferent arteriole mediated by renin-angiotensin-aldosterone (RAAS) vasoconstriction. Increased afferent arteriolar tone and decreased efferent arteriolar tone leads to decreased intraglomerular pressure and reduced SNGFR.

Hyperfiltration or increased SNGFR is an important factor in the initiation and progression of kidney disease. Hyperfiltration is accentuated in diabetes mellitus because hyperglycaemia increases SGLT2 expression in PCT, leading to increased proximal reabsorption of sodium and glucose, decreased sodium delivery to the macula densa. This results in maladaptive inhibition of TGF. SGLT2 inhibitors decrease sodium and glucose reabsorption in TCP, increase distal solution delivery, activate TGF, decrease intraglomerular pressure and reduce hyperfiltration-mediated renal impairment. This results in an average decrease in eGFR of 3-6 ml/min per 1.73m² within a few weeks of SGLT2 inhibitor initiation with stabilization and slowing of the GFR decline over time.

Patients with diabetes mellitus may have different degrees of hyperfiltration, so the initial decrease in GFR under treatment with SGLT2 inhibitors may be different.

SGLT2 inhibitors reduce GFR when hyperfiltration is present, but may not affect GFR in the absence of hyperfiltration. Therefore, the level of hyperfiltration may determine the ability of SGLT2 inhibitors to modulate TGF.

TGF activation through SGLT2 inhibition is observed more frequently in animal models of diabetic kidney disease (DKD) than in non-DKD models. Similarly, in the dapagliflozin-treated heart failure study, non-DKD patients were more likely to be among the 30% of participants who did not experience a decrease in RFG within 14 days of initiating dapagliflozin.

Since the renal benefits of SGLT2 inhibitors are similar in individuals with and without DM in clinical trials, mechanisms other than TGF activation must be predominant. Exclusive activation of TGF would have a stronger favourable influence on patients with DM compared to those without DM.

Different nutrients or drugs can influence TGF:

- Increased intake of salt and protein reduces the effects of the SGLT2 inhibitor on TGF as does furosemide treatment.

- Low salt and protein intake as well as renin-angiotensin-aldosterone system (RAAS) inhibitors increase the effects of the SGLT2 inhibitor on TGF.

Renal protection achieved by this therapeutic class may also be by indirect mechanisms.

Optimization of kidney energy substrate utilization and delivery occurs because SGLT2 inhibitors create a negative energy balance.

Renally 90% of glucose is reabsorbed via SGLT2, but pharmacologic blockade of SGLT2 inhibits only 30-50% of glucose reabsorption because of compensatory increases in distal glucose reabsorption. This results in a loss of 50-90 g glucose, i.e., a caloric minus of 200-360 kcal daily in patients who filter about 180g glucose daily.

Energy loss is greater when GFR and blood glucose are higher. This state is perceived by the body as caloric restriction, triggering mechanisms for efficient utilization of energy substrates. SGLT2 inhibitors thus lead to lipolysis and ketogenesis. It increases the release of free fatty acids from the liver and decreases the insulin/glucagon ratio.

Ketone bodies are a source of energy for organs under stress.

SGLT2 inhibitors increase β-hydroxybutyrate which can be used by the kidneys and heart as an energy substrate. Stressed organs take up β-hydroxybutyrate by an insulin-independent transport mechanism. β-hydroxybutyrate is converted to acetyl-coenzyme A under the action of mitochondrial β-hydroxybutyrate dehydrogenase. Acetyl-coenzyme A enters the tricarboxylic acid cycle for oxidative phosphorylation leading to ATP generation. Compared to pyruvate, a product of glucose metabolism, the oxidation of β-hydroxybutyrate requires less oxygen and provides better mitochondrial efficiency. In addition, β-hydroxybutyrate serves as a signalling molecule that activates adaptive stress response pathways, suppresses oxidative stress and decreases inflammation. It follows that in a state of kidney stress β-hydroxybutyrate may have a role in attenuating renal injury.

SGLT2 inhibitors reduce oxygen consumption and may reduce hypoxia-induced kidney damage. In clinical trials SGLT2 inhibitors increased haematocrit by 2%-4%, probably by stimulating erythropoietin secretion.

SGLT2 inhibitors decrease oxygen utilization in the proximal convoluted tubule and improve oxygenation of renal tissues. They may also increase oxygen release through erythropoietin-mediated increases in haematocrit, angiogenesis and mitochondrial function. Improved tissue oxygenation reduces inflammation associated with chronic hypoxia, reduces

extracellular tissue remodelling and fibrosis. Another way in which SGLT2 inhibitors improve energy metabolism is by influencing the leptin/adiponectin ratio. Leptin is secreted by the adipocyte and is associated with insulin resistance, inflammation and oxidative stress. Adiponectin is anti-inflammatory and increases insulin sensitivity.

In CKD, the leptin/adiponectin ratio is increased. Adiponectin decreases the risk of CKD.

These observations have been exemplified in clinical trials with SGLT2 inhibitors where patients with T2DM had low leptin and increased adiponectin levels.

Regulating autophagy and maintaining cell homeostasis are renoprotective mechanisms of SGLT2 inhibitors.

This class of drugs creates a negative energy balance that stimulates nutrient deprivation sensors in tissues. Tissues respond to nutrient deficiency by inducing pathways that inhibit mTORC1 (mammalian target of rapamycin, protein complex 1) and stimulate AMPK (5'adenosine monophosphate-activated protein kinase) and SIRT1 (sirtuin1).

SIRT1 stimulates AMPK and HIF-2α and suppresses HIF-1α (hypoxia-inducible factors HIF). These pathways contribute to renal injury by enhancing autophagy and decreasing inflammation and fibrosis. SIRT1 deficiency accelerates kidney damage, and SIRT1 activation attenuates renal injury. Experimental studies show that SIRT1 expression increases in animal models exposed to SGLT2 inhibitors. HIFs are a family of transcription factors that regulate cellular responses to hypoxia. HIF1α and HIF-2α are isoforms of HIFs that are upregulated by hypoxia and promote gene expressions that enhance oxygen delivery and reduce oxygen consumption. HIF1α activation increases inflammation, fibrosis, angiogenesis. Activation of HIF-2α decreases inflammation, fibrosis and increases erythropoietin production. In diseases of overnutrition, such as DM and obesity, HIF1α is hyperactivated, and HIF-2α is suppressed in renal tissues promoting inflammation and fibrosis. SGLT2 inhibition suppresses hypoxia-induced HIF-1α expression in proximal convoluted tubules, reduces tubular injury and interstitial fibrosis. In addition, SGLT2 inhibitors can also increase HIF-2α expression by SIRT1-dependent mechanism. Thus, SGLT2 inhibitors protect the kidney by restoring the balance between HIF-1α and HIF-2α expression in renal cells.

SGLT2 inhibitors decrease the loss of podocytes produced by albumin loading. They also prevent infiltration of macrophages into renal tissue and their differentiation into profibrotic subtypes. Overactivity of the sympathetic nervous system contributes to CKD progression,

shows an unfavourable prognosis and is improved by treatment with SGLT2 inhibitors. Increased central sympathetic outflow contributes to increased heart rate and BP, LVH (left ventricular hypertrophy), CVD (cardiovascular disease). SGLT2 expression is increased in PCT (proximal convoluted tubule), NH1 (NA+/H+ exchanger isoform 1) is activated in myocardium and NH3 (NA+/H+ exchanger isoform 3) in the PCT.

SGLT2 inhibitors attenuate the effects of increased sympathetic tone by stimulating natriuresis, lowering BP, inhibiting NH3 activity, improving arterial and endothelial function. Improvement of vascular health and microvascular function by SGLT2 inhibitors is accomplished by decreasing arterial stiffness, decreasing endothelin-1, improving endothelial function, reducing reactive oxygen species, and increasing endothelium-derived nitric oxide.

1.6. Theoretical aspects of iSGLT2 in T2DM

This chapter of the paper highlights theoretical aspects of SGLT2 inhibitors. Indications, clinical trials and their results, mechanism of action, pharmacokinetics, mode of administration, adverse effects, contraindications, toxicity are analysed. The treatment monitoring subchapter includes warnings on blood pressure control (risk of volume depletion), risk of ketoacidosis with blood glucose <250mg%, serum creatinine. A decrease in eGFR should be anticipated at treatment initiation, which is not an indication for discontinuation of the SGLT2 inhibitor if the decrease is below 30% due to progression of chronic kidney disease, subsequently improved.

2. Personal contributions

The second part of the paper, "Personal Contributions" includes 4 research studies.

2.1. Research Study I

We conducted a retrospective population-based cohort study of adults aged ≥66 years with diabetes who had recently undergone SGLT2 inhibitor therapy in an outpatient setting. The study was conducted in Bucharest, between July 1, 2021 and August 30, 2023, using healthcare-related databases in Bucharest.

We chose the DPP4 inhibitors as a control because they are also a first, second and third line drug for diabetes and, unlike SGLT2 inhibitors, have no known risk of AKI.

The primary outcome of the research was requiring secondary care (hospitalization or ED presentation) due to AKI, defined by the 2012 KDIGO 2012 thresholds: ≥50% increase in SCr concentration from baseline or an absolute increase of at least 27 μmol/L (0.3 mg/dL) or receiving dialysis for AKI. As secondary outcomes, we assessed hospital admissions for AKI and hospital events with moderate to severe AKI (SCr increase meeting the KDIGO threshold of stage 2 or more)

In this population-based cohort study of older adults, there was no higher risk of AKI in new users of SGLT2 inhibitors compared with DPP4 inhibitors in any analysis.

2.2. Research Study II

This study aimed to explore the factors affecting physicians caring for patients with diabetes mellitus and ASCVD/CKD in the public healthcare setting in prescribing iSGLT2 to patients with diabetes mellitus using a qualitative approach. A qualitative research using semi-structured interviews was conducted from January to May 2023 in four hospitals in Bucharest, CF2 Clinical Hospital Bucharest, Colentina Clinical Hospital, Elias University Emergency Hospital, "Sfânta Maria" Clinical Hospital.

Interviews were conducted with 17 doctors caring for patients with diabetes. Four general themes were identified: prior knowledge and practice patterns influencing prescribing, balancing risks and benefits, physicians' professional responsibilities, and system barriers. The most prominent barrier found in the research study was lack of understanding that the cardio-renal benefits of iSGLT2 were independent of glycaemic control.

2.3. Research Study III

Research Study III aims to describe the role of type 2 sodium-glucose cotransporter type 2 inhibitors in the treatment of diabetes mellitus. The information needed to write this research study was conducted in the first semester of 2023. It was obtained from the evaluation of various reviews, research and web pages, which were generally less than 10 years old, in Romanian or English. As a conclusion, although they constitute a pharmacologic group that can be used as monotherapy, SGLT2-I are generally used as adjuvants in the treatment of

patients with T2DM who are already receiving pharmacologic treatment with other regular or hypoglycaemic drugs, if they have not achieved control targets.

2.4. Research Study IV

This study aims to report personal experience with the use of this type of medication in type 2 diabetics treated as outpatients. We selected 77 patients with type 2 diabetes mellitus aged 59 ± 11 years (45 men) who started iSGLT2 on the advice of their treating physician. This was an observational outpatient study, performed on patients treated at the C.F. 2. Hospital Clinic, Bucharest. The conclusion of this study is that the metabolic and extra-glycaemic effects of SGLT2 inhibitors in the study group of patients with T2DM are consistent with those observed in international studies and, therefore, it is very likely that the new evidence obtained in relation to this pharmacologic class can be extrapolated to our population in the future.

3. Conclusions

In conclusion, iSGLT2 is characterized by beneficial effects confirmed by large clinical studies on the kidney and the heart. However, sodium-glucose 2 cotransporters are also found, in comparatively small percentages, in other major organs such as muscle, brain and thyroid. It thus proves that exploring the impact of this therapy on individuals holistically is a modern necessity.

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