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Role of SGLT-2 Inhibitors in Ultrafiltration Failure in Peritoneal Dialysis: A Narrative Review

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Abstract

Purpose of review: Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are glucose lowering agents with protective effects on cardiovascular health and the ability to slow chronic kidney disease (CKD) progression. The benefits of SGLT-2 inhibitors have not been studied in patients with advanced CKD or on maintenance dialysis. Ultrafiltration failure is a common reason for failure of peritoneal dialysis (PD). Glucose transporters, such as SGLT-2, are involved in the progression to ultrafiltration failure, and hence, SGLT-2 inhibitors might be beneficial in patients on PD to prevent ultrafiltration failure.
Source of information: Here, we review data from animal models and ongoing clinical trials of SGLT-2 inhibitors in advanced CKD, as well as considerations for a phase III trial in patients on PD.
Methods: A literature search was conducted and information on clinical trials was obtained from clinicaltrials.gov.
Key findings: Animal models of PD have shown upregulation of glucose transporters in the peritoneal membrane and a potential effect of SGLT-2 inhibitors on glucose absorption and ultrafiltration. Several clinical trials are currently ongoing with SGLT-2 inhibitors in patients on PD. We discuss their study designs and propose a mixed-methods, patient-centered approach to studying SGLT-2 inhibitors in PD patients. We also discuss the potential implications of SGLT-2 inhibitors on people living with kidney failure, especially in remote communities.

Abrégé

Motif de la revue: Les inhibiteurs du cotransporteur sodium-glucose de type 2 (SGLT-2) sont des hypoglycémiants qui ont des effets protecteurs sur la santé cardiovasculaire et qui peuvent ralentir la progression de l'insuffisance rénale chronique (IRC). Les effets bénéfiques des inhibiteurs du SGLT-2 n'ont pas été étudiés chez les patients atteints d'IRC de stade avancé ou sous dialyse d'entretien. L'échec de l'ultrafiltration est une cause fréquente d'échec de la dialyse péritonéale (DP). Les transporteurs de glucose comme les SGLT-2 sont impliqués dans l'évolution vers l'échec de l'ultrafiltration; les inhibiteurs du SGLT-2 pourraient, par conséquent, être bénéfiques pour prévenir l'échec de l'ultrafiltration chez les patients sous DP.
Source de l'information: Nous avons examiné les données provenant des modèles animaux et des essais cliniques en cours sur les inhibiteurs du SGLT-2 en contexte d'IRC avancée, de même que les paramètres d'un essai de phase III chez des patients sous DP.
Méthodologie: Une recherche de la littérature a été effectuée et les informations sur les essais cliniques en cours ont été obtenues à partir de clinicaltrials.gov.
Principales observations: Les modèles animaux de DP ont montré une régulation positive des transporteurs de glucose au niveau de la membrane péritonéale et un possible effet des inhibiteurs de SGLT-2 sur l'absorption du glucose et l'ultrafiltration. Plusieurs essais cliniques sur les inhibiteurs du SGLT-2 sont en cours chez des patients sous DP. Nous discutons de leurs plans d'étude et nous proposons une approche mixte, centrée sur le patient, pour étudier les inhibiteurs du SGLT-2 chez les patients sous DP. Nous discutons également des implications potentielles des inhibiteurs du SGLT-2 pour les personnes vivant avec une insuffisance rénale terminale, en particulier dans les communautés éloignées.

Keywords

SGLT-2 inhibitor, peritoneal dialysis, ultrafiltration failure, proof-of-concept study, animal models

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Introduction

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors were initially developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus. Subsequently, they were found to protect against cardiovascular events and to slow down the progression of chronic kidney disease (CKD) in people with and without CKD at baseline.[1,2] However, SGLT-2 inhibitors have not been studied in patients with advanced CKD, including those with kidney failure on maintenance dialysis.

Peritoneal dialysis (PD) is a kidney replacement therapy technique with important medical and logistical advantages. It provides efficient fluid removal without rapid fluid shifts and can be better tolerated hemodynamically, especially in patients with concomitant heart failure.[3] In addition, PD is associated with better preservation of residual kidney function,[4] improves quality of life,[5,6] provides higher patient autonomy,[7] and has a significantly lower cost, compared with in-center hemodialysis (HD).[8,9]

Ultrafiltration (UF) failure is a common cause of technique failure in PD.[10] Chronic exposure of human peritoneal mesenchymal cells to glucose-based PD fluids is an important underlying pathophysiological mechanism of UF failure and is mediated by increased transport of glucose through upregulated glucose transporters.[11] This review aims to discuss the rationale of a proof-of-concept mechanistic study of SGLT-2 inhibitors in PD and the possible clinical implications of such a study.

Methods

A comprehensive literature search was conducted and information on clinical trials was obtained from clinicaltrials.gov.

Results

Sodium-Glucose Co-Transporter-2 Inhibitors Expression in the Peritoneum and Animal Models

The SGLTs, which comprise a family of at least 6 different isoforms in humans, co-transport glucose and sodium simultaneously into the cells using the sodium concentration gradient. Sodium-glucose co-transporter-1 (SGLT-1) is responsible for glucose absorption—although with low capacity—in the small intestine, prostate, testis, trachea, heart, and skeletal muscle. On the contrary, SGLT-2 is responsible for glucose reabsorption in the kidney.[12] The SGLT-2 is mainly expressed in the S1 segment of the proximal convoluted tubule on the luminal side, where it reabsorbs >90% of the glucose filtered in the glomerulus. The glucose in the tubule that escapes SGLT-2 is reabsorbed in the more distal segment 2 of the proximal convoluted tubule and segment 3 of the proximal straight tubule via SGLT-1. Overall, SGLT-2 inhibition results in excretion of 50% to 60% of glucose, due to upregulation of SGLT-1.[12]

The SGLT-1 and SGLT-2 are both expressed on the apical site of the peritoneal membrane, mainly in the single mesothelial cell layer. This was seen in peritoneal biopsies of healthy controls, pre-dialysis patients, and patients on dialysis, and similarly in mice and rats using immunohistochemistry.[13] Another group also reported evidence of SGLT-2 expression in the peritoneal membrane on an RNA and protein level.[11] Protein expression was comparable in healthy patients, patients with CKD, and patients on PD; however, protein expression was significantly enhanced in patients with complications, such as encapsulating peritoneal sclerosis,[11] indicating that glucose uptake might be an important driver of this phenomenon. In mouse models, SGLT-2 expression has also been reported to be upregulated if they have been receiving high-glucose PD fluid.[13]

Several trials in rats[14-19] and also in a PD mouse model[13] on the role of SGLT-2 inhibitors in PD have been performed. Overall, some of these studies showed a decrease in mesothelial fibrosis and reported improved UF.[13,14] This is in contrast with a more recent study using the same rat model, where empagliflozin, a selective SGLT-2 inhibitor, did not reduce glucose uptake during PD; however, phlorizin, a combined SGLT-1/2 inhibitor, was effective in reducing glucose uptake and improving ultrafiltration.[15] A follow-up study showed that some of the effects of phlorizin were due to nonspecific inhibition of different glucose transporters, GLUTs—other possible targets that are under development.[15,16] In addition, other mechanistic studies in rats showed that SGLT-2 inhibitors might decrease peritoneal fibrosis via suppressing transforming growth factor (TGF)-β/Smad1 signaling.[18,19] In diabetic nephropathy, SGLT-2 inhibitor luseogliflozin was shown to inhibit hypoxia-induced hypoxia-inducible factor 1-alpha (HIF-1α) accumulation by suppressing mitochondrial oxygen consumption.[20]

Current Status of Clinical Research on Sodium-Glucose Co-Transporter-2 Inhibitors in Peritoneal Dialysis and Ongoing Clinical Trials

For patients with kidney failure on PD, UF failure is a common cause of technique failure and subsequent transfer to

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Table 1. Current Evidence and Ongoing Trials With SGLT-2 Inhibitors in Peritoneal Dialysis in Humans.

Study	Design	Participants	Intervention	Primary outcome
Hamdan et al[23]	Prospective interventional cohort study (pre-post)	Prevalent PD patients (N = 20)	Dapagliflozin 10 mg daily for 30 days	Changes in PET parameters
PRESERVE (NCT05250752)	Prospective interventional cohort study (pre-post)	PD patients (N = 10)	Dapagliflozin 10 mg daily for 3 days	D4/D0 ratio
EMPA-PD (NCT05671991)	Crossover randomized study[a]	PD patients with residual urine output ≥400 mL/24 h (N = 30)	Empagliflozin 25 mg (single dose) or placebo	Total glucose absorption
EMPOWERED[24] (jRCTs051230081)	Crossover randomized study	PD patients with heart failure (N = 36)	Empagliflozin 10 mg or placebo for 8 weeks	Change in daily UF volume from baseline
CANARY (NCT05715814)	Single-arm, open-label study	PD patients with residual renal function[b]	Empagliflozin 25 mg daily for 2 weeks	Change in measured GFR from baseline
RENAL LIFECYCLE (NCT05374291)	Randomized controlled trial	PD patients with residual urine output >500 mL/24 h (N = 100)[c]	Dapagliflozin 10 mg daily or placebo	Mortality or heart failure hospitalization

Note. SGLT-2 = sodium-glucose co-transporter 2; PD = peritoneal dialysis; N = number of participants; PET = peritoneal equilibration test; D4/D0 = ratio of 4 hours to 0 hours dialysate glucose; UF = ultrafiltration; GFR = glomerular filtration rate.
[a]This study will be followed by an open-label extension phase with empagliflozin 10 mg once daily for 8 weeks for all participants.
[b]Defined as a urine output of at least 250 mL/24 h and a measured glomerular filtration rate of at least 2 mL/min/1.73 m^2.
[c]Substudy of the main trial (which will include participants with an estimated GFR ≤ 25 mL/min/1.73 m^2).

HD.[10] Although much less frequent, UF failure also occurs in children on long-term PD.[21] The UF failure is defined as failure to achieve at least 400 mL of net UF during a 4-hour dwell using 2 L of a 4.25% dextrose PD solution. Most cases are due to type 1 UF failure characterized by rapid diffusion of solutes, resulting in good clearance but poor UF due to rapid loss of the osmotic gradient across the peritoneal membrane.

As detailed above, preclinical studies in rat models of PD have shown upregulation of glucose transporters in the peritoneal membrane and a potential effect of SGLT-2 inhibitors on glucose absorption from peritoneal mesenchymal cells.[13,14,17-19] Therefore, blocking the overexpressed SGLT-2 receptors in the peritoneal membrane would result in reduced uptake of dialysate glucose from the membrane, increased glucose concentration in the dialysate, increased UF, and ultimately prevention of chronic fibrotic changes leading to UF failure. Similarly, other glucose transporters like SGLT-1 and GLUT1 contributed to fibrosis in a PD rat model.[22] The phenotype was mitigated by treatment with phloretin, a potent GLUT1 inhibitor.[22] The SGLT-2 inhibitors might be an encouraging therapy option, but combined blockage of SGLT-2 with other glucose transporters might be needed to optimize outcome.[15,22]

The encouraging results achieved in animal studies have resulted in several small clinical trials (see Table 1). Hamdan et al[23] recently tested the effect of SGLT-2 inhibitors in a pilot trial in 20 patients on continuous ambulatory PD. All patients received 10 mg of dapagliflozin once daily for 30 days. A modified peritoneal equilibration test (PET) was performed at baseline and at the end of the study period. There was no difference in the ratio of dialysate glucose at 4 hours and at 0 hours in the modified PET (D4/D0 ratio) before and after treatment with dapagliflozin. However, there was wide variation in patient response to treatment with 13 patients having an increase and 7 patients having a decrease in D4/D0 ratio from baseline. It remains unclear which factors may influence response to treatment and whether there is a difference in baseline transporter status of responders vs non-responders.

Several clinical trials are currently ongoing with SGLT-2 inhibitors in patients on PD. The first study (NCT05250752) from Denmark will enroll 10 participants on PD for at least 2 weeks who will receive dapagliflozin 10 mg daily for 3 days. The primary outcome will be glucose uptake by the peritoneum at the beginning and the end of the study, as expressed by the D4/D0 ratio. The current status of this study, initially posted in 2021, is unclear. The second study (NCT05671991) from Yale University will enroll 30 patients on stable PD prescription for at least 3 months who have residual urine output of at least 400 mL/24 h and are treated with loop diuretics. Participants will be randomized to receive each of the following treatments in random order: single dose of empagliflozin 25 mg or matching placebo. Subsequently, all participants will enter an open-label extension phase with empagliflozin 10 mg once daily for 8 weeks. The primary outcome will be total glucose absorption with empagliflozin vs placebo on day 0 and day 63. Secondary outcomes include UF volume, natriuresis, change in PET parameters, and change in peritoneal fluid inflammatory biomarkers. The study is currently actively recruiting participants.

A third clinical trial (jRCTs051230081) from Japan will enroll 36 patients with clinically diagnosed heart failure and kidney failure on PD for at least 3 months (EMPOWERED trial).[24] Patients will be randomized to receive empagliflozin 10 mg daily or matching placebo, each for 8 weeks, in random order, with a 4-week washout period between the 2 interventions. The primary endpoint is the change in daily ultrafiltration volume from baseline in each intervention period. Secondary outcomes include changes in heart failure biomarkers, PET parameters, and anemia-related parameters.

Finally, the meChANisms and sAfety of SGLT-2 Inhibition in peRitoneal dialysis (CANARY) study will enroll 20 patients on stable PD prescription with residual kidney function, defined as a urine output of at least 250 mL/24 h and a measured glomerular filtration rate (GFR) of at least 2 mL/min/1.73 m^2 (NCT05715814). In this single-arm, open-label study, all patients will receive 25 mg of empagliflozin once daily for 2 weeks. The primary endpoint is the change in measured GFR before and 2 weeks after empagliflozin initiation, as determined from the average creatinine and urea clearance from a 24-hour urine collection. Secondary outcomes will include changes in ultrafiltration volume, PET parameters, blood pressure, urine excretion of sodium, and safety parameters. The study is not yet recruiting participants.

Although there is limited clinical experience with SGLT-2 inhibitors in kidney failure, pharmacokinetic data are suggestive of a favorable safety profile with these agents in this setting.[25,26] The SGLT-2 inhibitors induce a dip in GFR that is reversible after discontinuation. The exact clinical relevance of this phenomenon in patients already on PD is unknown. It is possible that attenuation of hyperfiltration with these agents might be nephroprotective with preservation of residual kidney function for a longer time period. However, this has not yet been studied. Furthermore, SGLT-2 inhibitors are associated with a higher incidence of fungal genital infections. Nevertheless, glucose excretion in the failing kidney may be severely compromised, and the frequency of this common side effect might be less than expected in patients with kidney failure.

Another important consideration is drug administration. Although the oral route is more convenient, patients with kidney failure have a high pill burden, which may affect compliance. Therefore, intraperitoneal administration presents important advantages. Balzer et al[13] delivered dapagliflozin intraperitoneally in C57Bl/6N mice. As dapagliflozin is easily soluble in aqueous solution, no vehicle was required. There are no studies with intraperitoneal administration of SGLT-2 inhibitors in humans.

A definite answer on the potential clinical utility and safety of SGLT-2 inhibitors in PD can only be provided by an event-driven multicenter phase III randomized study. However, more evidence from proof-of-concept mechanistic studies in patients with kidney failure is required before such a trial can be designed. Importantly, these studies need to include patients from diverse ethnic backgrounds and pediatric patients with kidney failure.

Next Steps for Studying Sodium-Glucose Co-Transporter-2 Inhibitors in Peritoneal Dialysis Patients in a Multidimensional Way

Given Canada's vast geographical expanse, the advantages of PD are particularly significant for patients residing in remote areas or those facing challenges accessing dialysis centers regularly, as well as in the notable reduction in travel expenses and health care infrastructure costs. PD offers Canadian patients with a unique, home-based, and flexible alternative to in-center HD, potentially providing greater cost-effectiveness. Studying SGLT-2 inhibitors in individuals receiving PD presents an innovative approach to advancing our understanding and guiding patient care and health policies. These studies may involve (1) a trial to evaluate their clinical effects, (2) investigation of biological markers to better understand their mechanisms in this patient population, and (3) a mixed-methods, patient-centered approach to assess the potential benefits and acceptance of SGLT-2 inhibitors. Combining these studies with careful research designing can enhance cost-effectiveness but often requires interdisciplinary collaboration among researchers.

"Hard outcomes" to assess clinical effects of sodium-glucose co-transporter-2 inhibitors in peritoneal dialysis patients. Although several clinical trials have explored SGLT-2 inhibitors in patients with less severe CKD,[1,27-29] there is a lack of studies in patients with advanced CKD or on dialysis. The only event-driven study in this population is the RENAL LIFE-CYCLE Trial (NCT05374291), an ongoing randomized control trial to assess the effect of dapagliflozin on kidney and cardiovascular outcomes in patients with severe CKD (eGFR $\leq$25 mL/min per 1.73 m^2). One substudy of this trial is to study the treatment effect on cardiac function in a subset of 100 patients treated with peritoneal dialysis, who must have a residual diuresis $>$500 mL/24 h at 3 months after the start of dialysis. When designing a clinical trial to assess the effect of SGLT-2 inhibitors in patients on peritoneal dialysis, hard clinical endpoints should include mortality and cardiovascular events (myocardial infarction, stroke, or hospital admission for heart failure), as done with these agents in the general population or mild-to-moderate CKD.[1] In addition, clinical outcomes may include core outcomes of PD infection and technique survival, which have been established by the Standardised Outcomes in Nephrology-Peritoneal Dialysis (SONG-PD) study.[30] Assessing the effect of SGLT-2 inhibitors on the duration of effective peritoneal dialysis may help determine whether the intervention affects time on peritoneal dialysis (eg, less likely to switch to HD).

Biological markers to assess mechanisms of action. Monitoring changes in residual kidney function, urine flow rate, and solute clearance can provide insights into these drugs' potential protective effects on the kidneys. Given that hypertension and diabetes are prevalent in people with kidney failure and the known antihyperglycemic and antihypertensive effects of SGLT-2 inhibitors,[12] investigating blood pressure control, glycemic control, metabolic parameters, and biomarkers of inflammation can enhance our holistic understanding of SGLT-2 inhibitors' mechanisms in PD patients.

Mixed-methods, patient-centered approach. This approach may involve qualitative exploration of patients' and clinicians' perspectives on the value of SGLT-2 inhibitors in PD and acceptance and tolerance of these medications. Semi-structured interviews with patients and clinicians involved in the care of PD patients may elucidate perceptions, attitudes, benefits, concerns, side effects, and adherence behavior. Incorporating a range of functional, symptomatic, and patient-reported outcomes in clinical trial designs, such as dyspnea scores and quality-of-life assessments, can provide a comprehensive understanding of SGLT-2 inhibitors' role in PD management. For example, due to the high burden of cardiovascular comorbidity in peritoneal dialysis patients, dyspnea scores may be used to assess the treatment effects on heart failure symptoms, the Kansas City Cardiomyopathy Questionnaire (KCCQ) to evaluate heart failure–related health status, and the distance in 6-minute walk test to evaluate the impact of SGLT-2 inhibitors on cardiovascular endurance. Because dialysis patients usually have worse health-related quality of life than the general healthy population,[31] surveys and questionnaires, such as the Kidney Disease Quality of Life (KDQOL), can be used to capture various aspects of physical, mental, and social well-being.[32]

Benefits to the Community and the Society

Peritoneal dialysis has many benefits including lower cost,[9] it improves patient quality of life[5,6] and allows for more patient autonomy,[9] which makes PD the ideal method for patients with kidney failure living in remote communities. Therefore, reducing technique failure and keeping more patients on peritoneal dialysis for a longer time period has important implications from a population health perspective. Increasing uptake of PD has been a focus of many recent government initiatives in Canada;[33] however, the national and provincial uptake is still low.[34] Barriers include lack of knowledge about PD and its potential benefits, misinformation about PD, and reluctance to learn a new treatment modality.[34] In addition, UF failure is reported as a significant challenge leading to hospitalizations and the need for travel. With the utilization of SGLT-2 inhibitors, these risks can likely be reduced, thereby addressing the geographical and access to care barriers reported among the rural and remote communities.[6,35] Prasad et al[34] reported that many First Nation communities in Saskatchewan are located hundreds of kilometers away from a nearest HD unit, and the median travel distance is 137 km between their home and the HD unit. Thus, the First Nations, Inuit and Métis (FNIM) communities can particularly benefit from PD through improved "at-home" care within their local communities[6] in comparison to far-off institutional settings.[35] This will improve their access to kidney care and transplant that has been reported to be reduced among the FNIM communities in Canada.[35,36]

Outlook/Conclusion

In conclusion, animal models have been encouraging and solidified the need to investigate the role of SGLT-2 inhibitors in PD. In addition to their theoretical benefits at the cellular levels, these agents could also possibly affect technique survival, residual kidney function, and cardiovascular endpoints in this population. The time is ripe for human mechanistic and clinical trials to study the physiologic and clinical effects of glucose transport inhibitors in pediatric and adult patients on PD.[37] Results from these studies might significantly affect the management of patients on PD and might prove particularly helpful for those in remote communities who mostly benefit from this technique.

Ethics Approval

Not applicable.

Consent to Participate

Not applicable.

Consent for Publication

All authors reviewed the final manuscript and provided consent for publication.

Availability of Data and Materials

Not applicable.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Mavrakanas has received speaker honoraria from Bayer, BMS Canada, Janssen, Astra Zeneca, and Pfizer, and has served on advisory boards for Boehringer Ingelheim, Bayer, GSK, and Servier outside the submitted work. He has also received research grants from Astra Zeneca and Pfizer. The remaining authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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