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Heart Transplant Recipients: A New Test for Gliflozins

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THE COMPLEX CARE OF PATIENTS AFTER HEART TRANSPLANT

The current gold standard therapy for patients with advanced heart failure (HF) is heart transplantation.[1] Patients with a prior heart transplant are at high risk of various multiorgan complications, requiring specifying care. Currently, there is limited evidence on preventing and treating these conditions. Gliflozins have recently been introduced in the standard care for patients with HF, type 2 diabetes (T2D), and chronic kidney disease (CKD), as they have been shown to substantially improve outcomes in these patients.[2-4] Additionally, preclinical studies in the context of heart transplantation suggest a cardioprotective effect of these drugs during the cold storage of the donor heart.[5] These discoveries may assist in enhancing the quality of care for heart transplant recipients.

CURRENT ROLE OF GLIFLOZINS IN NON–HEART TRANSPLANTED PATIENTS

The mechanism of action that gives gliflozins their name is the inhibition of sodium/glucose cotransporter-2 (SGLT2), but their effects on several other important signaling pathways have also been demonstrated and are critical to their multiorgan benefit.[6] The effects of SGLT2 inhibitors (SGLT2-i) on the outcomes of noncardiovascular diseases, such as T2D and CKD, are highly relevant for HF specialists treating heart transplanted patients because these are unfortunate events following heart transplantation that are favored by the specific drugs required at this stage. However, the main trials on gliflozins excluded patients with previous solid organ transplantation. The available data from clinical trials show that gliflozins reduce the decline in glomerular filtration rate (GFR) both in patients with HF (with or without CKD) and patients with CKD.[2,3] Additionally, gliflozins play an intuitive role in the glycemic control of patients with T2D, another problem often faced after heart transplantation.[4] SGLT2-i have also been shown to have a positive effect on anemia, both preventing and improving hemoglobin levels in patients with HF.[7] Finally, a stunning impact of SGLT2-i on the prognosis of patients with HF has been demonstrated, which is a nonnegligible long-term complication in heart transplant recipients.[2]

ROLE OF GLIFLOZINS AFTER HEART TRANSPLANTATION

Immunosuppressive therapy, especially calcineurin inhibitors, can promote several long-term complications in heart transplant recipients, such as CKD, T2D, anemia, and cancer. Severe kidney disease occurs in 25% of patients 5 y after heart transplantation and is linked with HF syndrome before heart transplant, perioperative kidney injury, and, above all, the use of calcineurin inhibitors.[8] The latter mechanism is quite complex and includes the oxidative stress produced in the kidney's interstitium, the afferent arteriole hyalinosis, T2D, and glomerular sclerosis.[9] In this perspective, it was initially hypothesized that SGLT2-i would reduce the progression of renal failure by reducing intraglomerular pressure, with a vasoconstrictive effect on the afferent arteriole and a vasodilatory effect on the efferent arteriole. However, this theory has recently been challenged by Professor Packer as, soon after initiation of gliflozins therapy, patients with renal dysfunction experience a smaller initial reduction in GFR related to the changes in intraglomerular hemodynamics, as they have a smaller number of active glomeruli. Nevertheless, these patients receive the same benefit in terms of renal protection as those with normal renal function, reflecting

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the minor role of intraglomerular hemodynamics in renal protection.[6] This hypothesis is further supported by the beneficial effects on renal function in mice in which SGLT2 was knocked out, prompting that the pharmacological inhibition of SGLT2 cannot be the main mechanism of renal protection.[10] This is a crucial information to apply to calcineurin inhibitor–mediated kidney damage. Previous studies have shown that calcineurin inhibitors reduce the activity of sirtuins in the kidney, which supports the oxidative-mediated renal injury caused by these drugs.[11] Thus, the antioxidant effect of gliflozins, mediated by the direct modulation of sirtuins and mechanistic target of rapamycin (mTOR) activity, may straight counteract the progressive deterioration of renal function in heart transplant recipients. Concerning posttransplant T2D (PTDM), occurring in >20% of patients in the short-medium term, inhibition of SGLT2 directly reduces glycemia (providing supplemental protection for renal function), but a further mechanism of gliflozins might be essential in treating PTDM. Indeed, the occurrence of PTDM has been shown to be closely related to the increased activity of mTOR caused by calcineurin inhibitors, resulting in a toxic effect on pancreatic beta-cells and reduced insulin secretion.[12] The downregulatory effect of gliflozins on mTOR activation could precisely counteract this pathological pathway and form the basis for a positive prognostic effect. HF is a long-term complication after heart transplantation. The pathophysiology of HF in this context is related to cellular and antibody rejections, coronary allograft macro- and microvasculopathy, and consequent oxidative stress and myocardial fibrosis.[13] Also, the cytoplasmic concentration of calcium and sodium is usually higher in failing ventricles, and the increased activity of the sodium/hydrogen exchanger could worsen this mechanism.[14] According to current theories and evidence, gliflozins reduce oxidative stress in patients with HF, restore physiologic mitochondrial function, downregulate proinflammatory pathways and sodium/hydrogen exchanger activity, improve endothelial function, and preserve cellular integrity.[6] These actions may powerfully contrast the autoimmunity-related fibrosis on transplanted hearts and the consequently reduced heart function. Finally, the risk of anemia in heart transplant recipients is high, with a pathophysiological role played by antiproliferative immunosuppressive therapy, reduced production and attenuated response to erythropoietin, and reduced absorption and utilization of nutrients. After ruling out other common causes of anemia (eg, gastrointestinal bleeding, nutrient deficiencies), gliflozins could be of help. Indeed, the lower incidence/severity of anemia in patients in the SGLT2-i arms of clinical trials appears to be related to increased synthesis of erythropoietin, erythrocytopoiesis as a typical response to nutritional deprivation, improved nutrient utilization, and reduced renal oxidative stress, all factors that could directly counteract the mechanism of post–heart transplant anemia[7] (Figure 1). Whether gliflozins effectively improve clinical outcomes in these patients should be tested in clinical trials.

POTENTIAL COMPLICATIONS OF GLIFLOZINS IN HEART TRANSPLANT PATIENTS

Heart transplant recipients are a particularly frail population, and any therapy can lead to complications, which in some cases can be severe. First, there are no pharmacokinetic interactions between glflozins and any major immunosuppressive drugs currently used for prophylaxis of heart transplant rejection. The presence of glucose in the urine of all patients treated with SGLT2-i, regardless of the presence of T2D, increases the risk of urinary tract infection (UTI), which could be even higher in patients on immunosuppressive therapy. The evidence of UTIs in retrospective experiences focusing on transplanted patients treated with gliflozins for T2D is quite contrasting. In an analysis of 22 patients after heart transplantation who received gliflozins for T2D, none of the patients reported UTI.[15] In contrast, in a study of 316 post–kidney transplant patients treated with SGLT2-i, it was reported that 14% of the sample had a UTI, with female gender and a history of UTI being a risk factor.[16] A systematic review, predominantly focusing on patients after kidney transplant, sporadically reported cases of UTI, diabetic ketoacidosis, and acute kidney injury.[17] Finally, patients requiring immunosuppressive therapy have

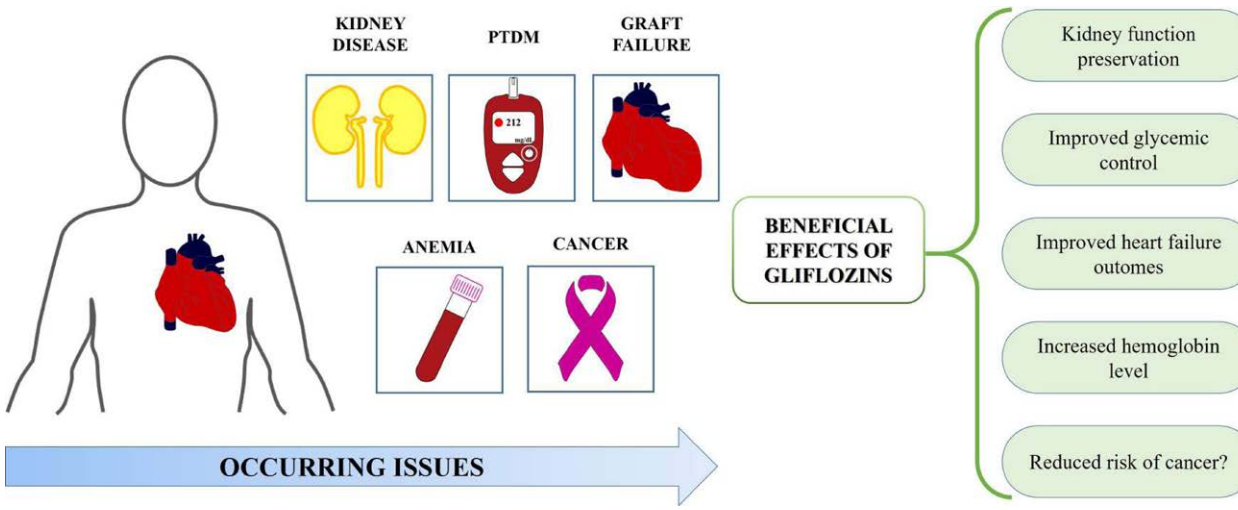

FIGURE 1. Heart transplant recipients during the follow-up are exposed to an increased risk of complications, including CKD, PTDM, and HF due to graft failure, anemia, and cancer. Gliflozins showed improved outcomes in all these conditions in non–heart transplant recipients. CKD, chronic kidney disease; HF, heart failure; PTDM, posttransplant type 2 diabetes.

a higher risk of developing cancer. The role of gliflozins in this risk has not been investigated in targeted clinical trials. A large meta-analysis of clinical trials has shown that the risk of cancer is not modified by treatment with gliflozins compared with other antidiabetic agents, apart from a possible protective role in gastrointestinal cancer and a potential higher risk of bladder cancer.[18] However, this point requires focused prospective research.

CURRENT EVIDENCE AND ONGOING INVESTIGATIONS

The outcomes investigated in studies on gliflozins in this setting are quite weak, and only retrospective registry studies are available. A previous analysis in kidney transplant recipients with diabetes has shown that gliflozins improve metabolic parameters, including blood pressure, glycemic control, body weight, and uric acid, alongside a reduction in urinary protein levels and an increase in hemoglobin and serum magnesium.[16] Studies in heart transplant recipients treated with SGLT2-i are limited to a small sample size in which a reduction in body weight and daily dose of diuretics were demonstrated over a follow-up period of 12 mo.[15] A randomized, placebo-controlled, double-blind clinical trial, the DAPAgliflozin for Renal Protection in Heart Transplant Recipients trial (DAPARHT trial), is currently ongoing, recruiting patients who have a GFR of ≥25 mL/min/1.73 m^2 at least 1 y after heart transplantation with or without PTDM.[19] The main outcome will be the efficacy of gliflozins in the prevention of GFR deterioration after 12 mo of follow-up. Empagliflozin will be tested in another randomized clinical trial, the EMPA-HTx, which will evaluate the safety and efficacy of early initiation of empagliflozin (6–8 wk after heart transplantation). The primary endpoint will be the change in glycosylated hemoglobin, whereas renal function and cardiac fibrosis will be assessed as secondary endpoints.[20]

CONCLUSIONS

Gliflozins have a dramatic impact on the outcomes of comorbidities commonly seen in heart transplant recipients. These benefits are due to mechanisms that may directly counteract the pathophysiology underlying heart transplant complications. Prospective clinical trials are currently ongoing to determine whether SGLT2-i offer a new perspective.

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