Review

The Therapeutic Target of SGLT2 Inhibitors and GLP-1 Agonists Is Superoxide Induced Diuretic Resistance

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The Therapeutic Target of SGLT2 Inhibitors and GLP-1 Agonists Is Superoxide Induced Diuretic Resistance

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Abstract: Diuretic resistance is a servomechanism involving superoxide that results from the use of escalating doses of diuretics in the treatment of heart failure. Without intervention this may lead to increased heart failure mortality. Recent heart failure studies involving the use of SGLT2 inhibitors and GLP-1 agonists have shown reductions in the need for loop diuretics along with reductions in hospitalizations for heart failure and cardiovascular mortality. Multiple mechanisms have been proposed to explain the benefits of both these drug classes but this paper is the first to explain and propose superoxide induced diuretic resistance as a therapeutic target for the treatment of heart failure.

Keywords: superoxide; SGLT2 inhibitors; GLP-1 agonists; cardiorenal syndrome; diuretic resistance; heart failure

Introduction

This paper is a response to a recent editorial on SGLT2 inhibitors which states 'there is currently an absence of a conceptual model that explains the actions of these drugs and that they are not diuretics or natriuretic despite being found to reduce diuretic requirements in patients with heart failure" (1). It is submitted to provide a conceptual model which focuses on superoxide as a therapeutic target that explains the benefits of SGLT2 as inhibitors of diuretic resistance. Based on findings of renal superoxide suppression and recent heart failure studies showing a reduction in need for diuretics by GLP-1 agonists, this paper also provides the rationale for using SGLT2 inhibitors and GLP-1 agonists in combination in the treatment of advanced heart failure.

Heart Failure Leads to Increased Renal Superoxide Levels

Heart failure itself, unrelated and prior to treatment, leads to increased renal superoxide levels via hypoperfusion, mitochondrial dysfunction, eNOS uncoupling, and NADPH oxidase upregulation with OONO (-) formation (2,3). This leads to cardiorenal syndrome (3).

Superoxide Causes Diuretic Resistance and Increases Mortality

Superoxide has been shown to inhibit urine Na+ excretion in an animal renal medullary blood flow and renal function study (4). This leads to failure to increase urine Na+ excretion sufficient to relieve volume overload in heart failure. Over time this leads to escalating doses of loop diuretics and a servomechanism with increasing superoxide levels that, without intervention, ultimately results in death. This explains why increased doses of loop diuretics are independent predictors of total mortality and/or cause specific mortality in patients with advanced heart failure (5). And diuretic resistance explains the failure to reduce mortality of many drugs used recently to treat acute or worsening heart failure. These drugs are vasodilators that either failed to improve diuretic resistance or, more recently, made it worse (6).

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SGLT2 Inhibitors Reduce Diuretic Resistance and Mortality

Dapagliflozin has been shown to protect human proximal tubule cells from oxidative Stress (7). A recent review (8) describing the SGLT2 receptor as a site of superoxide production and its effect on Na+ handling by the proximal tubule further explains dapagliflozin's antioxidative effect. This protective effect on proximal tubule function, often confused with being a diuretic or natriuretic mechanism, serves to normalize urine Na+ excretion in response volume increases of patients with heart failure thereby avoiding resistance to the effects of high dose loop diuretics and their metabolic side effects. This results in reversal or prevention of diuretic resistance as seen by the reduction in diuretic doses needed in patients treated with empagliflozin in the EMPEROR-Preserved and EMPAG –HF trials (9,10). Furthermore, a recent meta-analysis of nine acute heat failure trials revealed a higher volume of diuresis with lower doses loop diuretics and a reduction in all-cause death with SGLT2 inhibitors (11).

GLP-1 Agonists Suppress Superoxide and Reduce Diuretic Resistance

Regarding GLP-1 agonists, GLP-1 receptor knockout mice have been found to have increased glomerular superoxide, upregulated renal NAD(P)H oxidase, and reduced renal cAMP and PKA activity (12). These changes may lead to renal pathology that would include the development of diuretic resistance. Activation of the cyclic adenosine monophosphate–protein kinase A (cAMP–PKA) pathway halts the synthesis of reactive oxygen species. GLP-1 receptor agonists activate cAMP-PKA pathway and protect against oxidative stress. Liraglutide reduced NADPH oxidase activity and increased cAMP-PKA activity in mice. It also enhanced glomerular hyperfiltration by improving glomerular nitric oxide and decreasing mesangial expansion (12,13). Reversal of diuretic resistance by semaglutide may explain the reduction in loop diuretics, improvement in heart failure related symptoms and physical limitations of patients with HFpEF seen in the STEP-HFpEF study (14).

Use of SGLT2 Inhibitors in Combination with GLP-1 Agoniists

Regarding the use of these two agents in combination, this was first suggested for the treatment of diabetes (15). And thus far there have been no randomized trials designed to look specially at heart failure that would allow the evaluation the combination in the development of cardiorenal syndrome and synergy in the reduction of loop diuretic usage in heart failure. Trials of the combination like EMPEROR-Preserved, EMPAG-HF and STEP-HFpEF are needed. However, there are three non-randomized studies that looked at heart failure hospitalizations with the combination.

The first of these studies looked at adding sulfonylureas vs SGLT2s to baseline GLP-1 agonist therapy and found SGLT2s to be superior. (16). Another study in diabetes found the combination slightly better than SGLT2 inhibitors and GLP-1 agonists used alone and that either agent used alone or in combination was better at preventing heart failure than other older anti-diabetic regimens (17). A third population-based cohort study found a 43% decrease in the incidence of heart failure with the combination vs the use of GLP-1 agonists alone. In addition there was a 57% reduction in serious renal events with the combination (18). Altogether these three studies can be viewed as "hypothesis generating" in support of a large, randomized, double blinded, placebo controlled clinical trial of the combination used in the treatment of advanced heart failure.

Summary and Conclusions

1] Despite having multiple mechanisms with potential for cardiovascular benefits, the conceptual model that best explains the benefits of SGLT2 inhibitors and GLP-1 agonists in heart failure is the reversal or prevention of diuretic resistance from increased superoxide levels seen in pathophysiology leading to the development of heart failure and the cardiorenal syndrome

2] Targeting superoxide with SGLT2 inhibitors and GLP-1 agonists reduces diuretic resistance, heart failure hospitalizations and cardiovascular mortality

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3] Randomized trials looking at additive or synergistic benefits of the combination of SGLT2 inhibitors and GLP-1 agonists on diuretic resistance, heart failure hospitalizations and mortality in heart failure are needed.

4] The therapeutic target for future drugs for heart failure should include superoxide induced diuretic resistance.

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Conflicts: none to declare

Competing interests: none

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