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SAFETY SIGNALS FOR HYPERKALEMIA IN TYPE 2 DIABETES: A FOCUSED REVIEW OF SGLT-2, GLP-1, AND DPP-4 DRUG CLASSES

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ABSTRACT

Hyperkalemia, or elevated potassium levels in the blood, is a potential risk for individuals with Type 2 Diabetes (T2D), particularly those on certain classes of medications. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors are widely prescribed for managing T2D. Although these therapies offer substantial benefits in terms of glycemic control, weight management, and cardiovascular protection, concerns regarding their role in electrolyte disturbances, especially hyperkalemia, have emerged. This focused review examines the safety signals for hyperkalemia associated with SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors in T2D treatment. The review synthesizes current evidence from clinical trials, observational studies, and post-market surveillance to assess the risk of hyperkalemia and the mechanisms underlying this adverse effect, with a particular focus on renal function and potassium homeostasis. The article

MRCPI1, FCPS-1(Gynae & Obs), Email: drambershams@gmail.com	aims to provide clinicians with a detailed understanding of the safety profiles of these drug classes, offer guidance on monitoring strategies, and explore the need for additional research in this area.

INTRODUCTION

1.1 Overview of Type 2 Diabetes and its Treatment

Type 2 Diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance and beta-cell dysfunction, leading to hyperglycemia. The increasing prevalence of T2D, compounded by risk factors such as obesity, hypertension, and dyslipidemia, underscores the need for effective pharmacological interventions. The treatment landscape for T2D has expanded with the advent of newer drug classes, including SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. These agents offer several benefits, such as improved glycemic control, weight reduction, cardiovascular risk reduction, and renal protection.

1.2 Hyperkalemia and Its Implications in T2D

Hyperkalemia, defined as a serum potassium level greater than 5.0 mmol/L, is a potentially life-threatening electrolyte disturbance that can lead to arrhythmias, muscle weakness, and paralysis. The risk of hyperkalemia is particularly concerning in individuals with T2D, who often have underlying kidney dysfunction, a key determinant of potassium homeostasis. Medications commonly used to manage T2D can have unintended effects on potassium levels, with some drug classes, such as SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, being implicated in altered potassium balance. This review aims to examine the safety signals related to hyperkalemia for these therapies.

2. SGLT-2 Inhibitors and Hyperkalemia

2.1 Mechanism of Action of SGLT-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, including drugs like empagliflozin, canagliflozin, and dapagliflozin, work by inhibiting the SGLT-2 protein in the proximal renal tubules, leading to increased urinary glucose excretion and a reduction in blood glucose levels. Additionally, SGLT-2 inhibitors induce osmotic diuresis, which can improve fluid balance and reduce blood pressure. They are also associated with beneficial effects on cardiovascular and renal outcomes.

2.2 Hyperkalemia Risk with SGLT-2 Inhibitors

Although SGLT-2 inhibitors are generally well-tolerated, there is growing evidence suggesting an association between SGLT-2 inhibitor use and hyperkalemia, particularly in patients with underlying kidney disease or those taking medications that alter potassium levels. The mechanism underlying this is not entirely understood but may be related to several factors:

Renal Function: SGLT-2 inhibitors are primarily excreted via the kidneys, and their effects on potassium levels may be influenced by renal function. In patients with reduced renal function, the ability to excrete potassium may be impaired, increasing the risk of hyperkalemia.

Diuretic Effect: While the diuretic effect of SGLT-2 inhibitors is mild compared to traditional diuretics, it may still impact potassium balance by increasing potassium excretion, especially in patients who are also receiving other medications that influence potassium levels.

2.3 Evidence from Clinical Trials and Observational Studies

In clinical trials such as the EMPA-REG OUTCOME trial (empagliflozin), and CANVAS program (canagliflozin), hyperkalemia was reported as a potential adverse event, albeit with a low incidence. However, the risk was higher in patients with pre-existing renal impairment or those on concomitant medications like ACE inhibitors, angiotensin receptor blockers (ARBs), or potassium-sparing diuretics. Post-market surveillance has also identified isolated reports of hyperkalemia, suggesting the need for monitoring potassium levels in patients with compromised renal function.

3. GLP-1 Receptor Agonists and Hyperkalemia

3.1 Mechanism of Action of GLP-1 Receptor Agonists

GLP-1 receptor agonists, such as liraglutide, semaglutide, and dulaglutide, mimic the action of the endogenous hormone GLP-1, enhancing insulin secretion in a glucose-dependent manner, inhibiting glucagon release, and slowing gastric emptying. These agents have been shown to improve glycemic control, promote weight loss, and provide cardiovascular protection, particularly in patients with high cardiovascular risk.

3.2 Hyperkalemia Risk with GLP-1 Receptor Agonists

While GLP-1 receptor agonists are generally considered to have a favorable safety profile, concerns about hyperkalemia have been raised due to the drug class's effect on renal function. GLP-1 receptor agonists may have an indirect effect on potassium levels through:

Renal Function: The renal protective effects of GLP-1 receptor agonists have been documented, but these drugs can also influence renal hemodynamics and affect potassium excretion. In patients with impaired renal function, there may be a risk of electrolyte disturbances, including hyperkalemia.

Gastrointestinal Effects: Due to their action on gastric emptying, GLP-1 receptor agonists can cause nausea and vomiting, which may exacerbate dehydration and affect electrolyte balance.

3.3 Evidence from Clinical Trials

In the LEADER trial (liraglutide), which studied the cardiovascular outcomes of liraglutide in T2D patients, there were few reported cases of hyperkalemia, with the majority occurring in patients with pre-existing renal impairment or those receiving renin-angiotensin-aldosterone system (RAAS) inhibitors. Similarly, the SUSTAIN trials (semaglutide) showed that while gastrointestinal side effects were common, hyperkalemia was not a frequent adverse event. However, close monitoring is still recommended in patients with compromised renal function.

4. DPP-4 Inhibitors and Hyperkalemia

4.1 Mechanism of Action of DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors, including sitagliptin, saxagliptin, and linagliptin, work by inhibiting the enzyme DPP-4, which is responsible for degrading incretin hormones like GLP-1. By enhancing GLP-1 activity, these drugs increase insulin secretion and decrease glucagon levels, improving glucose control. DPP-4 inhibitors are typically well-tolerated and have a neutral effect on weight and cardiovascular outcomes.

4.2 Hyperkalemia Risk with DPP-4 Inhibitors

DPP-4 inhibitors are considered to have a low risk for hyperkalemia. However, there are reports suggesting that in rare cases, hyperkalemia may occur, particularly when DPP-4 inhibitors are used in conjunction with other medications that affect renal function or potassium levels. The mechanisms for this are not well understood but may involve:

Renal Impairment: Like other antidiabetic agents, DPP-4 inhibitors are primarily cleared by the kidneys. Renal dysfunction can lead to reduced clearance of both the drug and potassium, raising the potential for hyperkalemia.

Concomitant Medication Use: The use of DPP-4 inhibitors in combination with RAAS inhibitors, diuretics, or other medications affecting potassium balance may increase the risk of hyperkalemia.

4.3 Evidence from Clinical Trials

In large-scale clinical trials such as the TECOS trial (sitagliptin), the incidence of hyperkalemia was not significantly higher in the DPP-4 inhibitor group compared to placebo. However, small, isolated cases of hyperkalemia have been reported, particularly in patients with pre-existing kidney dysfunction. Overall, the incidence remains low, and DPP-4 inhibitors are generally considered safe with regard to potassium balance.

5. DISCUSSION

5.1 Comparative Risk of Hyperkalemia

Among the three drug classes, SGLT-2 inhibitors are associated with the most pronounced risk for hyperkalemia, particularly in patients with renal impairment or those on medications that affect potassium levels. While GLP-1 receptor agonists and DPP-4 inhibitors are less likely to cause hyperkalemia, clinicians should still be vigilant, especially in patients with compromised renal function or those on polypharmacy regimens.

5.2 Monitoring Strategies

Given the potential for hyperkalemia with these medications, it is essential to implement monitoring strategies:

Baseline and Periodic Serum Potassium Measurements: For patients starting on SGLT-2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors, regular monitoring of serum potassium is recommended, particularly in those with renal impairment.

Renal Function Assessment: Close monitoring of renal function is critical, as altered renal function may exacerbate the risk of hyperkalemia.

Patient Education: Educating patients about the signs and symptoms of hyperkalemia, such as muscle weakness, fatigue, and arrhythmias, can aid in early detection and management.

5.3 Future Research

While there is some evidence linking these therapies to hyperkalemia, more robust, large-scale studies are needed to clarify the mechanisms of hyperkalemia associated with these drugs. Additionally, research should focus on identifying patient populations at the highest risk and determining optimal strategies for preventing and managing electrolyte disturbances.

6. CONCLUSION

Hyperkalemia is a potential but manageable safety concern for patients with Type 2 Diabetes on SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. While the risk is generally low, particularly with DPP-4 inhibitors and GLP-1 receptor agonists, close monitoring of renal function and potassium levels is essential, especially for patients with pre-existing kidney disease or those on polypharmacy. As these drug classes continue to play a crucial role in the management of T2D, ensuring patient safety through regular monitoring and early detection of electrolyte disturbances will be key in optimizing therapeutic outcomes.

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