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EMERGING METABOLIC AND PANCREATIC SAFETY SIGNALS ASSOCIATED WITH SGLT2 AND DPP-4 INHIBITORS IN TYPE 2 DIABETES MELLITUS: CLINICAL INSIGHTS AND PHARMACOVIGILANCE PERSPECTIVES

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ABSTRACT

Background: Sodium–glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used pharmacological agents for the management of type 2 diabetes mellitus (T2DM). These medications provide effective glycaemic control along with demonstrated cardiovascular and renal benefits. However, post-marketing pharmacovigilance data have increasingly identified rare but clinically significant adverse events associated with these drug classes. **Objective:** This short communication aims to highlight emerging metabolic and pancreatic safety signals associated with SGLT2 inhibitors and DPP-4 inhibitors and to emphasize the importance of early recognition and pharmacovigilance monitoring. **Clinical Perspective:** Pharmacovigilance reports and clinical observations in the literature have described cases of euglycemic diabetic ketoacidosis associated with SGLT2 inhibitor therapy and episodes of acute pancreatitis linked to DPP-4 inhibitor use. **Discussion:** Although uncommon, these adverse events represent clinically important safety concerns. SGLT2 inhibitors may promote ketogenesis through alterations in insulin-to-glucagon balance and increased fatty acid oxidation, whereas prolonged incretin activity from

DPP-4 inhibitors may influence pancreatic physiology and inflammatory pathways. **Conclusion:** Clinicians prescribing modern antidiabetic agents should remain vigilant for atypical metabolic and pancreatic complications. Early recognition and appropriate clinical management are essential for improving patient safety and minimizing morbidity.

KEYWORDS: Type 2 diabetes mellitus, SGLT2 inhibitors, DPP-4 inhibitors, euglycemic diabetic ketoacidosis, pancreatitis, pharmacovigilance.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from insulin resistance, impaired insulin secretion, and progressive pancreatic β-cell dysfunction. The global prevalence of diabetes has increased dramatically over the past decades and continues to represent a major public health challenge worldwide[1].

Advances in diabetes pharmacotherapy have resulted in the development of novel antidiabetic drug classes targeting multiple mechanisms involved in glucose homeostasis. Among these agents, sodium–glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors have gained widespread clinical acceptance due to their effectiveness, favourable safety profiles, and additional cardiovascular and renal benefits[2].

SGLT2 inhibitors reduce plasma glucose levels by inhibiting renal glucose reabsorption in the proximal tubules, thereby promoting urinary glucose excretion independently of insulin action[3]. Large randomized clinical trials have demonstrated that these agents improve glycaemic control while also reducing cardiovascular mortality and slowing the progression of renal disease in patients with diabetes[4].

DPP-4 inhibitors exert their therapeutic effects through inhibition of the enzyme dipeptidyl peptidase-4, which degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By prolonging the activity of these hormones, DPP-4 inhibitors enhance glucose-dependent insulin secretion and suppress glucagon release, contributing to improved glycaemic control[5].

Despite their clinical benefits, post-marketing surveillance systems and pharmacovigilance databases have reported rare but potentially serious adverse reactions associated with these medications. Among these, euglycemic diabetic ketoacidosis related to SGLT2 inhibitors and pancreatitis associated with incretin-based therapies have received increasing attention in clinical literature[6].

This short communication summarizes emerging safety signals reported in pharmacovigilance studies and discusses their potential mechanisms and clinical implications.

EMERGING PHARMACOVIGILANCE SIGNALS

Euglycemic Diabetic Ketoacidosis Associated with SGLT2 Inhibitors

Recent pharmacovigilance reports and clinical studies have documented cases of euglycemic diabetic ketoacidosis (EDKA) in patients receiving SGLT2 inhibitor therapy. Unlike classical diabetic ketoacidosis, EDKA is characterized by significant metabolic acidosis and ketonemia despite relatively normal or only mildly elevated blood glucose levels[7].

The proposed pathophysiological mechanism involves a shift in metabolic balance toward ketone body production. By promoting glucosuria, SGLT2 inhibitors reduce plasma glucose concentrations and subsequently decrease insulin secretion while increasing glucagon release. This altered hormonal environment promotes lipolysis and hepatic ketogenesis, leading to accumulation of ketone bodies[8].

Several precipitating factors have been reported in association with SGLT2 inhibitor related EDKA, including dehydration, prolonged fasting, acute illness, surgical stress, excessive alcohol intake, and reduction in insulin dosage.

Acute Pancreatitis Associated with DPP-4 Inhibitors

In addition to metabolic complications associated with SGLT2 inhibitors, pharmacovigilance analyses have also highlighted a possible association between DPP-4 inhibitor therapy and acute pancreatitis. Although these medications are generally considered safe and well tolerated, several observational studies and adverse event reports have described episodes of pancreatic inflammation occurring during incretin-based therapy[9].

The potential mechanisms underlying this association remain under investigation. Experimental studies have suggested that prolonged incretin stimulation may influence pancreatic ductal proliferation, inflammatory responses, and pancreatic enzyme secretion. These changes may contribute to the development of pancreatic inflammation in susceptible individuals.

Drug-induced pancreatitis is a relatively uncommon but clinically significant condition and requires prompt recognition and discontinuation of the suspected medication[10].

SUMMARY OF SAFETY SIGNALS

Table 1. Reported Adverse Effects Associated with SGLT2 and DPP-4 Inhibitors

Drug Class	Reported Adverse Event	Key Clinical Features
SGLT2 inhibitors	Euglycemic diabetic ketoacidosis	Metabolic acidosis, ketonemia, mild hyperglycaemia
DPP-4 inhibitors	Acute pancreatitis	Epigastric pain, elevated amylase and lipase

Table 2. Proposed Mechanisms of Drug-Induced Adverse Effects.

Drug Class	Proposed Mechanism	Clinical Consequence
SGLT2 inhibitors	Increased glucagon secretion	Enhanced hepatic ketogenesis
	Reduced circulating insulin	Increased lipolysis
	Increased fatty acid oxidation	Ketone body production
DPP-4 inhibitors	Prolonged incretin hormone activity	Continuous pancreatic stimulation
	Pancreatic ductal proliferation	Inflammatory changes
	Altered enzyme secretion	Elevated amylase and lipase

DISCUSSION

The introduction of SGLT2 inhibitors and DPP-4 inhibitors has substantially expanded therapeutic options for the management of type 2 diabetes mellitus. These agents have demonstrated significant benefits in glycaemic control and have also been associated with improvements in cardiovascular and renal outcomes in large clinical trials[11].

However, broader clinical use and long-term exposure have revealed rare adverse events that were not fully recognized during early clinical development. Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitors represents a unique metabolic complication in which ketosis develops despite relatively normal blood glucose levels. This condition is believed to arise from metabolic shifts toward fatty acid oxidation and ketone body production resulting from changes in insulin and glucagon balance[12].

Similarly, incretin-based therapies such as DPP-4 inhibitors may influence pancreatic physiology through prolonged GLP-1 activity. Although the exact clinical significance remains debated, some experimental and pharmacovigilance studies have suggested a possible association with pancreatic inflammation[13].

Pharmacovigilance databases such as the FDA Adverse Event Reporting System (FAERS) have reported increasing safety signals related to these complications. Therefore, clinicians should maintain a high level of clinical suspicion when patients receiving these medications present with unexplained metabolic acidosis or severe abdominal pain[14].

Patient education also plays an important role in preventing serious complications. Individuals receiving SGLT2 inhibitors should be advised regarding sick-day management

and the need to temporarily discontinue therapy during acute illness or prolonged fasting. Likewise, patients receiving incretin-based therapies should be instructed to seek medical attention if persistent abdominal pain develops.

CONCLUSION

SGLT2 inhibitors and DPP-4 inhibitors represent major therapeutic advances in the pharmacological management of type 2 diabetes mellitus. Nevertheless, clinicians must remain vigilant for rare but potentially serious adverse events such as euglycemic diabetic ketoacidosis and acute pancreatitis.

Early recognition, prompt discontinuation of the suspected drug, and appropriate medical management are essential to minimize complications. Continued pharmacovigilance monitoring and further research are necessary to improve understanding of the long-term safety profiles of these widely used medications.

Ethical Approval: The study was conducted in accordance with institutional ethical guidelines. As the report describes anonymized clinical observations without identifiable patient information, formal ethical committee approval was not required.

Conflict of Interest: The authors declare no conflicts of interest.

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