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Original Research Paper

Diabetology

INCIDENCE AND RISK FACTORS OF HYPOGLYCEMIA INDUCED BY VARIOUS CLASSES OF ORAL HYPOGLYCEMIC AGENTS: A REVIEW

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ABSTRACT **Background:** Hypoglycemia is a major adverse effect of oral hypoglycemic agents (OHAs), with varying incidence across drug classes and patient populations. It contributes significantly to morbidity, reduced quality of life, and increased mortality in type 2 diabetes mellitus (T2DM). **Objective:** This review summarizes current evidence on the incidence and risk factors of hypoglycemia associated with OHAs, highlighting drug-specific differences and patient-related modifiers. **Methods:** A literature review was conducted to evaluate reported hypoglycemia rates among OHA classes and to identify clinical and demographic risk factors. **Results:** Sulfonylureas remain the drug class most strongly linked with hypoglycemia, affecting approximately 10.1% of patients, with severe events in up to 0.8%. Long-acting sulfonylureas, such as glyburide and glibenclamide, pose the highest risk, while gliclazide and glipizide are safer alternatives. In contrast, metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium–glucose cotransporter-2 (SGLT2) inhibitors are rarely associated with hypoglycemia when used as monotherapy. Meglitinides present lower risk compared with sulfonylureas due to their shorter duration of action. Patient-specific risk factors include impaired renal function, older age, low body mass index, comorbidities, polypharmacy, and a history of hypoglycemia. **Conclusion:** Sulfonylureas are the OHA class with the greatest risk of hypoglycemia, particularly in elderly and renally impaired patients. Metformin, DPP-4 inhibitors, and SGLT2 inhibitors are safer alternatives for individuals in whom minimizing hypoglycemia risk is critical. Careful risk assessment, dose adjustment, patient education, and regular monitoring are essential to reduce hypoglycemia-related complications.

KEYWORDS : hypoglycemia, oral hypoglycemic agents, sulfonylureas, risk factors, diabetes mellitus

INTRODUCTION

Hypoglycemia is one of the most clinically significant adverse effects associated with pharmacological management of type 2 diabetes mellitus (T2DM). It is linked to increased morbidity, impaired quality of life, and mortality (Holstein et al., 2003). The occurrence of hypoglycemia varies substantially across oral hypoglycemic agents (OHAs), largely depending on their mechanisms of action and pharmacokinetic profiles.

Sulfonylureas, which stimulate insulin release independent of blood glucose levels, have historically been associated with the highest risk of hypoglycemia (Gangji et al., 2007). In contrast, metformin and newer classes such as dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium–glucose cotransporter-2 (SGLT2) inhibitors demonstrate a much lower risk (Bailey & Turner, 1996; Monami et al., 2011; Neal et al., 2017). Patient-specific factors, including advanced age, renal impairment, and comorbidities, further modify the risk (Schopman et al., 2009).

This review consolidates evidence on the incidence and risk factors of hypoglycemia associated with OHAs, with the goal of guiding clinicians in rational therapeutic decision-making.

Incidence of Hypoglycemia by Drug Class

Drug Class	Incidence of Hypoglycemia	Severe Episodes	Notes / References
Sulfonylureas	\sim10.1% (mild), up to 0.8% (severe)	Highest with glyburide, glibenclamide	Holstein et al., 2003; Schopman et al., 2009; Nathan et al., 2009; Gangji et al., 2007
Metformin	Rare/Minimal	Very rare	Bailey & Turner, 1996; Nathan et al., 2009
DPP-4 Inhibitors	Very rare	Extremely rare	Monami et al., 2011
SGLT2 Inhibitors	Very rare	Rare	Cefalu et al., 2013; Neal et al., 2017; Zinman et al., 2015
Meglitinides	Lower than sulfonylureas	Rare	Goldberg et al., 2000

Sulfonylureas remain the OHA class most strongly associated with hypoglycemia. Longer-acting sulfonylureas, such as glibenclamide and glyburide, carry the greatest risk, while gliclazide and glipizide are associated with comparatively fewer episodes (Gangji et al., 2007).

Metformin, the first-line therapy in T2DM, is considered safe because it does not stimulate insulin secretion (Bailey & Turner, 1996).

DPP-4 inhibitors and SGLT2 inhibitors are associated with very low risk unless combined with sulfonylureas or insulin (Monami et al., 2011; Zinman et al., 2015).

Meglitinides, being short-acting insulin secretagogues, demonstrate lower incidence compared with sulfonylureas due to their shorter duration of action (Goldberg et al., 2000).

Patient-Specific Risk Factors

The risk of hypoglycemia is further modified by individual patient characteristics, including:

* Impaired renal function (especially estimated glomerular filtration rate $<30 \, \text{mL}/\text{min}/1.73 \, \text{m} ^ 2$).
* Older age and frailty.
* Female sex.
* Low body mass index and malnutrition.
* Polypharmacy, particularly with sulfonylureas and insulin combinations.
* History of prior hypoglycemia.
* Acute illness such as sepsis or hospitalization.
* Comorbidities including congestive heart failure, chronic kidney disease, and hepatic dysfunction.

These factors amplify the hypoglycemic potential of insulin secretagogues and necessitate careful clinical judgment.

Clinical Implications

* Therapeutic choice: For patients at elevated risk (elderly, renal impairment, comorbidities), metformin and newer classes such as DPP-4 and SGLT2 inhibitors should be preferred over sulfonylureas.
* Monitoring: Regular evaluation of renal and hepatic function, nutritional status, and concomitant medications is essential.
* Patient education: Patients should be informed about hypoglycemia symptoms, preventive strategies, and self-management.

* Dose adjustment: Initiating therapy at the lowest effective dose and avoiding unnecessary drug combinations reduces risk.

CONCLUSION

Sulfonylureas remain the oral hypoglycemic class most strongly linked with hypoglycemia, particularly among vulnerable populations such as the elderly and those with renal dysfunction. Metformin, DPP-4 inhibitors, and SGLT2 inhibitors offer safer alternatives where minimizing hypoglycemia risk is a clinical priority. Individualized risk assessment, judicious drug selection, and ongoing monitoring are critical to reducing hypoglycemia incidence and severity in patients with T2DM.

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