

Frequency of asymptomatic hypoglycemia in patients with diabetes

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ABSTRACT

The risk of hypoglycemia with anti-hyperglycemic agents is an important limiting factor in the management of type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. While hypoglycemia is more common in T1DM, the incidence is high in T2DM patients who use insulin or secretagogues, particularly patients with longer duration of diabetes. The underlying cause of hypoglycemia in diabetes is a complex interaction between hyperinsulinemia and compromised physiologic and behavioral responses to falling glucose levels. Pancreatic dysfunction also causes loss of normal therapeutic response to hypoglycemia—a reduction in circulating insulin (in T2DM only) and an increase in glucagon secretion. In T1DM and advanced T2DM, the third defense against hypoglycemia is increase in adrenomedullary sympathoadrenal epinephrine secretion, which is also compromised, causing the syndrome of defective glucose counterregulation. Diminished increase in epinephrine, also called hypoglycemia-associated autonomic failure (HAAF), is largely responsible for defective glucose counterregulation. HAAF can result in recurrent hypoglycemia and lowering of glycemic threshold that typically triggers sympathoadrenal response to hypoglycemia. This results in hypoglycemia without warning symptoms, or “hypoglycemia unawareness,” which increases the risk of severe hypoglycemia associated with substantial morbidity and mortality. Long-term effects of severe hypoglycemia, aside from causing accidents, may include adverse cardiovascular outcomes and cognitive impairment. To reduce the impact of hypoglycemia, it is important to identify patients at risk and use careful consideration when choosing antidiabetes medications. Newer insulin analogs that more accurately replicate endogenous insulin secretion and incretin therapies that cause glucose-sensitive insulin secretion may ultimately reduce the risk of hypoglycemia.



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1. Introduction

Hypoglycemia is among the most feared consequences of diabetes and its treatment, and is frequently an important limiting factor in effective glycemic control. In addition, symptomatic hypoglycemia is a greater

burden among patients with type 2 diabetes (T2DM) than is estimated by administrative claims since it occurs more frequently than is usually reported, can negatively impact the health status of patients, can result in fear of future hypoglycemic events, and may result in increased overall healthcare utilization and costs [1]. For years the American Diabetes Association (ADA) has recommended an HbA1c target of <7% [2]. Despite this recommendation, data from the National Health and Nutrition Examination Survey (NHANES) 2007-2008 showed that 45% of patients with diagnosed diabetes had HbA1c levels $\geq 7.0\%$ [3]. One reason the goal of <7% cannot be reached in practice, and in fact is seldom reached in clinical trials as well, is the limitation imposed on aggressive therapy by the fear of hypoglycemia. The new diabetes management guidelines published in April 2012 by the ADA and the European Association for the Study of Diabetes (EASD) [4] take this into account, allowing for a spectrum of targets from a more stringent goal of 6%-6.5% to a less stringent goal of 7.5%- 8% based on several pertinent factors, including risk of hypoglycemia. This individualization of target HbA1c will allow for safer care of patients. While insulin therapy is often considered the most effective treatment for controlling hyperglycemia when it is dosed appropriately, data from earlier NHANES surveys indicate that patients using insulin therapy alone had the poorest control of hyperglycemia, likely due to the severity of their diabetes [5], [6] and possibly due to the fear of hypoglycemia. Data indicate that many patients fear severe hypoglycemia as much as they fear diabetes complications such as blindness and kidney disease [7].

2. Conclusions

Hypoglycemia is a troubling complication of antidiabetes therapies that presents a barrier to glycemic control for many individuals. Although the risk of hypoglycemia is greatest among patients with T1DM, the risk of hypoglycemia with T2DM increases with the duration of the disease and approaches the risk seen in T1DM in patients with a long history of insulin use. Moreover, because the number of patients with T2DM is so much greater than the number with T1DM, most cases of hypoglycemia—even severe hypoglycemia—that the physician will encounter will be in patients with T2DM. Regardless of the type of diabetes, minimizing the risk of hypoglycemia requires an understanding of the pathophysiologic mechanisms of hypoglycemia, the risk factors for hypoglycemia, and the interventions that can provide the greatest improvements in hyperglycemia without an increased risk of hypoglycemia. For this reason, there is a trend away from the use of sulfonylurea drugs and an increase in the use of DPP-4 inhibitors and GLP-1 agonists. Therapies are currently in development that may help clinicians to assist their patients in achieving their glycemic goals with even less hypoglycemia.

3. References

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