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Hypoglycemia in Diabetes: Epidemiology, Impact, Prevention and Treatment

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ABSTRACT

Studies have shown that intensive glycemic control in patients with diabetes reduces risk of micro and macrovascular complications of diabetes. The current treatment guidelines recommend glycated hemoglobin of < 7% for most patients with diabetes. However, one of the limiting factors in achieving this goal is risk of hypoglycemia particularly in patients treated with insulin and insulin secretagogues. The International Hypoglycemia Study Group recommends a glucose concentration of <3.0 mmol/L (<54 mg/dL) be counted as hypoglycemia in clinical trials and that hypoglycemia requiring assistance of another for treatment to be defined as severe hypoglycemia. When plasma glucose falls below physiologic threshold; the body initiates physiologic responses designed to raise the plasma blood glucose. One of the first physiologic responses is reduction in the secretion of pancreatic beta-cell hormone insulin and the release of glucagon. In patients with type 1 diabetes and advanced type 2 diabetes; these defense mechanisms are absent due to absence of endogenous insulin production. The prevalence of hypoglycemia in patients with diabetes is much higher in type 1 vs. type 2 diabetes. The clinical presentation of hypoglycemia can range from mild symptoms to coma and death. It causes economic burden on the individual and health care. When it comes to clinical management of hypoglycemia; prevention is the key. Patient education that addresses the conventional risk factors of hypoglycemia and appropriate therapy for episodes plays a crucial role. Continuous glucose monitoring **(CGM)** has become an

important tool in assessing glycemic trends and alerting the individual a fall in glucose that could lead to hypoglycemia. Recent technological advances; sensor-augmented insulin pump with Threshold suspend features and a closed-loop insulin pump with built in algorithms that adjust the rates of basal insulin administration based on data collected from the continuous glucose monitor; have shown promise in reducing the frequency of hypoglycemia.

INTRODUCTION

Multiple studies have documented that intensive glycemic therapy reduces the risk for the development of the microvascular complications of diabetes, including nephropathy, retinopathy and neuropathy [1-8]. There is also some evidence that suggests that intensive glycemic treatment reduces the risk of macrovascular complications in patients with diabetes [1,9,10]. The Diabetes Control and Complications Trial - Epidemiology of Diabetes Complications **(DCCT-EDIC)** perhaps demonstrated this best with their observation that intensive diabetes treatment for 6.5 years reduced the incidence of coronary vascular disease in patients with type 1 diabetes 30 years later. Therefore, current treatment guidelines recommend targeting plasma glucose levels in patients with diabetes as close to the non-diabetic range as much as possible. One of the limiting factors in achieving such glycemic goals in patients treated with insulin and insulin secretagogues is hypoglycemia [11,12].

In clinical trials, episodes of severe hypoglycemia where a person with diabetes requires the assistance of another for treatment have been relatively easy to track because the events are memorable and often associated with the intervention of emergency personnel. However, it has been much more challenging to detect "non-severe" episodes of hypoglycemia in which the person with diabetes does not have serious neuroglycopenia because individuals do not always confirm that their blood sugar is low when they have symptoms associated with hypoglycemia or because episodes are asymptomatic. To address this issue, the International Hypoglycemia Study group **(IHSG)** recently published a position statement [13] on the glucose concentrations that should be used to define hypoglycemia in clinical trials (Table 1). This statement has been adopted by the American Diabetes Association and the European Association for the Study of Diabetes. The IHSG recommends that glucose concentration level of <3.0 mmol/L (<54 mg/dL) be counted as hypoglycemia in clinical trials and that hypoglycemia requiring the assistance of another for treatment continue to be called severe hypoglycemia [13]. The group acknowledges that the glycemic threshold for symptoms of hypoglycemia is moving targets in patients treated with insulin and oral hypoglycemic agents. It is higher in patients with poor glycemic control and lower in patients with tight glycemic control. However, experiencing glucose concentrations of <2.8 mmol/L (<50 mg/dL) have been associated with subsequent risk of mortality [14,15] and puts patients at risk for the development of impaired awareness of hypoglycemia, which in turn increases the risk of experiencing severe hypoglycemia. The IHSG also suggested that a glucose level of <70 mg/dl be called an alert value because it suggests the patient may be dropping to a value of <3.0 mmol/l (54 mg/dl) and that actions to avoid this drop should be taken.

Table 1: Proposed glucose levels when reporting hypoglycemia in clinical trials (adopted from the IHSG position statement [13]).

Level 1	A glucose alert value of 3.9 mmol/L (70 mg/dL) or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study.
Level 2	A glucose level of less than 3.0 mmol/L (54 mg/dL) is sufficiently low to indicate serious, clinically important hypoglycemia.
Level 3	Severe hypoglycemia, denotes severe cognitive impairment requiring external assistance for recovery.

PREVALENCE OF HYPOGLYCEMIA IN PATIENTS WITH TYPE 1 DIABETES AND ADVANCED TYPE 2 DIABETES

Defining the prevalence of hypoglycemia in patients with diabetes been challenging because studies differ in the definitions used, which was one of the issues that prompted the IHSG to publish their position statement. Nonetheless, rates of severe hypoglycemia defined as an episode that required the assistance of another to treat can be reliably collected from patients because of the impact such episodes have on patients and their families. In most observational studies, the rates of severe hypoglycemia are much higher in type 1 vs. type 2 diabetes [16]. Two studies done in UK [16,17] reported annual prevalence rate of severe hypoglycemia 11.5 to 42.8 per patient-year for Type 1 diabetes and 3.2 to 16.37 per patient-year for Type 2 diabetes.

Assessment of the frequency with which patients with diabetes experience more moderate episodes is more problematic, particularly because few studies have used continuous glucose monitoring to measure hypoglycemia and without collection of such data, asymptomatic episodes or episodes that occur without measurement of a blood sugar are usually not captured. According to a population based study completed in the UK based on self-reported frequency and effects of hypoglycemia in patients with diabetes treated with insulin; the frequency of non-severe hypoglycemia episodes in patients with Type 1 diabetes is 129.7 per year and 57.6 per year for insulin treated type 2 diabetes patients [18]. A similar rate was reported in other studies done in developed countries [19-22]. These observations demonstrate that moderate hypoglycemia is more common than severe hypoglycemia and that the rates of even moderate hypoglycemia are much higher in patients with type 1 as opposed to type 2 diabetes.

PREDICTING WHICH PATIENTS ARE AT RISK FOR HYPOGLYCEMIA

The risk of severe hypoglycemia has been linked to intensity of glycemic control in several clinical trials [5]. The incidence of severe hypoglycemia in the DCCT trial was three times higher (653 vs. 205) in the intensive therapy group than in the conventional therapy group [5,23]. Studies done in patients with Type 2 diabetes also show an associated between the risk of experiencing severe hypoglycemia and intensity of glycemic control. In the Action to Control Cardiovascular Risk in Diabetes **(ACCORD)** study, the rate of hypoglycemia requiring medical assistance was 3.1% in the intensive-therapy group and 1.0 % in the standard-therapy group [24-26]. The Veterans Affairs Diabetes Trial **(VADT)** [27] also showed similar finding with the annual

rate of severe hypoglycemia being 3.8% and 1.8% in the intensive and standard therapy groups; respectively. However, data collected from clinical populations now raise questions about whether such a relationship between severe hypoglycemia and A1c targets exists in practice. In the Type 1 Diabetes Exchange Registry, patients with an A1c <6.5 % had the same risk of hypoglycemia as did those with an A1c of >9.0% [28]. Similar observations were made in patients with type 2 diabetes enrolled in care system [29].

In patients with Type 2 diabetes, hypoglycemia is associated with several clinical risk factors including older age, diabetes duration, burden of co-morbidities, glycemic treatment intensification, current insulin treatment and duration of insulin treatment [17,30-34]. Within ACCORD, severe hypoglycemia was associated with the following baseline factors: sex, race, peripheral neuropathy, duration of diabetes, body mass index **(BMI)**, albuminuria, serum creatinine, age, educational level, insulin use and higher HbA1c [31].

A recent analysis of the ACCORD database indicated that C-peptide or GAD antibodies might be useful tools in predicting the odds of severe hypoglycemia and death in patients with Type 2 diabetes [35]. The study found that the ACCORD cases who experienced severe hypoglycemia and subsequent mortality had a higher prevalence of insulin deficiency than did ACCORD subjects who had severe hypoglycemia but not mortality. Based on this finding; the authors concluded that fasting C-peptide and GAD antibody may be useful markers to identify patients at risk for severe hypoglycemia and mortality in patients with Type 2 diabetes [35].

CONSEQUENCES OF HYPOGLYCEMIA

The impact of hypoglycemia on patients with diabetes range from the "inconvenience" associated with interrupting current activities to treat a low blood sugar, to coma, seizures, and death. It is estimated that 6-10% of patients with Type 1 diabetes die from hypoglycemia [36-38]. The cause of death in patients with hypoglycemia includes cardiac arrhythmias [30,39-41], as was so clearly shown in the case report of Tanenberg *et al*. where both continuous glucose and EKG monitor captured the point of death in a patient with type 1 diabetes [42].

Cardiovascular Disease and Mortality

In type 2 diabetes, the link between mortality and hypoglycemia was first shown in the Action to Control Cardiovascular Risk in Diabetes **(ACCORD)** Study. A retrospective analysis of the ACCORD study showed that severe hypoglycemia was associated with increased risk of death [14]. Similar findings were made in the ADVANCE study as well; severe hypoglycemia was associated with increased risk of death from both cardiovascular and non-cardiovascular causes [30]. A meta-analysis of 903, 510 people with Type 2 diabetes; indicated that severe hypoglycemia is associated with an increased risk of cardiovascular disease [43].

A detailed analysis of participants in the ACCORD trial indicated that participants who experienced severe hypoglycemia had greater risk of death than those who have not experienced

any episodes of hypoglycemia [14]. The mechanism of increased mortality among patients with severe hypoglycemia is not fully understood. However, there is some evidence to suggest that cardiac ischemia or arrhythmia precipitated by hypoglycemia might play a role especially in patients with cardiac autonomic neuropathy [44-46]. The sympatho-adrenal activation and catecholamine release induced by hypoglycemia has also been described in causing cardiac arrhythmia, increased thrombogenesis, inflammation, and vasoconstriction and thereby leading to cardiovascular disease or death [47]. Recent analysis of the VADT data suggests that hypoglycemia may accelerate the progress atherosclerosis in patients under less than optimal glycemic control [27].

Cognition

The evidence regarding the effect of hypoglycemia on cognitive function has been mixed. In the DCCT trial; there was no evidence of substantial long-term declines in cognitive function in patients with type 1 diabetes who were followed for an average of 18 years despite high rates of recurrent severe hypoglycemia; while other studies indicated a possible link between hypoglycemia and cognitive dysfunction [48-51]. Whitmer and colleagues examined the relationship between episodes of hypoglycemia that required hospitalization or an emergency department visit between 1980-2002 and the 1822 incident cases of dementia identified after 2003 using a registry of more than 16,000 individuals who were older than 55 years of age in 2003 and had a diagnosis of type 2 diabetes [52]. They found that after adjustment for age, demographics, co-morbidities, and characteristics of diabetes treatment, the hazard ratio for incident dementia was 1.44 (1.25-1.66) in those who had one or more episodes of severe hypoglycemia. However, in ACCORD, subjects in the lowest tertile of performance on a cognitive test had at baseline had a significantly higher risk of experiencing hypoglycemia during the subsequent twenty months as compared to subjects who performed better on the same cognitive test [53]. From these studies, it isn't clear if severe hypoglycemia causes dementia or if pre-clinical forms of cognitive dysfunction increase the risk of severe hypoglycemia. Additional prospective analysis of well-characterized individuals with diabetes and normal cognition will be necessary to address this point.

Health Economics and Quality of Life

Hypoglycemia has significant health care economic burden on the society through frequent emergency room visits, ambulance utilization and hospitalizations costs [54,55]. A study which looked at economic burden of hypoglycemia in patients with Type 2 diabetes on basal insulin reported that hypoglycemia-related medical expenses accounted for 12.6% of total healthcare expenditure with hypoglycemia-related hospitalizations accounting for 19.7% of total health care hospitalization expenditure [54]. Between 2007 and 2001, nearly 100,000 persons with diabetes were treated in emergency rooms for hypoglycemia, with an annual cost exceeding $100 million [56]. Hypoglycemia also impacts on the economic wellbeing of the individual. Non-severe hypoglycemia episodes result in lost work-time and reduced work productivity and studies show that about 20% of non-severe hypoglycemia episodes resulted in lost work time [18,57].

The fear of hypoglycemia also has a significant impact on the quality of life experienced by patients and their families. This has been best studied in patients with type 1 diabetes where this fear can result in increased vigilance and immobilizing distress [58,59], but a recent study in Japan demonstrated that 27% of patients with type 2 diabetes had high measures of fear of hypoglycemia [60]. This fear often limits patient adherence to treatment regimens and leads to behaviors that will prevent hypoglycemia [60] at the cost of experiencing substantial hyperglycemia [61].

PHYSIOLOGY AND PATHOPHYSIOLOGY

Under normal circumstances, the plasma glucose level is kept within a narrow range (70-100 mg/dl). When the plasma glucose level fall below this threshold the body initiates physiologic responses designed to raise the plasma blood glucose. The first physiologic response is a reduction in the secretion of pancreatic beta-cell hormone insulin. This occurs at a blood glucose of ~80 mg/dl and in a healthy person not receiving insulin or an insulin secretagogues, this reduction in insulin secretion will ensure that normoglycemia is maintained. If blood glucose continues to fall, glucagon is released at a blood glucose level of ~65 mg/dl. At this glucose level, the sympathetic nervous system is activated resulting in epinephrine release from the adrenal gland and norepinephrine release at the sympathetic nerve terminals. Together these responses will increase hepatic glucose production and reduce glucose uptake into muscle and fat, thereby supporting the return to normoglycemia. In addition, the activation of the sympathetic nervous system leads to the appearance of symptoms that prompt the ingestion of food.

In patients with type 1 diabetes or advanced type 2 diabetes where pancreatic beta cell function is essentially absent, the first defense mechanism preventing hypoglycemia is lost. Because these individuals do not make insulin, they are unable to reduce its secretion to restore hypoglycemia. Such patients are also unable to release glucagon in response to hypoglycemia, presumably because this response is dependent on a hypoglycemia - induced reduction in insulin secretion [62]. Consequently, they become dependent on hypoglycemia-induced activation of the sympathoadrenal system to prevent the development of hypoglycemia. However, exposure to repeated hypoglycemia reduces the glucose level at which this sympathetic response is elicited and reduces the magnitude of the response. As a result, patients may not trigger the counterregulatory response until the blood glucose level is below that associated with neuroglycopenia. When this occurs, the patient is said to have hypoglycemia induced autonomic failure and impaired awareness of hypoglycemia (Figure 1). Hypoglycemia unawareness is associated with a 6-fold increase in the risk of iatrogenic hypoglycemia [63].

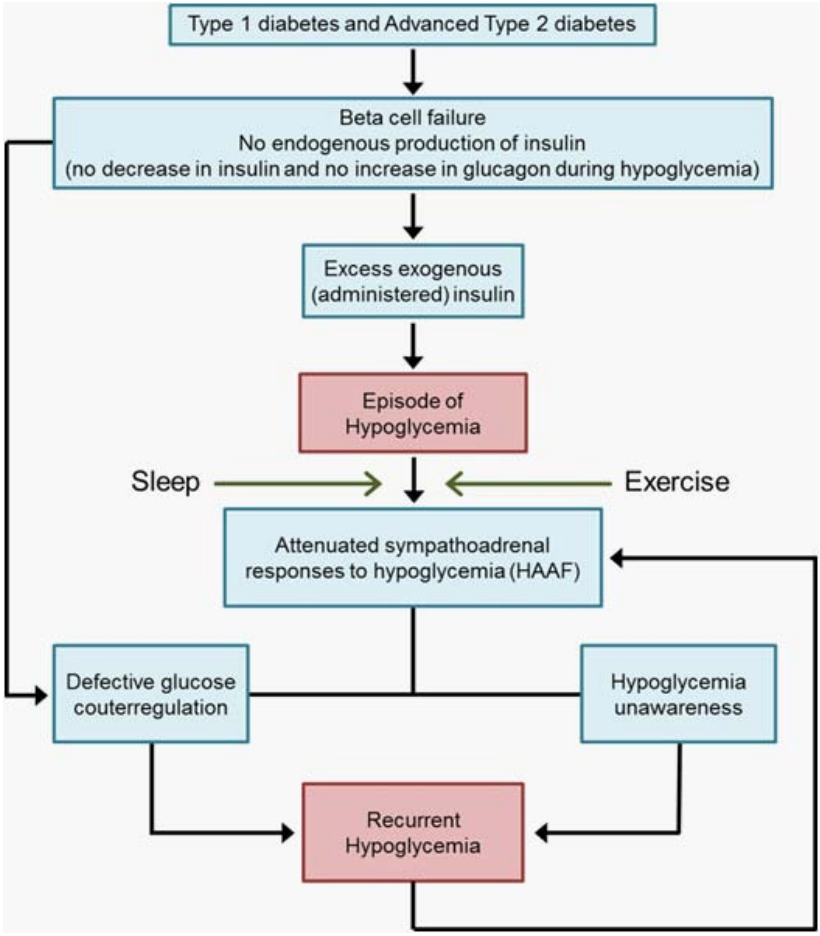

Figure 1: Schematic Diagram of Hypoglycemia-Associated Autonomic Failure (HAAF) in Diabetes. Adapted from Cryer [62].

PREVENTION OF HYPOGLYCEMIA

How do we avoid or reduce risk of hypoglycemia in patients with Type 1 and advanced Type 2 diabetes patients? The ADA working group on hypoglycemia recommends [64] that persons with drug-treated diabetes become concerned about the possibility of developing hypoglycemia when self-monitoring concentration is falling rapidly or equal to or below 70mg/dl (3.9 mmol/liter). This concentration should be viewed as an alert value that prompts the patient time to take action to prevent further fall in plasma glucose or from developing symptomatic hypoglycemia [64].

Patients need to be educated in how to anticipate when they may be at greatest risk for the development of hypoglycemia so that can prevent episodes from occurring. The greatest risk likely occurs when they have excessive amounts of insulin on board for the current physiological need such as when insulin (or insulin secretagogues) doses are excessive, ill-timed or of the wrong

type, when exogenous glucose delivery is decreased (such as following missed meals and during the overnight fast, with gastroparesis or celiac disease), when glucose utilization is increased (as during and shortly after exercise), when endogenous glucose production is decreased (as following alcohol ingestion), when sensitivity to insulin is increased (as in the middle of the night or following weight loss, improved fitness or improved glycemic control), or when insulin clearance is decreased (as in renal failure) [64,65]. This education can be provided in individual sessions or group classes. Programs such the Blood Glucose Awareness training have been shown to be effective in reducing the risk of experiencing hypoglycemia [66].

Continuous glucose monitoring **(CGM)** has become an important tool in assessing glycemic trends and can assist patients in recognizing a fall in glucose that could lead to hypoglycemia. CGM has an advantage over SMBG because it can provide real time blood glucose reading and display the direction and rate of change of interstitial blood glucose. This prompts the individual wearing the monitor to make an informed decision before hypoglycemia occurs or to act on it immediately if hypoglycemia occurs. The recently published DIAMOND trial [67] showed that CGM use decreased the time spent with glucose concentrations less than 70mg/dl during the day and night in patients with type 1 diabetes taking insulin injections.

Recent technological advances have created devices in which a continuous glucose monitor is coupled to an insulin pump. In one such system, the insulin infusion is suspended for up to two hours if the continuous glucose monitor shows that interstitial glucose has fallen into the hypoglycemic range. A randomized control trial that compared this system to a non-integrated pump and continuous glucose monitor demonstrated that the sensor-augmented insulin pump reduced nocturnal hypoglycemia without increasing glycated hemoglobin values [68]. More recently, algorithms have been developed that adjust the rates of basal insulin administration based on data collected from the continuous glucose monitor. The first device on the market is the The MiniMed 640G sensor-augmented pump and it has been shown to reduce the time spent in hypoglycemia increasing risk of hyperglycemia [69].

TREATMENT OF HYPOGLYCEMIA

Patients should be instructed to treat hypoglycemia with the ingestion of 15-20 grams of carbohydrate [70]. Orange juice (which contains fructose) and glucose tablets remain a popular treatment for hypoglycemia [71]. Blood glucose levels should be checked to monitor resolution of hypoglycemia; most studies support waiting 10-15 minutes after treatment before rechecking [70,71]. If the patient is not capable of taking glucose by mouth or has neuroglycopenic symptoms; it is recommended to give glucagon 1mg IM [72]. This can be given by family members and care givers must be certain that families are trained in the administration of glucagon. Intravenous glucose can also be given to hypoglycemia patients if they have IV access and are under the care of a medical team. Once the episode is resolved, the reasons for its occurrence should be determined and changes in diabetes management should be made to prevent other hypoglycemic episodes from occurring in the future.

In patients with refractory hypoglycemia who continue to experience life threatening hypoglycemia despite expert endocrine care, pancreas [73] or islet transplantation [74] may be considered. When successful, both have been showed to achieve normal blood glucose values and substantially reduce hypoglycemia. However, to maintain graft function requires life-long immunosuppression.

CONCLUSION

Hypoglycemia is a common occurrence in patients with diabetes who are treated with insulin or insulin secretagogues. Consequences of hypoglycemia include confusion, coma, seizure, and death. Fear of hypoglycemia often prevents patients from achieving the glycemic control necessary to reduce the complications of the disease. Patient education that addresses the conventional risk factors of hypoglycemia and appropriate therapy for episodes of low sugars are often successful in reducing hypoglycemia. Current technological advances appear to hold promise in reducing the frequency of hypoglycemia in intensively treated patients. Guidelines on indication of the use of these technologies are needed.

References

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352: 854-865.
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352: 837-853.
3. American Association of Diabetes E. Intensive diabetes management: implications of the DCCT and UKPDS. Diabetes Educ. 2002; 28: 735-740.
4. Chrisholm DJ. The Diabetes Control and Complications Trial (DCCT). A milestone in diabetes management. Med J Aust. 1993; 159: 721-723.
5. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329: 977-986.
6. Nathan DM. Long-term complications of diabetes mellitus. N Engl J Med. 1993; 328: 1676-1685.
7. Reenders K, de Nobel E, van den Hoogen HJ, Rutten GE, van Weel C. Diabetes and its long-term complications in general practice: a survey in a well-defined population. Fam Pract. 1993; 10: 169-172.
8. Wikby A, Hornquist JO, Stenstrom U, Andersson PO. Background factors, long-term complications, quality of life and metabolic control in insulin dependent diabetes. Qual Life Res. 1993; 2: 281-286.
9. Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes. 2006; 55: 3556-3565.
10. DCCT/EDIC Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. Diabetes care. 2016; 39: 686-693.
11. Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocr Pract. 2008; 14: 750-756.
12. Cryer PE. Hypoglycemia is the limiting factor in the management of diabetes. Diabetes Metab Res Rev. 1999; 15: 42-46.
13. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2017; 40: 155-157.
14. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010; 340: b4909.

15. Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al. Hypoglycemia and Risk of Death in Critically Ill Patients. New England Journal of Medicine. 2012; 367: 1108-1118.

16. U. K. Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007; 50: 1140-1147.

17. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabet Med. 2005; 22: 749-755.

18. Frier BM, Jensen MM, Chubb BD. Hypoglycaemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. Diabet Med. 2016; 33: 1125-1132.

19. Farmer A, Balman E, Gadsby R, Moffatt J, Cradock S, et al. Frequency of self-monitoring of blood glucose in patients with type 2 diabetes: association with hypoglycaemic events. Curr Med Res Opin. 2008; 24: 3097-3104.

20. Giorda CB, Ozzello A, Gentile S, Aglialoro A, Chiambretti A, et al. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. Acta Diabetol. 2015; 52: 845-853.

21. Orozco-Beltran D, Mezquita-Raya P, Ramirez de Arellano A, Galan M. Self-reported frequency and impact of hypoglycemic events in Spain. Diabetes Ther. 2014; 5: 155-168.

22. Weitgasser R, Lopes S. Self-reported frequency and impact of hypoglycaemic events in insulin-treated diabetic patients in Austria. Wien Klin Wochenschr. 2015; 127: 36-44.

23. Jacobson AM, Musen G, Ryan CM, Silvers N, Cleary P, et al. DCCT/EDIC Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med. 2007; 356: 1842-1852.

24. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, et al. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358: 2545-2559.

25. Bonds DE, Kurashige EM, Bergenstal R, Brillon D, Domanski M, et al. Severe hypoglycemia monitoring and risk management procedures in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007; 99: 80i-89i.

26. Seaquist ER, Miller ME, Bonds DE, Feinglos M, Goff DC, et al. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes care. 2012; 35: 409-414.

27. Saremi A, Bahn GD, Reaven PD. Veterans Affairs Diabetes Trial. A Link Between Hypoglycemia and Progression of Atherosclerosis in the Veterans Affairs Diabetes Trial (VADT). Diabetes care. 2016; 39: 448-454.

28. Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013; 98: 3411-3419.

29. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes care. 2013; 36: 3535-3542.

30. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010; 363: 1410-1418.

31. Miller ME, Bonds DE, Gerstein HC, Seaquist ER, Bergenstal RM, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010; 340: b5444.

32. Alsahli M, Gerich JE. Hypoglycemia. Endocrinology and metabolism clinics of North America. 2013; 42: 657-676.

33. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. Diabet Med. 2008; 25: 245-254.

34. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009; 52: 2288-2298.

35. Chow LS, Chen H, Miller ME, Marcovina SM, Seaquist ER. Biomarkers related to severe hypoglycaemia and lack of good glycaemic control in ACCORD. Diabetologia. 2015; 58: 1160-1166.

36. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, et al. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia. 2006; 49: 298-305.

37. DCCT/EDIC Study Research Group. Mortality in Type 1 Diabetes in the DCCT/EDIC Versus the General Population. Diabetes care. 2016; 39: 1378-1383.

38. Feltbower RG, Bodansky HJ, Patterson CC, Parslow RC, Stephenson CR, et al. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of diabetes in children and young adults. Diabetes care. 2008; 31: 922-926.

39. Nordin C. The proarrhythmic effect of hypoglycemia: evidence for increased risk from ischemia and bradycardia. Acta Diabetol. 2014; 51: 5-14.

40. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes care. 2011; 34: S132-S137.

41. Hanefeld M, Frier BM, Pistrosch F. Hypoglycemia and Cardiovascular Risk: Is There a Major Link? Diabetes care. 2016; 39: S205-S209.

42. Tanenberg RJ, Newton CA, Drake AJ. Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract. 2010; 16: 244-248.

43. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ. 2013; 347: f4533.

44. Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, et al. Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes. 2009; 58: 360-366.

45. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes care. 2003; 26: 1485-1489.

46. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes care. 2010; 33: 1389-1394.

47. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? Diabetes Metab Res Rev. 2008; 24: 353-363.

48. Austin EJ, Deary IJ. Effects of repeated hypoglycemia on cognitive function: a psychometrically validated reanalysis of the Diabetes Control and Complications Trial data. Diabetes care. 1999; 22: 1273-1277.

49. Whitmer RA. Type 2 diabetes and risk of cognitive impairment and dementia. Curr Neurol Neurosci Rep. 2007; 7: 373-380.

50. Whitmer RA. Cognitive impairment in ORIGIN: timing is everything. Lancet Diabetes Endocrinol. 2014; 2: 531-532.

51. Aung PP, Strachan MW, Frier BM, Butcher I, Deary IJ, et al. Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabet Med. 2012; 29: 328-336.

52. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby JV. Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus. JAMA-J Am Med Assoc. 2009; 301: 1565-1572.

53. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, et al. Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes Post hoc epidemiologic analysis of the ACCORD trial. Diabetes care. 2012; 35: 787-793.

54. Fonseca V, Chou E, Chung HW, Gerrits C. Economic burden of hypoglycemia with basal insulin in type 2 diabetes. Am J Manag Care. 2017; 23: 114-122.

55. Foos V, Varol N, Curtis BH, Boye KS, Grant D, et al. Economic impact of severe and non-severe hypoglycemia in patients with Type 1 and Type 2 diabetes in the United States. J Med Econ. 2015; 18: 420-432.

56. Geller AI, Shehab N, Lovegrove MC, Kegler SR, Weidenbach KN, et al. National Estimates of Insulin-Related Hypoglycemia and Errors Leading to Emergency Department Visits and Hospitalizations. Jama Internal Medicine. 2014; 174: 678-686.

57. Chubb B, Jensen MM, Frier BM. Self-Reported Frequency and Impact of Non-Severe Hypoglycaemia in Insulin-Treated Adults in the UK. Value Health. 2014; 17: A354-A355.

58. Anderbro T, Gonder-Frederick L, Bolinder J, Lins PE, Wredling R, et al. Fear of hypoglycemia: relationship to hypoglycemic risk and psychological factors. Acta Diabetol. 2015; 52: 581-589.

59. Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, Nemeth J, Quinn L. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention - a review. J Diabetes Complications. 2016; 30: 167-177.

60. Sakane N, Kotani K, Tsuzaki K, Nishi M, Takahashi K, et al. Fear of hypoglycemia and its determinants in insulin-treated patients with type 2 diabetes mellitus. J Diabetes Investig. 2015; 6: 567-570.

61. Harris SB, Khunti K, Landin-Olsson M, Galbo-Jorgensen CB, Bogelund M, et al. Descriptions of health states associated with increasing severity and frequency of hypoglycemia: a patient-level perspective. Patient Prefer Adherence. 2013; 7: 925-936.

62. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med. 2013; 369: 362-372.

63. Olsen SE, Asvold BO, Frier BM, Aune SE, Hansen LI, et al. Hypoglycaemia symptoms and impaired awareness of hypoglycaemia in adults with Type 1 diabetes: the association with diabetes duration. Diabet Med. 2014; 31: 1210-1217.

64. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes care. 2013; 36: 1384-1395.

65. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009; 94: 709-728.

66. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, et al. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes care. 2001; 24: 637-642.

67. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. Jama. 2017; 317: 371-378.

68. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, et al. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 2013; 369: 224-232.

69. Choudhary P, Olsen BS, Conget I, Welsh JB, Vorrink L, et al. Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management. Diabetes Technol Ther. 2016; 18: 288-291.

70. Vindedzis S, Marsh B, Sherriff J, Dhaliwal S, Stanton K. Dietary treatment of hypoglycaemia: should the Australian recommendation be increased? Intern Med J. 2012; 42: 830-833.

71. McTavish L, Wiltshire E. Effective treatment of hypoglycemia in children with type 1 diabetes: a randomized controlled clinical trial. Pediatr Diabetes. 2011; 12: 381-387.

72. Chabenne J, Chabenne MD, Zhao Y, Levy J, Smiley D, et al. A glucagon analog chemically stabilized for immediate treatment of life-threatening hypoglycemia. Mol Metab. 2014; 3: 293-300.

73. Robertson P, Davis C, Larsen J, Stratta R, Sutherland DE, American Diabetes A. Pancreas transplantation in type 1 diabetes. Diabetes care. 2004; 27: S105.

74. Rickels MR, Peleckis AJ, Markmann E, Dalton-Bakes C, Kong SM, et al. Long-Term Improvement in Glucose Control and Counterregulation by Islet Transplantation for Type 1 Diabetes. J Clin Endocrinol Metab. 2016; 101: 4421-4430.