



Quantitative study – other

People with diabetes and self-reported severe hypoglycaemia have increased mortality risk over 5 years

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Commentary on: **McCoy RG, Van Houten HK, Ziegenfuss JY, et al.** Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;**35**:268–901.

Implications for practice and research

- This retrospective survey of ambulatory patients with diabetes indicates that self-reported severe hypoglycaemia is associated with increased risk of 5-year mortality.
- Although the mechanisms are unclear, evaluation of patients with diabetes should include documentation of hypoglycaemia history and management approaches should focus on patient education and scrupulous avoidance of iatrogenic hypoglycaemia.

Context

Hypoglycaemia (<70 mg/dl; 3.9 mmol/l) in people with diabetes is frequently due to exposure to insulin or insulin secretagogues. The acute effects of hypoglycaemia in symptomatic patients, and the disabling effect of severe hypoglycaemia, are well known. However, data on the frequency of hypoglycaemia and magnitude of hypoglycaemia-related mortality are less certain. The investigators set out to determine whether self-reported hypoglycaemia is associated with increased mortality among outpatients attending a specialty diabetes clinic.

Methods

A total of 1013 outpatients (21.3% with type 1 diabetes and 78.7% with type 2 diabetes) completed a hypoglycaemia questionnaire between August 2005 and July 2006. Mild hypoglycaemia was defined as an episode not requiring assistance, and severe hypoglycaemia as one requiring external assistance. Using data from electronic medical records and the Social Security Death Index, the investigators compared mortality rates across groups of patients stratified by self-reported hypoglycaemia (none, mild or severe) 5 years after the initial questionnaire.

Findings

The 5-year all-cause mortality among the patients (aged between 18 and 93 years) was 13.8%, and was predicted by older age, male gender, longer duration of diabetes and greater baseline comorbidity index. Mild hypoglycaemia was reported by 61.7%, and severe hypoglycaemia by 7.5% (n=76) of participants. Persons who reported severe hypoglycaemia had a 3.4-fold higher 5-year death rate than persons reporting mild or no hypoglycaemia. The higher mortality persisted after controlling for the aforementioned predictive variables. Mild hypoglycaemia also showed an insignificant trend towards higher mortality. Notably, baseline glycated

haemoglobin values were similar between survivors and deceased subjects.

Commentary

Hypoglycaemia (<70 mg/dl; 3.9 mmol/l) is uncommon among diabetic patients not receiving treatment with insulin or sulphonylureas. Iatrogenic hypoglycaemia is often due to exposure to insulin or insulin secretagogues.¹ Hypoglycaemia is often suspected, but seldom provable, as a cause of death in ambulatory diabetic patients. Nonetheless, data from randomised controlled trials (RCT) indicate that hypoglycaemia is associated with increased risk of death.^{2–3} In a study published recently, McCoy and colleagues observed that self-reported severe hypoglycaemia was associated with a 3.4-fold greater risk of 5-year mortality compared with mild or no hypoglycaemia. Besides the retrospective, single-centre design, this study has other limitations. First, hypoglycaemia was not objectively verified; second, the self-report was elicited on a single occasion, without information on recurrent episodes; third, hypoglycaemia burden was not quantified and fourth, cause of death was not adjudicated. Also, 13.8% mortality over 5 years and the frequency of severe hypoglycaemia (7.5%) seem higher than data reported in clinical trials.⁴ Nonetheless, the observation that male gender, older age, longer duration of diabetes and greater comorbidity burden all predicted 5-year mortality is consistent with clinical experience.

Regarding mechanisms, it would be helpful to determine whether the increased 5-year mortality was driven by recurrent episodes of hypoglycaemia. Based on the small absolute number with severe hypoglycaemia (n=76),⁴ a single-centre RCT may not be feasible. However, a multicentre trial could be designed to randomise persons with self-reported hypoglycaemia to usual care versus interventions that prevent iatrogenic hypoglycaemia, and assess mortality outcome. Such a study would provide much-needed insights. Despite its limitations, this report has elements that should inform current practice. First, clinicians need to document hypoglycaemia history as part of the routine diabetes assessment. Second, patients with self-reported hypoglycaemia (particularly, if severe) should be provisionally recognised as being at high-mortality risk, either from subsequent hypoglycaemia, fatal cardiovascular events or as yet undetermined mechanisms. Pending data from RCTs, a judicious empirical approach in such patients should focus on optimisation of glycaemic control to

avoid or minimise iatrogenic hypoglycaemia,¹ and control of comorbid conditions.

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Competing interests None.

References

1. Dagogo-Jack S. Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. *Treat Endocrinol* 2004;3:91–103.
2. Bonds DE, Miller ME, Bergenstal RM, *et al*. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: a retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b4909.
3. Zoungas S, Patel A, Chalmers J, *et al*. ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–18.
4. Gerstein HC, Miller ME, Byington RP, *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;358:2545–59.