Hyperglycaemia and mortality

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SUMMARY

Several studies over the last decade have linked hyperglycaemia on hospital admission with subsequent mortality risk. The evidence is strongest for patients with myocardial infarction or acute coronary syndromes, but evidence also links hyperglycaemia with mortality from stroke and other medical illnesses. The effect seems independent of a previous diagnosis of diabetes mellitus; indeed, some studies suggest that mortality may be higher in patients with hyperglycaemia and no previous diabetes diagnosis compared with known diabetic patients. The effect on outcome of therapeutically lowering blood glucose levels has been considered in a small number of studies, but so far the results are conflicting. Further work is needed, focusing on more standardized surveys—previous studies vary in their use of blood or plasma, as well as cut-off levels for hyperglycaemia—and larger intervention studies.

INTRODUCTION

For acutely ill patients admitted to hospital, the ability to identify those at high risk of inpatient death is helpful for health workers, as well as for patients and their families. Identification of such patients would also allow more appropriate allocation of medical resources. A measurement which has emerged as highly predictive of poor inpatient outcome is hyperglycaemia, not necessarily in the context of known diabetes mellitus. Admission hyperglycaemia has been studied extensively, and in many clinical situations it appears to be positively associated with adverse outcome.[1–4] There is also some evidence that therapeutically reducing plasma glucose levels may improve outcomes.[5] We have therefore critically examined the existing literature on hyperglycaemia and hospital outcome, searching for key words 'hyperglycaemia', 'high blood glucose', 'high plasma glucose', 'mortality', 'inpatient mortality' and 'hospital mortality' in literature published between 1970 and 2005, using the PubMed and Ovid databases.

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PROBLEMS OF DEFINITION

Relatively high levels of plasma glucose may be detected in hospitalized patients in the absence of diabetes, but criteria for defining hyperglycaemia vary amongst available reports. In the USA, Umpierrez *et al.* found hyperglycaemia to be present in large numbers of hospitalized patients, about one-third of whom had no history of diabetes.[1] These workers used cut-off levels of blood glucose (not plasma) of >7.0 mmol/L fasting, or >11.1 mmol/L random. These are not equivalent to current World Health Organization (WHO) diagnostic criteria for diabetes, which are 6.1 and 10.0 mmol/L respectively for fasting and random glucose.[6] In the UK, Weir *et al.* examined random plasma glucose concentrations in stroke patients on admission, to show a possible association between glycaemia and stroke outcome.[2] Above a cut-off plasma glucose of 8.0 mmol/L, they found lower levels of survival, and in survivors a lower rate of eventual independent existence. A systematic overview of hyperglycaemia and myocardial infarction (MI) mortality used 'banding' of blood glucose levels (e.g. 6.1–8.0 mmol/L, etc).[3] Overall, therefore, there is no agreed level to separate 'normal' from 'abnormal' plasma or blood glucose concentrations for the investigation of outcome effects of hospital admission glycaemia, and the variable biological fluid assayed makes comparisons between studies even more difficult.

PREVALENCE OF HYPERGLYCAEMIA

A study from the USA showed that 38% of all patients admitted to an urban general hospital had fasting blood glucose levels exceeding 7.0 mmol/L, or two or more random blood glucose levels exceeding 11.1 mmol/L.[1] Another US study investigated unrecognized diabetes in a hospital population and found that 13% of all adult patients admitted to hospital had one or more plasma glucose values over 11.1 mmol/L, and approximately one-third of these hyperglycaemic patients had no prior history of diabetes.[7] There is evidence that at least some hyperglycaemic hospital patients may actually have previously undiagnosed diabetes. In 1983, Husband *et al.* reported on 26 'non-diabetic' patients admitted with acute MI and admission hyperglycaemia (blood glucose >10.0 mmol/L).[8] There were 16 survivors two months later, all of whom had an oral glucose tolerance test (OGTT) and 10 showed diabetes (63%). All

10 had an elevated HbA_1c on admission, strongly suggesting pre-existing diabetes.

EFFECT OF HYPERGLYCAEMIA ON MORTALITY AND MORBIDITY

Identification of hyperglycaemia at the time of hospital admission is important both because of its impact on mortality and morbidity, and because reduction of hyperglycaemia may improve outcome.[9–11] Numerous studies have linked admission hyperglycaemia with both hospital and long-term outcome. The endpoint has usually been mortality, but some reports have also examined markers of morbidity. Major studies are summarized in Table 1; most have examined the outcome in patients with MI or stroke, with a smaller number evaluating general morbidity or other disease-specific outcomes.

Coronary artery disease

Numerous studies have linked hyperglycaemia and coronary mortality, usually in acute MI (Table 1), again with varying cut-off points and definitions of hyperglycaemia.[3,4,12–15] All suggest a significant effect of hyperglycaemia on mortality, not explainable by an association with diabetes. In a recent Estonian study, an admission plasma glucose of >11.0 mmol/L in MI patients was taken to indicate hyperglycaemia. Mortality was assessed at 180 days post-admission and was significantly higher in the hyperglycaemic group (48% versus 14%, $P<0.0001$).[12] The effect was seen in both diabetic and non-diabetic patients, and interestingly the mortality in non-diabetic patients with an admission plasma glucose >11.0 mmol/L was similar to that of diabetic patients with an admission plasma glucose <11.0 mmol/L. A further study by Stranders *et al.* reported admission blood glucose levels after MI as an independent predictor for long-term mortality in patients with and without known diabetes.[13] They also found that an increase of 1.0 mmol/L in blood glucose level was associated with a 4% increase in mortality risk in non-diabetic patients and 5% in diabetic patients (both $P<0.05$). A recent German study found that MI patients with high glucose levels at hospital admission developed greater myocardial necrosis, and that hyperglycaemia was associated with shorter survival in patients with and without diabetes.[14] Other, retrospective studies have examined admission glucose levels in fatal and non-fatal MI cases,[4,15] or have used statistical regression analysis models.[15]

Admission glucose levels have also been associated with inpatient death or left ventricular dysfunction in patients admitted with acute coronary syndromes (ACS).[16] A further recent ACS study has shown mortality of 9% after a mean 1.6 year follow-up if admission glucose (sample type not specified) was <7.8 mmol/L, but 25% if it was >11.1 mmol/L ($P=0.001$)[17]. Interestingly, in this study elevated HbA_1c—presumably reflecting previous diabetes or glucose intolerance—did not predict mortality.

Stroke disease

Again, major studies are shown in Table 1. Small studies of stroke patients about 20 years ago suggested that 'stress hyperglycaemia' (raised blood glucose levels without a previous diagnosis of diabetes) was associated with a poorer outcome.[18,19] In one of these studies, Italian patients were divided into normoglycaemic, known diabetic and non-diabetic hyperglycaemic groups.[18] Interestingly, there was a significant ascending mortality between the groups of 29%, 45% and 78%, respectively. A similar effect was noted in a later and larger Danish study, where the hospital mortality was 17% for non-diabetic patients, 24% for those with known diabetes and 32% for 'new diabetes' (hyperglycaemia with no history of previous diabetes).[20] A small, early study suggested that the deleterious association between admission glucose levels and mortality was confined to haemorrhagic rather than thrombotic strokes.[21] However, a more recent meta-analysis suggests the reverse: that thrombotic stroke mortality is particularly associated with hyperglycaemia.[22] Hyperglycaemia also appears to affect cerebral infarct size, clinical stroke severity and long-term functional outcome.[23–25]

Other diseases

A US study has examined mortality in general hospital admissions (Table 1) and defined hyperglycaemia as a blood glucose concentration >7.0 mmol/L (fasting) or >11.1 mmol/L (random).[1] Mortality was 2% in euglycaemic non-diabetic patients, 3% in those with known diabetes and 16% in hyperglycaemic patients without known diabetes. A Canadian study of hospitalized pneumonia patients[26] used a blood glucose cut-off of 11.0 mmol/L, and found a mortality of 13% above this level and 9% below it (just significant, $P=0.03$).

MECHANISM OF ACTION

The question clearly arises as to how hyperglycaemia causes, or is associated with, clinical outcome. One possibility is that it is a marker for diabetes mellitus—either known or undiagnosed—but as discussed already, several studies have demonstrated that hyperglycaemia in the absence of diabetes is associated with increased mortality risk. Hyperglycaemia can have 'toxic' effects; for example, it may suppress immune function[27] and increase circulating inflammatory cytokine concentrations.[28] A recent study has suggested that acute hyperglycaemia in critically ill patients may be associated with insulin-independent cellular uptake of glucose, with subsequent toxic intracellular effects.[29]

Table 1 **Summary of studies relating hyperglycaemia on admission to hospital with outcome in various conditions**

Medical condition	*Country & Reference*	*Study years*	*Type of study*	*Patients (n)*	*Male : Female ratio (%)*	*Mean age (years) (SD)*	*Setting*	*Definition of hyperglycaemia (mmol/L)*	*Outcome*
Myocardial infarction	Canada[3]	1966–1998	Meta-analysis	3387	-	-	Hospital MI patients	Variable*	3.9 times mortality risk with hyperglycaemia
	Sweden[4]	1995–1997	Retrospective with prospective follow-up	197	72:28	68 ± 12	Consecutive MI admissions to ICU	Mean plasma glucose 8.1 ± 3.0	30% mortality at first hospitalization and 15% during the follow up period
	France[15]	2000–2001	Prospective	146	68:32	63 ± 15	Consecutive MI admissions	Not-defined	Admission glucose level higher in those who died (11.7 vs 8.0 mmol/L, P=0.002)
	Holland[13]	1989–1996	Retrospective and prospective	846	70:30	65 ± 12	Consecutive MI admissions to CCU	Plasma glucose > 11.1	Increase of 1 mmol/L plasma glucose associated with 4% mortality increase (non-diabetic) and 5% mortality increase (diabetic)
	Estonia[12]	2001–2002	Retrospective	779	59:41	68 ± 12	Consecutive MI admissions	Plasma glucose > 11.0	180-day mortality was 48% in patients with plasma glucose > 11.0 vs 14% in those with plasma glucose =11.0 (P < 0.0001)
	Germany[14]	1991–1997	Prospective	314	–	–	Consecutive MI admissions	Not defined	Mortality risk increase of 1.42 in diabetic and 1.54 in non-diabetic patients for each 2.6 mmol/L rise in admission plasma glucose.
Stroke	UK[2]	1990–1993	Prospective with long-term follow-up	811	50:50	70 (Median)	Stroke admissions with outpatient follow-up	Plasma glucose > 8.0	3 months mortality: 22% overall, 40% in patients with hyperglycaemia (P=0.0003)
	Denmark[20]	1991–1993	Prospective	1169	47:53	74 ± 11	Acute stroke admissions	Plasma glucose > 11.0	17% mortality in non-diabetic patients, 24% in known diabetic patients, 32% in patients with new diabetes (P=0.03)
	Italy[18]	1984	Prospective with 30 days follow-up	72	68:32	68 (38-91)	Consecutive stroke admissions	Fasting serum glucose > 6.1	78% mortality in non-diabetic patients, 45% in diabetic patients, 29% in normoglycaemic patients (P < 0.001)
	Canada[22]	1966–2000	Meta-analysis	3068	-	-	Hospitalized patients with stroke	Variable*	Patients with hyperglycaemia and ischaemic (but not haemorrhagic) stroke had increased mortality risk (RR 3.3; 95% CI 2.3–4.8)
Other diseases	USA[1]	1998	Retrospective	2030	38:62	59 ± 5	General hospital admissions	Fasting blood glucose ⩾ 7.0 Random blood glucose ⩾ 11.1	16% mortality in unknown diabetic patients, 3% in known diabetic patients, 1.7% in normoglycaemic patients (P < 0.01)
	Canada[26]	2000–2002	Prospective (multicentre)	2471	48:52	75	Consecutive pneumonia admissions	Plasma glucose > 11.0	13% mortality with blood glucose >11.0 mmol/L vs 9% with blood glucose ⩽ 11.0 mmol/L (P=0.03)

*Hyperglycaemia definitions varied between studies analysed
CCU: Coronary Care Unit; ICU: Intensive Care Unit; MI: Myocardial Infarction

Finally, it may be that hyperglycaemia is a marker of a subgroup of hypercatabolic and sicker patients who are likely to have a poorer outcome than their normoglycaemic counterparts.

INTERVENTION STUDIES

Control of hyperglycaemia during acute illness among diabetic and non-diabetic patients has been associated with improved outcome. Van den Berghe and colleagues conducted a randomized trial of intensive glycaemic control (blood glucose 4.4–6.6 mmol/L) compared to routine care in a surgical intensive care unit (ICU). At the end of the study period, patients with a mean blood glucose concentration of 5.7 mmol/L (intensive group) experienced a 42% lower mortality than patients with mean blood glucose level of 8.5 mmol/L (routine care).[11] However, reproduction of these results in critically ill medical patients has been less successful. A German multi-centre trial of patients with severe sepsis was stopped early because of an early excess of severe hypoglycaemia in the intensively insulin-treated group, with no mortality benefit.[30] A similar study from Belgium showed benefit in mortality only amongst those who were in ICU for more than three days.[31]

A number of studies have investigated the effect of glucose–potassium–insulin (GKI) infusions on outcome, particularly in patients with stroke and MI.[5,32–35] Not all these studies, however, were associated with lowering of plasma glucose levels, and even when glucose-lowering was achieved, it was not possible to exclude an intrinsic metabolic benefit of GKI on outcome.

CONCLUSION

There is persuasive evidence that elevation of blood or plasma glucose levels in hospitalized patients is strongly associated with an adverse outcome. A number of disease situations have been examined, but evidence is strongest for patients admitted with myocardial infarction, acute coronary syndromes, or thrombotic strokes. The risk is independent of a diagnosis of diabetes, and indeed a relatively consistent finding is that hyperglycaemic patients without previously known diabetes have a poorer outcome than established diabetic patients. Mortality risk may be modifiable by therapeutic lowering of glucose levels with insulin, though the literature here is inconsistent.

Unfortunately, though the literature on the subject is large, many studies have used variable cut-off glucose concentrations to define hyperglycaemia, and the body fluid for measurement (blood or plasma) has not been standardized. This makes assessment of the degree and extent of risk difficult, and further long-term, standardized studies are needed, addressing in particular the effect of therapeutic glucose-lowering. Such studies are urgently needed by clinicians, as hyperglycaemia in acutely ill patients is common, and more detailed risk–benefit analysis of interventions is essential.

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