Outcomes for general medical inpatients with diabetes mellitus and new hyperglycaemia

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ABSTRACT

Objectives: To investigate the relationship between admission glycaemic status and inpatient mortality in patients with and without pre-existing diabetes.

Design: Prospective observational cohort study.

Setting: A general medical ward in an Australian tertiary referral hospital.

Participants: 903 patients admitted to the general medical ward between February 2003 and July 2004.

Main outcome measure: Inpatient death.

Results: The overall inpatient mortality was 5.4% ($n = 49$). In the total cohort, age > 75 years and admission fasting plasma glucose (FPG) levels ⩾ 5.6 mmol/L were independent predictors of mortality. For patients without a known history of diabetes, each 1 mmol/L rise in admission FPG was associated with a 33% increase in mortality. In these patients, elevated (> 6.0%) and normal glycated haemoglobin (HbA_{1c}) levels were associated with mortalities of 11.3% and 4.4%, respectively (odds ratio, 2.47; 95% CI, 1.16–5.26). In contrast, in patients with known diabetes, there was no association between admission FPG levels, HbA_{1c} and mortality. Length of stay was not independently associated with FPG, HbA_{1c}, or diabetes status.

Conclusions: In patients without known diabetes, the risk of death was increased for admission FPG levels ⩾ 5.6 mmol/L. However, pre-existing abnormal glucose metabolism, reflected by elevated HbA_{1c} levels, appeared a more important predictor of inpatient mortality than glucose levels in patients without known diabetes.

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A 2002 study of hospital inpatients in Atlanta, USA, reported prevalences for diabetes mellitus and new hyperglycaemia of 26% and 12%, respectively.[1] New hyperglycaemia was associated with adverse outcomes, including increased mortality, increased hospital length of stay, and increased rates of high-level residential care placement. Inpatient hyperglycaemia in the non-diabetic patient is a risk factor for in-hospital mortality and heart failure in the setting of acute myocardial infarction.[2-6] Hyperglycaemia at the time of acute ischaemic stroke is also linked to worse functional outcome and increased mortality.[7-9] A more recent study has linked hyperglycaemia with adverse outcomes in patients with community-acquired pneumonia.[10]

It has been unclear whether hyperglycaemia directly affects the outcome of disease, or whether hyperglycaemia merely reflects a stress response to the severity of the intercurrent illness. It is also difficult to differentiate true "stress hyperglycaemia" from existing but previously undiagnosed diabetes mellitus. However, one study has suggested that a glycated haemoglobin (HbA_{1c}) level > 6.0% in acutely ill inpatients with hyperglycaemia on admission can reliably diagnose diabetes.[11]

The prevalence of diabetes in Australian tertiary referral hospitals has been estimated to be 23%.[12] The prevalence of newly diagnosed hyperglycaemia and its associations has not been documented in Australian hospitals. The aim of this prospective study was to determine the prevalence of known diabetes mellitus and new hyperglycaemia in patients admitted to a general medical ward in a tertiary referral hospital, and to investigate their relationship with in-hospital mortality and length of stay.

METHODS

Subjects

We studied 903 consecutive admissions in three recruitment periods spread across the year (25 Feb 2003 to 24 Apr 2003; 18 Nov 2003 to 8 Apr 2004; 5 Jul 2004 to 12 Jul 2004). A total of 139 patients were excluded because of readmissions (only the first admission during the recruitment period was included), death or discharge during the first 24 hours, or missed pathology testing. Background demographics (age, sex), admission diagnosis, diabetes status (non-diabetic, type 1 or type 2 diabetes), and information regarding intravenous fluid therapy administered (none, normal saline, 4% dextrose + 1/5 normal saline, or 5% dextrose) were recorded, as well as the outcome of each patient's admission (discharge or death), cause of death, and length of stay.

Ethics approval

The study was approved by the Human Research Ethics Committee of Austin Health.

Measurements

Fasting plasma glucose (FPG) and HbA_{1c} levels were measured the morning after admission. The fasting sample was drawn after at least 6 hours of overnight fasting. The American Diabetes Association definition of normoglycaemia, FPG < 5.6 mmol/L, was used to define the euglycaemic threshold, and hyperglycaemia was defined as FPG ⩾ 7.0 mmol/L in subjects not known to have pre-existing diabetes.[13] Patients with known diabetes were classified as "Group 1". The remaining patients with no documented history of diabetes were subdivided according to their FPG as either patients with new hyperglycaemia (FPG, ⩾ 7.0 mmol/L, "Group 2"), patients with indeterminate or uncertain glucose status (FPG, 5.6–6.9 mmol/L, "Group 3"), or patients with normoglycaemia (FPG, < 5.6 mmol/L, "Group 4").

Plasma glucose levels were measured using a hexokinase method (Beckman Coulter, Fullerton, Calif, USA). HbA_{1c} was measured using Primus CLC 330 (Primus Diagnostics, Kansas City, Mo, USA) affinity high performance liquid chromatography, which was calibrated against the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) approved reference measurement procedure.[14]

Statistical analysis

Categorical data were analysed by χ^2 test. Continuous variables were not normally distributed, so characteristics of Groups 1–4

1 Characteristics of 903 patients admitted to a general medical ward

	Group 1 $n = 202$ (22%)	Group 2 $n = 78$ (9%)	Group 3 $n = 174$ (19%)	Group 4 $n = 449$ (50%)	*P*
Age (years)	78 (70–84)	79 (72–84)	80 (71–86)	79 (71–86)	0.36
Sex (males)	52%	41%	49%	46%	0.35
HbA_{1c} level	7.0% (6.2%–8.0%)	5.9% (5.6%–6.3%)	5.7% (5.5%–6.0%)	5.6% (5.4%–5.9%)	< 0.001
Prevalence of HbA_{1c} level > 6%	81%	41%	22%	11%	< 0.001
FPG (mmol/L)	7.1 (5.7–8.9)	7.6 (7.2–8.4)	6.0 (5.8–6.3)	4.9 (4.6–5.2)	< 0.001
Mortality	5.0%	10.3%	8.0%	3.8%	0.04
Age of death (years)	82 (74–91)	81 (78–93)	85 (83–90)	82 (77–88)	0.37
Length of stay (days)	7 (4–12)	8 (5–14)	6 (4–11)	6 (4–11)	0.18

FPG = fasting plasma glucose level. Group 1 = known diabetes. Group 2 = new hyperglycaemia (FPG ⩾ 7 mmol/L). Group 3 = uncertain glycaemic status (FPG, 5.6–6.9 mmol/L). Group 4 = normoglycaemia (FPG, < 5.6 mmol/L). HbA_{1c} = glycated haemoglobin. Results are shown as median (interquartile range) for continuous variables. *P* values were determined by Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables. ◆

2 Odds ratios for mortality

	Odds ratio (95% CI)
Age	1.06 (1.03–1.10)
Length of stay	1.01 (0.996–1.03)
Female sex	0.80 (0.44–1.45)
Glycaemic group:	
Known diabetes (Group 1)	1.41 (0.63–3.16)
FPG 5.6–6.9 mmol/L (Group 3)	2.20 (1.05–4.62)
FPG ⩾ 7.0 mmol/L (Group 2)	2.87 (1.17–7.00)

FPG = fasting plasma glucose. Odds ratios were estimated using logistic regression. Female sex relative to male; glycaemic group relative to normoglycaemia (Group 4, FPG < 5.6 mmol/L). ◆

3 Characteristics of patients without a history of diabetes (Groups 2, 3 and 4) according to glycated haemoglobin (HbA_{1c}) level

	$HbA_{1c} \leqslant 6.0\%$ ($n = 569$)	$HbA_{1c} > 6.0\%$ ($n = 115$)	*P*
Age (years) (median [IQR])	79 (71–84)	80 (72–86)	0.28
Sex (male)	45%	50%	0.35
Fasting plasma glucose (mmol/L) (median [IQR])	5.2 (4.7–5.8)	5.9 (5.2–7.1)	< 0.001
Length of stay (days) (median [IQR])	6 (4–12)	7 (4–12)	0.62
Mortality	4.4%	11.3%	0.006

IQR = interquartile range. Continuous data were analysed by Mann–Whitney test and categorical data analysed by χ^2 test. ◆

were analysed using the Kruskal–Wallis test and characteristics of high and normal HbA_{1c} groups were analysed by the Mann–Whitney test. Logistic regression was used to determine (i) the relationship between mortality and the following variables: age either as a categorical (⩽ 75 years or > 75 years) or continuous variable, length of stay, sex, and category of glycaemia; (ii) the relationship between mortality and the following variables in non-diabetic patients: (a) age, HbA_{1c} level, length of stay, sex, and FPG; (b) age, length of stay, sex, and category of FPG and/or HbA_{1c} level (⩽ 6.0% or >6.0%). Analyses were performed using SPSS, version 11 (SPSS Inc, Chicago, Ill, USA).

RESULTS

The characteristics and outcomes for subjects with and without a history of diabetes are shown in Box 1. Of the total patient population, 49 (5.4%) died during their inpatient stay, with age > 75 years (odds ratio [OR], 4.6; 95% CI, 1.8–11.8; $P = 0.001$) and admission FPG ⩾ 5.6 mmol/L (OR, 2.0; 95% CI, 1.1–3.7; $P = 0.02$) being the only independent predictors of mortality. In patients without a known history of diabetes (Groups 2 to 4), mortality increased with increasing admission FPG levels, with a mortality of 3.8% in Group 4, compared with 8.0% in Group 3 and 10.3% in Group 2 ($P = 0.04$). Compared with those with FPG < 5.6 mmol/L (Group 4), uncertain glycaemic status and new hyperglycaemia (Groups 3 and 2) were associated with significant increases in the risk of inpatient death (Box 2). In those without known diabetes, there was a 33% increase in mortality for each 1 mmol/L rise in admission FPG ($P = 0.02$). There was a linear association between mortality and admission FPG in these patients ($P = 0.005$). Patients in Group 2 represented 16% of those who died and 8% of those who survived ($P = 0.04$); conversely, patients in Group 4 represented 35% of those who died and 51% of survivors ($P = 0.04$, Group 2 v Group 4). Comorbidities did not vary significantly across the groups.

HbA_{1c} measurements were used to attempt to identify undiagnosed diabetes in patients without a documented history of diabetes at admission. Patients without a prior diagnosis of diabetes and an HbA_{1c} level > 6.0% (elevated), suggestive of unrecognised pre-existing hyperglycaemia, had a mortality of 11.3%, whereas non-diabetic patients with an HbA_{1c} level ⩽ 6.0% (normal) had a mortality of 4.4% ($P = 0.006$). FPG levels were significantly higher in patients with an elevated HbA_{1c} level (Box 3). In a multivariate analysis that included age, sex, length of stay, HbA_{1c} level (normal or elevated) and FPG category, only age and HbA_{1c} level showed a significant relationship with mortality, with odds ratios of 1.06 (95% CI, 1.03–1.10; $P = 0.001$) and 2.47 (95% CI, 1.16–5.26; $P = 0.005$), respectively.

There was no significant difference in mortality between those with normoglycaemia and those with known diabetes. In patients with known diabetes, there was no association between admission FPG levels,

HbA_{1c} level and mortality. There was no variation in FPG according to the type of intravenous therapy administered.

The most common causes of death, ascertained from the medical records, were infections (51%), including urinary and respiratory sepsis and septicaemia. There was no significant relationship in the total study population between glycaemic status and cause of death, perhaps due to the small number of deaths. No differences in length of stay were found among the four groups. Patients who died had a longer length of stay than survivors (median, 9 v 6 days; $P = 0.01$), but this relationship was of borderline significance after accounting for age, sex and glycaemic group using multivariate logistic regression (Box 2).

DISCUSSION

The background prevalence of diabetes mellitus in the Australian adult population is 7.4%, with an undiagnosed case for every known case of diabetes.[15] The prevalence rises to 23% for people older than 75 years.[15] We found that only half of a general medical inpatient population had a normal FPG level, with a prevalence of known diabetes of 22% and a further 28% having an FPG level ≥ 5.6 mmol/L. Mortality and length of stay for patients with known diabetes were similar to those of the group with FPG < 5.6 mmol/L. This suggests that identification of patients with diabetes before hospital admission may be beneficial in reducing mortality in this older population. Nearly half (41%) of those with admission fasting hyperglycaemia had an HbA_{1c} level > 6.0%. One study found that an HbA_{1c} level > 6.0% in hospital inpatients with an admission random glucose level > 7 mmol/L and no prior history of diabetes was 100% specific and 57% sensitive for diagnosing diabetes.[11] However, the utility of HbA_{1c} level in diagnosing and stratifying patients in the acute setting may be limited by results not being available within the first 24 hours of admission. This raises the importance of outpatient screening for diabetes, especially in at-risk populations, as preadmission diagnosis and treatment of patients with known diabetes may lead to better inpatient outcomes.

It has been shown that elevated HbA_{1c} level has prognostic significance in non-diabetic patients undergoing percutaneous coronary intervention.[16] In a study of patients admitted for coronary artery bypass surgery, admission HbA_{1c} level $\geq 7.0\%$, suggestive of undiagnosed diabetes, predicted increased length of stay; however, patients with HbA_{1c} levels of 6.0%–6.9% had no increased length of stay.[17] In our study, we found no significant difference in length of stay for patients with or without diabetes, regardless of HbA_{1c} level. However, an elevated HbA_{1c} level in patients without known diabetes at admission was associated with a significantly higher mortality than for patients with a normal HbA_{1c} level (11.3% v 4.4%). Interestingly, when FPG and HbA_{1c} categories were both entered as independent variables in the logistic regression analysis, FPG appeared to be a less powerful predictor of mortality than HbA_{1c}. It should be noted that these two variables are correlated (Spearman $\rho = 0.27$; $P < 0.001$). The very high accuracy and precision of the HbA_{1c} level method at our centre (bias of < 0.1% compared with the recently endorsed IFCC standardisation system;[14] coefficient of variation, 1.9% [Mr Ian Goodall, Senior Scientist, Special Chemistry, Austin Health, personal communication]) allows confidence in discriminating between normal and abnormal HbA_{1c} values; this may require further validation in centres using other methods.

Improved inpatient glycaemic control has been shown to be beneficial in specific hospital populations, including cardiac surgery,[18] myocardial infarction,[19] and intensive care[20] settings. More recently, studies have been published which failed to confirm these findings,[21-23] suggesting that more studies need to be performed to establish the benefit of tight glycaemic control, and to identify glycaemic targets for therapy and which inpatient populations are most likely to benefit from intensive glucose-lowering interventions. A recently published study of intensive care patients found a twofold higher mortality in non-diabetic patients compared with patients with diabetes, despite lower blood glucose levels in the non-diabetic group.[24] This suggests that target levels for glycaemic control may differ between patients with and without diabetes. Further studies are required to evaluate whether improvements in glycaemic control in the older general medical inpatient population, especially in people with likely undiagnosed diabetes, results in reduced mortality.

Our study has some limitations. First, as the patients admitted to the general medical ward were older (median age, 79 years), survival bias could potentially explain the similar mortality rates between the diabetic and normoglycaemic groups. This may limit the extent to which these results can be generalised to the population at large, but the study group is representative of patients in the general medical wards of Australian tertiary referral hospitals. Admission criteria for diabetic and non-diabetic patients did not differ, so this cannot explain the similar mortality rates in the diabetic and normoglycaemic groups.

Second, patients who were discharged home or died within the first 24 hours after admission were excluded from the study, as they were unable to have the fasting blood test. Therefore, extremes of the clinical spectrum — the very well and the very sick — were excluded from the study. This could have resulted in a lower detection rate of new hyperglycaemic patients. One study found that patients with new hyperglycaemia had a longer hospital stay and an increased rate of intensive care unit (ICU) admission compared with patients with a history of diabetes or normoglycaemia.[1] We did not study the ICU admission or transfer rate, as considerations such as advanced age result in proportionally fewer critically unwell patients being considered candidates for intensive care management. Thus, ICU transfer does not accurately reflect deterioration in or severity of this cohort's condition, unlike in some other inpatient populations.

Third, post-discharge follow-up to confirm or reject a diagnosis of impaired glucose tolerance or diabetes proved difficult in the group with indeterminate plasma glucose levels. An outpatient post-discharge oral glucose tolerance test was performed in a small number of patients; however, testing a high percentage of patients with indeterminate FPG was not feasible because of their advanced age, with many requiring supported accommodation and assistance with travel. The abnormal FPG result was documented on patients' discharge summaries for primary health care provider follow-up. People in this study with an HbA_{1c} level > 6% and an FPG level ≥ 7.0 mmol/L were labelled as having diabetes, and appropriate therapy, including dietary and lifestyle advice, was instituted in hospital. Those with HbA_{1c} level $\leq 6\%$ and an FPG level ≥ 7.0 mmol/L were referred for repeat testing by their primary health care provider.

In conclusion, in patients without known diabetes, the risk of death was increased for admission FPG levels ≥ 5.6 mmol/L. However, pre-existing abnormal glucose metabolism, reflected by elevated HbA_{1c} level, appeared a more important predictor of inpatient mortality than glucose levels in patients without

known diabetes. Further studies are needed to determine if identification and early treatment of these patients leads to reduced inpatient mortality rates.

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COMPETING INTERESTS

None identified.

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REFERENCES

1 Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87: 978-982.
2 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; 355: 773-778.
3 Yudkin JS, Oswald GA. Hyperglycaemia, diabetes and myocardial infarction. *Diabet Med* 1987; 4: 13-18.
4 Norhammar AM, Ryden L, Malmberg K. Admission plasma glucose: independent risk factor for long-term prognosis after myocardial infarction. *Diabetes Care* 1999; 22: 1827-1831.
5 Oswald GA, Smith CC, Betteridge DJ, Yudkin JS. Determinants and importance of stress hyperglycaemia in nondiabetic patients with myocardial infarction. *BMJ* 1986; 293: 917-922.
6 Fava S, Aquilina O, Azzopardi J, et al. The prognostic value of blood glucose in diabetic patients with acute myocardial infarction. *Diabet Med* 1996; 13: 80-83.
7 Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001; 32: 2426-2432.
8 Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. *BMJ* 1997; 314: 1303-1306.
9 Williams LS, Rotich J, Qi R, et al. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 2002; 59: 67-71.
10 McAlister FA, Majumdar SR, Blitz S, et al. The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes Care* 2005; 28: 810-815.
11 Greci LS, Kailasam M, Malkani S, et al. Utility of HbA_{1c} levels for diabetes case finding in hospitalized patients with hyperglycemia. *Diabetes Care* 2003; 26: 1064-1068.
12 Rando L, Keith C, Sardjono DA, et al. Diabetes ward management — room for improvement. *J Pharm Pract Res* 2004; 34: 95-99.
13 Genuth S, Alberti KG, Bennett P, et al. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; 26: 3160-3167.
14 Mosca IF, Goodall I, Hoshino T, et al. Global standardization of glycated hemoglobin measurement: the position of the IFCC Working Group. *Clin Chem Lab Med* 2007; 45: 1077-1080.
15 Dunstan DW, Zimmet PZ, Welborn TA, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 2002; 25: 829-834.
16 Corpus RA, O'Neill WW, Dixon SR, et al. Relation of hemoglobin A1c to rate of major adverse cardiac events in nondiabetic patients undergoing percutaneous coronary intervention. *Am J Cardiol* 2003; 92: 1282-1286.
17 Medhi M, Marshall MC Jr, Burke HB, et al. HbA1c predicts length of stay in patients admitted for coronary artery bypass surgery. *Heart Dis* 2001; 3: 77-79.
18 Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract* 2004; 10 Suppl 2: 21-33.
19 Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; 26: 57-65.
20 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359-1367.
21 Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomised trial. *Ann Intern Med* 2007; 146: 233-243.
22 Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 2005; 293: 437-446.
23 Collier B, Diaz J, Forbes R, et al. The impact of a normoglycemic management protocol on clinical outcomes in the trauma intensive care unit. *JPEN J Parenter Enteral Nutr* 2005; 29: 353-359.
24 Rady MY, Johnson DJ, Patel BM, et al. Influence of individual characteristics on outcome of glycaemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc* 2005; 80: 1558-1567.

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