Original Article

# Glycosylated haemoglobin (HbA1c) and cortisol levels on admission to intensive care as predictors of outcome

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## Abstract

**Objective:** To evaluate the predictive value of glycosylated haemoglobin and cortisol on admission, in critical care patients.

**Design:** Prospective, observational, single centre study.

**Setting:** 14 bedded Intensive care unit of a tertiary-level university hospital.

**Patients:** 124 consecutive emergency medical and surgical patients.

## Keywords

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**Methods:** Data collected on admission included patient demographics, medical history, medication, diagnosis, type of nutrition, TISS28 score, serum blood glucose, Glycosylated haemoglobin (HbA1c), cortisol, mean arterial blood pressure, and the use of inotropes in the first 24hrs.

Daily baseline tests included complete blood count, urea and electrolytes, creatinine, twice weekly liver function tests.

The primary outcome measure was intensive care unit mortality. Secondary outcome measures were ITU stay, days of ventilation, peak urea, peak creatinine, lowest platelet count, peak bilirubin, lowest Pa/FiO2, and the number of transfusions.

**Measurements and results:** 124 patients (mean age 56.2 years SD 23.2) were included. Regression analysis was used to identify any potential predictors of outcome: HbA1c levels on admission were not found to be significantly associated with mortality ($p$=0.51), or any other secondary endpoints listed above. However, subgroup analysis revealed a predictive role of HbA1c with regards to length of ITU stay ($p$= 0.01) and number of days of ventilation ($p$=0.007) in those patients with a history of diabetes. Glucose level on admission emerged as an independent marker of mortality ($p$=0.009).

**Conclusions:** This study suggests that HbA1c may not be a predictor of outcome in the general ITU population but may be of predictive value in diabetic ITU patients. On the other hand, blood glucose levels on admission emerged as a predictor of mortality, whilst no association was found between HbA1c and cortisol levels on admission.

## Introduction

Hyperglycaemia has been well established as a factor determining mortality and morbidity in the intensive care setting. Furthermore, it has been demonstrated that actively maintaining tight glycaemic control has a direct effect on morbidity and mortality.[1,2]

The effect on outcome of the level of glycaemic control in the period of time prior to admission is unknown. Thus we set out to look at the glycosylated haemoglobin (HbA1c) level on admission, which reflects the average blood glucose levels in the preceding four weeks[3], to determine whether there is an effect on morbidity and mortality.

Furthermore, studies have shown that basal cortisol level may be an independent predictor of outcome.[4-11] Cortisol is also

a well known factor affecting glucose metabolism[12] promoting gluconeogenesis and having an anti-insulin effect in peripheral tissues. It has also been proposed that glucose levels may have a suppressor effect on cortisol production.[13] The study, proposes to investigate any possible association between the glycaemic status in the preceding four weeks, as reflected by admission HbA1c, and the cortisol levels on admission.

## Materials and methods

### Study population

All adults undergoing emergency admission to our intensive care unit over a three month period were included in the study. Exclusion criteria included all elective postoperative admissions, as it was felt that preoperative optimisation would have skewed HbA1c levels, and all patients on steroids. Ethical procedures and practices related to the observational study were duly enacted.

On admission, baseline patient data collected included demographics, past medical history, drug history, reason for admission, type of nutrition, serum blood glucose, $HbA_1c$, complete blood bount (CBC): haemoglobin, white cell count and platelet count, urea and electrolytes (U+E), creatinine and cortisol. A simplified Therapeutic Intervention Scoring System (TISS-28 score)[14] was calculated for the first twenty-four hours. Higher TISS-28 scores indicate a higher number of therapeutic interventions. Each intervention was assigned 1 to 4 points and the points were then summed to obtain the overall score. Daily baseline tests included a full blood count, electrolytes, urea and creatinine. Arterial blood gases were taken at least 4 times daily, frequency being dictated by clinical requirements. Twice weekly liver function tests were also performed.

### Outcome measures

The primary outcome measure was intensive care unit mortality. Secondary outcome measures were generic - number of days in the intensive care unit, and system specific. The latter were namely respiratory: number of days of ventilatory support, lowest Pa/FiO2 (arterial partial pressure of oxygen/inspiratory fraction of oxygen); renal: peak urea, peak creatinine; haematological: lowest platelet count and transfusion requirements during the entire patient stay; and hepatic: peak bilirubin. The choice of outcome variables was largely influenced by previous studies.[1-5]

The potential predictors under study included: HbA1c, cortisol on admission, glucose on admission, history of diabetes, age, gender. TISS28 score in the first twenty-four hours, MAP in the first twenty-four hours, and the use of inotropes in the first twenty-four hours served as indicators of disease severity in the patients under study.

### Statistical analysis

Univariate and multivariate regression analyses were performed to identify significant associations between the described outcome measures and potential predictors. Binary logistic regression was used to identify predictors of mortality, whereas linear regression was used to detect significant associations with morbidity. The Fisher's exact test was used in determining whether the use of inotropes in the first twenty four-hours reflected a worse outcome. For all statistical analysis, $P < 0.05$ was considered significant. SPSS statistical package version 10.0.1 for windows was used for all the statistical analysis.

## Results

### Study population

A total of 124 patients were enrolled in the study. Baseline characteristics are shown in Table 1. 29.8% had a history of diabetes and the mean HbA1c on admission was 6.63% (SD 1.83). Mean population blood glucose on admission was 11.7mmol/L (SD 7.55).

### Mortality

Mean outcome data for mortality and morbidity is shown in Table 2. 27.3% of patients enrolled in the study did not survive. No significant difference in mortality (p = 0.687) was observed between patients with a positive (29.7% mortality) and a negative (25.9% mortality) history of diabetes. Univariate analysis, using binary logistic regression, of the possible predictors of mortality identified glucose on admission and age. TISS-28 and use of inotropes in the first twenty-four hours were also significant, reflecting the increased severity of illness. All patients off inotropes in the first twenty-four hours survived. Multivariate analysis (Table 3) then maintained glucose on admission (OR 1.07) and TISS-28 (OR 1.17) as having an association with mortality. HbA1c levels were not found to have an effect on mortality ($p=0.138$). When the subgroup with a history of diabetes was analysed separately, non-significance persisted at a borderline p value of 0.06, as shown in Table 4. Regression analysis did not reveal any association between cortisol levels and mortality in neither the entire study group (table 3), nor in the diabetic subgroup ($p=0.647$, binary logistic regression).

### Morbidity

Multivariate analysis (Table 3) was carried out to identify any associations between the factors under study listed above, and the secondary outcome measures:

Length of ITU stay was associated with a history of diabetes and the use of inotropes in the first twenty-four hours. Patients without a history of diabetes spent an average 3.13 days more than their diabetic counterparts. Patients requiring inotropes in the first twenty-four hours (70 out of 124 patients) spent an average 4 days more on the unit. As shown in table 4, HbA1c was significantly associated with length of stay in those patients having a history of diabetes ($p=0.02$), such that for each unit increase in HbA1c levels there was an increase in stay by 1.26 days.

The number of days a patient was being ventilated was associated with higher TISS-28 scores in the first twenty-four

hours, such that for each unit increase in TISS-28 score, the patient spent 0.28 days more on the ventilator. Also, patients requiring inotropes in the first twenty-four hours required 3.38 days more of ventilation. Higher HbA1c levels were also associated with prolonged ventilation ($p$=0.03) in the subgroup having a history of diabetes, such that for each unit increase in HbA1c the patient spent an additional 1.36 days being ventilated.

Both peak serum creatinine and urea levels registered throughout the patients' stay were significantly associated with the use of inotropes in the first twenty four-hours. Patients on inotropes had an average peak creatinine which was 95.7μmol/l higher than those not on inotropes. Similarly, peak urea levels were on average 8.7mmol/l higher in patients requiring inotropes in the first twenty-four hours.

Furthermore it was observed that for each unit increase in the TISS-28 score, there was a reduction in the lowest platelet count by 3.2x10⁹/L.

Peak bilirubin levels were negatively associated with age; 2.96mmol/L less for each yearly increase in age.

Lowest Pa/FiO2 ratios were significantly associated with TISS-28 score and the use of inotropes in the first twenty-four

hours; those off inotropes had a ratio which was on average 76.04 higher.

Transfusion requirements were only significantly associated with TISS-28 score performed in the first twenty-four hours. An additional transfusion of 0.1 units of packed cells was administered for each unit increase in TISS-28 score.

Furthermore, no significant correlation between HbA1c and a specific cortisol response on admission ($n$=51, $p$=0.06, CI=11.826 to 578.33) was found, nor was there any significant association between cortisol levels on admission and blood glucose on admission ($n$=51, $p$=0.238, CI=4.885x10⁻⁴ to 1.918x10⁻³).

## Discussion

The main aim of the study was to determine whether there is any predictive value to HbA1c levels in patients on admission to the intensive care unit. From the statistical analysis presented above, it would seem that there is no such association when the study population is taken as a whole. However, when the subgroup with a history of diabetes was analysed, an association between HbA1c and the number of days of ventilation and ITU stay emerged. A weak non-significant association with mortality was also identified ($p$=0.06). This could be partially explained by the fact that the HbA1c values in the whole population were within a low and narrow range (with a mean of 6.63% (SD 1.47)). Conversely, it appears that HbA1c levels not within the normal range (i.e. 4.7% -6.4%), as in those patients with a history of diabetes (HbA1c mean 7.9%, SD 1.7) are of potential prognostic value.

However, the main weakness of the study is the relatively small cohort. As a result, this limitation is further accentuated when the sample is split into subgroups such that diabetic subgroup involves too small a population ($n$=37) for definitive conclusions to be drawn.

The secondary aim of the study was to look at both the potential predictive role of cortisol on admission, as well as to identify any link between HbA1c levels and the cortisol levels.

**Table 1:** *Baseline characteristics*

| Characteristic | No of patients (n=124) |
|---|---|
| Age/yrs (SD) | 56.2 (23.2) |
| Male Sex – no. (%) | 76.0 (61.3%) |
| History of Diabetes | 37.0 (29.8%) |
| History of ischaemic heart disease | 29.0 (23.4%) |
| History of chronic obstructive airways disease | 11.0 (8.9%) |
| History of chronic renal failure | 7.0 (5.6%) |
| | **Mean (SD)** |
| HbA1c% | 6.63 (1.83) |
| Glucose OA/mmol/L | 11.70 (7.55) |
| Cortisol OA/mmol/L | 1520.89 (1578.41) |
| Therapeutic intervention scoring system-28 in 1st 24hrs | 41.10 (23.1) |

| Reason for admission to intensive care | n (%) |
|---|---|
| Abdominal Surgery | 20 (16.6%) |
| Neurological | 20 (16.6%) |
| Pneumonia | 13 (10.8%) |
| Cardiopulmonary resuscitation | 12 (10%) |
| Pulmonary oedema | 10 (8.3%) |
| Trauma | 10 (8.3%) |
| Sepsis | 8 (6.6) |
| Drug overdose | 6 (5%) |
| Haematemesis | 4 (3.3%) |
| Cardiogenic shock | 3 (2.5%) |
| Others | 14 (14.4%) |

**Table 2:** *Patient outcome measures*

| Variable | Mean | SD | Min-Max |
|---|---|---|---|
| Mortality (total $n$) | (33) | | |
| ITU stay /days | 6.73 | 7.96 | 0-54 |
| Ventilation days | 4.90 | 7.47 | 0-51 |
| Peak Urea/mmol/l | 14.86 | 11.72 | 2-65 |
| Peak Creatinine /mmol/l | 187.12 | 220.42 | 30-1371 |
| Platelets lowest/10⁹/L | 165.16 | 80.85 | 8-448 |
| Peak bilirubin/mmol/l | 48.67 | 160.03 | 4-1157 |
| Lowest $PaO_2/FiO_2$ | 177.55 | 109.49 | 12-556 |
| Transfusions per patient | 0.60 | 2.10 | 0-15 |

$PaO_2$: *Arterial partial pressure of oxygen*
$FiO_2$: *Inspiratory fraction of oxygen*

The association between cortisol on admission and outcome is quite contentious and mixed results have been reported in the literature.[4,10,11] However, most studies have found cortisol levels on admission to be higher in non-survivors.[5-9] Small sample size prevented subset analysis according to background pathology, but no association was found between cortisol levels on admission and outcome in the total population. Furthermore, we wanted to see if cortisol levels had an effect on blood glucose. Firstly, it seems that glycaemic control in the weeks preceding admission, as reflected by the HbA1c levels, were independent of the cortisol levels on admission. This could be partly explained by the temporal factors involved, since HbA1c provided a snapshot of glycaemic status over the preceding four weeks, whereas cortisol on admission and its effects on glucose metabolism are only reflected at the time of sampling and there was no way of knowing the cortisol levels prior to that. Secondly, there seemed to be no association between the cortisol levels on admission and the immediate glucose levels on admission, which would suggest that other factors in the stress response may be responsible for the hyperglycaemia (mean glucose on admission 11.7mmol/l, SD 7.55).

Hyperglycaemia, both in the intensive care setting and in in-hospital care, has been known to be associated with a worse outcome in both diabetic and non-diabetic patients.[15-18] Our study suggests that the glucose level on admission is an independent marker of mortality in the population under study ($p=0.009$). The glycaemic status on admission did not seem to have an effect on morbidity in the total population (Table 3). However, when the subgroup having a history of diabetes was analysed separately, the trend seen above with HbA1c, was also reflected with the glucose level on admission. Thus, an association between glucose on admission and length of stay ($p=0.01$) and also the number of days of ventilation ($p=0.007$) is suggested. This is in keeping with previous studies which have shown that pulmonary oxygenation is impaired in diabetic patients, most likely due to pulmonary microangiopathy and nonenzymatic glycosylation-induced alteration of lung connective tissue.[19,20] Newer studies also show that glucose variability during the ITU stay is also a prognostic factor.[21] Diabetic patients are usually started early on insulin infusions, and this could contribute to artificial swings in blood glucose.[22]

The interesting finding that a history of diabetes was actually associated with a reduction of ITU stay (average 3.13 days less) was difficult to explain. The reduction in ITU stay persisted even after the patients admitted with diabetic ketoacidosis were excluded. Indeed, the mortality rate was slightly higher in the diabetic group at 29.7% as compared to 25.9% in the non-diabetic group, and could account for the shorter stay, but no significant differences in mortality between the two groups was registered ($p= 0.61$).

The use of resources, as gauged by the TISS-28 score, revealed some interesting findings. Indeed, the TISS-28 performed in the first twenty-four hours of admission emerged as a marker of illness severity, with significant associations with both mortality ($p=0.003$) and morbidity (Table 3). Indeed, as expected, patients requiring considerable resources on admission, were sicker, developed complications, required lengthier care, and were less likely to survive.

**Table 3:** *Outcome p values. N=124*

| | Age | Sex | HbA1c | Cortisol OA | Glucose OA | H/O Diabetes | Lowest Mean Arterial Pressure in 1st 24Hrs | TISS28 in 1st 24Hrs | Inotropes in 1st 24Hrs |
|---|---|---|---|---|---|---|---|---|---|
| Mortality[1] | 0.052 | 0.93 | 0.138 | 0.53 | **(0.009)** | 0.61 | 0.078 | **(0.003)** | **<0.001**[2] |
| ITU stay | 0.42 | 0.73 | 0.71 | 0.28 | 0.25 | **(0.046)** | 0.31 | **0.022** | **(0.005)** |
| Ventilation days | 0.129 | 0.73 | 0.497 | 0.428 | 0.109 | 0.100 | 0.15 | **(0.022)** | **(0.001)** |
| Peak Urea | 0.16 | **(0.017)** | 0.17 | 0.48 | 0.31 | (0.037) | 0.056 | **0.024** | **(<0.001)** |
| Peak Creatinine | 0.59 | **(0.008)** | 0.247 | 0.97 | 0.75 | 0.235 | 0.84 | 0.38 | **(0.02)** |
| Lowest Platelets | 0.29 | 0.71 | 0.06 | 0.89 | 0.39 | 0.28 | 0.16 | **(0.022)** | 0.732 |
| Peak Bilirubin | **(0.014)** | 0.33 | 0.331 | 0.82 | 0.40 | 0.565 | 0.61 | 0.32 | 0.513 |
| Lowest Pa/FiO$_2$ | 0.48 | 0.49 | 0.227 | 0.59 | 0.101 | 0.385 | **0.005** | **(<0.001)** | **(<0.001)** |
| Transfusions | 0.49 | 0.118 | 0.252 | 0.855 | 0.831 | 0.826 | 0.106 | **(0.002)** | 0.577 |

*Statistical test: Linear regression model unless stated otherwise*
*[1] Binary Logistic Regression*
*[2] Fisher's Exact Test*
*NB: Variables having statistical significance shown in bold. Variables significant after multivariate analysis shown in brackets*
*PaO$_2$: Arterial partial pressure of oxygen*
*FiO$_2$: Inspiratory fraction of oxygen*

Also, patients requiring the use of inotropes in their first twenty-four hours of admission had a worse prognosis. Use of inotropes in the first twenty-four hours was associated with higher mortality ($p<0.001$) and worse respiratory and renal endpoints (Table 3). This can be partially explained by the notion that the use of inotropes improves immediate haemodynamics, but does not provide a stable clinical improvement and outcome.[23] On the other hand, as with TISS-28 scores, the use of inotropes in the first twenty four-hours hours is more likely to reflect an increased disease severity and as expected[24] such patients have worse morbidity and mortality.

## Conclusions

Within the context of a limited sample size, this study suggests that HbA1c is not a predictor of outcome in the general ITU population, but may be of predictive value in diabetic ITU patients. Conversely, blood glucose levels on admission emerged as an independent predictor of mortality whilst no association was found between HbA1c and cortisol levels on admission.

## Acknowledgements

***Table 4:*** *Outcome measures in patients with a history of diabetes*

| | HbA1c | Glucose on admission |
|---|---|---|
| Mortality[1] | 0.06 | 0.060 |
| ITU stay | 0.02 | 0.010 |
| Ventilation days | 0.03 | 0.007 |
| Peak Urea | 0.85 | 0.650 |
| Peak Creatinine | 0.79 | 0.300 |
| Lowest Platelets | 0.66 | 0.510 |
| Peak Bilirubin | 0.56 | 0.220 |
| Lowest Pa/FiO$_2$ | 0.30 | 0.190 |
| Transfusions | 0.14 | 0.440 |

*Statistical test: Linear regression model unless stated otherwise*

*1 Binary Logistic Regression*

*PaO$_2$: Arterial partial pressure of oxygen*

*FiO$_2$: Inspiratory fraction of oxygen*

## References

1 Van den Berghe G, Wouters P, Weekers F, Verwaest C. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359-67.

2 Van den Berghe G, Wilmer A, Hermans G, Wouters PJ, Bouckaert B, Bruyninckx F, *et al.* Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–61.

3 Mortensen HB, Christophersen C. Glucosylation of human haemoglobin a in red blood cells studied in vitro. Kinetics of the formation and dissociation of haemoglobin A1c. Clinica Chimica Acta. 1983;134:317-26.

4 Ray DC, Macduff A, Drummond GB. Endocrine measurements in survivors and non-survivors from critical illness. Intensive Care Med. 2002;28:1301-8.

5 Jarek MJ, Legare EJ, McDermott MT. Endocrine profiles for outcome prediction from the intensive care unit. Crit Care Med. 1993;21:543-50.

6 Bain RJ, Fox JP, Jagger J. Serum cortisol levels predict infarct size and patient mortality. Int J Cardiol. 1992;37:145-50.

7 Nito I, Waspadji S, Harun S, Markum HM. Correlation between cortisol levels and myocardial infarction mortality among intensive coronary care unit patients during first seven days in hospital. Acta Med Indones. 2004;36:8-14.

8 Koh LK, Eng PH, Lim SC. Abnormal thyroid and adrencortical function test results in intensive care patients. Ann Acad Med Singapore. 1996;25:808-15.

9 Span LF, Hermus AR, Bartelink AK, Hoitsma AJ, Gimbrere JS. Adrenocortical function: an indicator of severity of disease and survival in chronic critically ill patients. Intensive Care Med. 1992;18:93-6.

10 Bouachour G, Tirot P, Gouello JP, Mathieu E, Vincent JF, Alquier P. Adrenocortical function during septic shock. Intensive Care Med. 1995;21:57-62.

11 Bollaert PE, Fieux F, Charpentier C, Levy B. Baseline cortisol levels, cortisol response to corticotropin, and prognosis in late septic shock. Shock. 2003;19:13-5.

12 William F. M.D Ganong. Review of Medical Physiology 22nd edition, Lange Basic Science S; 2005.

13 Fernández-Real JM, Ricart W, Casamitjana R. Lower cortisol levels after oral glucose in subjects with insulin resistance and abdominal obesity. Clin Endocrinol (Oxf). 1997;47:583-8.

14 Miranda DR. Simplified Therapeutic Intervention Scoring System: the TISS-28 items. Results from a multicenter study. Crit Care Med. 1996;24:64-73.

15 Umpierrez GE, Isaacs SD, Bazargan N. Hyperglycaemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endorinol Metab. 2002;87:978-82.

16 McCowen KC, Malhotra A, Bistrian BR. Stress induced hyperglycaemia. Crit Care Clin. 2001;17:107-24.

17 Fietsam R Jr, Basset J, Glover JL. Complications of coronary surgery in diabetic patients. Am Surg. 1991;57:551-7.

18 O'Neil PA, Davies I, Fullerton KJ. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke. 1991;22:842-7.

19 Seki S, Yoshida H, Momoki Y, Ooba O. Impaired pulmonary oxygenation in patients undergoing coronary artery bypass grafting. Cardiovasc Surg. 1993;1:72-8.

20 Sandler M. Is the lung a 'target organ' in diabetes mellitus? Arch Intern Med 1990; 150:1385-8.

21 Balasubramanyam A. Intensive Glycemic Control in the Intensive Care Unit: Promises and Pitfalls. J Clin Endocrinol Metab. 2009; 94:416-7.

22 Egi M, Bellomo R, Stachowski E, French CJ, HartG. 2006 Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 2006; 105:244–52.

23 Rapezzi C, Perugini E, Santi M, Bracchetti G, Branzi A. Inotropic therapy is unsuccessful: wrong conceptual target or wrong therapeutic tools? Ital Heart J. 2003; 4 Suppl 2:22S-6S.

24 Van Den Noortgate N, Vogelaers D, Afschrift M, Colardyn F. Intensive care for very elderly patients: outcome and risk factors for in-hospital mortality. Age Ageing. 1999;28:253-6.