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Stress hyperglycemia: A prospective study examining the relationship between glucose, cortisol and diabetes in myocardial infarction

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ABSTRACT

Aim: We aimed to explore the relationship between stress, hyperglycemia and diabetes in myocardial infarction (MI), using serum cortisol as a surrogate marker for the severity of stress.
Methods: Subjects with acute MI were prospectively recruited upon hospital admission. Serum glucose and cortisol were measured in addition to standard testing. Subjects were defined as having stress hyperglycemia (SH) if they had an admission glucose ≥7.8 mmol/L without a history of glucose intolerance. Subjects were followed up with glucose tolerance testing post-discharge.
Results: Of the 200 subjects in the study, 58 had known diabetes/impaired glucose tolerance (IGT), and 45 had SH. There was a positive association between admission glucose and cortisol for the entire cohort ($r_s = 0.26$, $p < 0.01$). This relationship was present in the subgroup who had SH and then normal glucose post-discharge ($r_s = 0.53$, $p = 0.03$), but not in SH subjects who had diabetes/IGT on post-discharge testing. It was also evident amongst all subjects with normal glucose ($r_s = 0.46$, $p < 0.01$), but not those with diabetes/IGT in general. On multivariate analysis, admission glucose was a positive predictor and cortisol a negative predictor of abnormal glucose tolerance.
Conclusions: Our data suggests that SH with MI reflects either underlying glucose intolerance or more severe stress in people without glucose intolerance.

1. Introduction

The phenomenon of hyperglycemia occurring in critically ill patients who have not previously been diagnosed to have diabetes, has been described as stress hyperglycemia (SH).[1] This is common, and has been reported to occur in up to 30–80% of various hospital cohorts.[2] Varying glucose thresholds for hyperglycemia have been used by different authors, but a recent Endocrine Society guideline has defined hyperglycemia as a glucose level > 7.8 mmol/L.[2] In an earlier study, we found that in a cohort of 6187 people admitted to hospital through the Emergency Department, 19% had established diabetes.[3] Of the other 5192 subjects, 692 (13%) had newly discovered hyperglycemia, or SH, by the Endocrine Society criterion.

It is unclear whether patients who develop SH have an underlying abnormality of glucose metabolism, an exaggerated hormonal response to stress during the episode of acute illness, or both. It has been demonstrated that cortisol secretion is elevated during acute illness and plays an important role with other counter-regulatory hormones in the pathophysiology of SH.[4] For example, cortisol production is increased in acute coronary syndromes and its levels correlate with severity of myocardial infarction and predict mortality.[5,6] Serum cortisol has also been shown to be one of the major determinants of serum glucose in non-diabetic myocardial infarction patients with SH.[7]

Until recently, there were no data examining the relationship between serum cortisol and glucose, and how this interacts with underlying glucose intolerance amongst subjects with myocardial infarction. In a small study of patients with SH during myocardial infarction, we had found that the severity of hyperglycemia was predictive of the likelihood of persistent glucose intolerance, whereas there was an inverse correlation between cortisol levels and persistent glucose intolerance.[8] This had led us to conclude that hyperglycemic patients with elevated stress hormones during acute myocardial infarction are hyperglycemic because of greater stress and therefore are less likely to have true

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underlying abnormal glucose tolerance. Conversely a low admission cortisol level in a hyperglycemic subject indicates underlying glucose intolerance or diabetes. The implication of this is that hyperglycemic patients who have a lower cortisol level are less unwell hence their hyperglycemia is caused by an underlying tendency to glucose intolerance rather than severity of stress.

The aim of the current study was to explore the relationship between glucose and cortisol in a larger prospective cohort of subjects with myocardial infarction. In particular, we were interested in how this relationship is influenced by the presence of glucose intolerance.

2. Subjects, materials and methods

2.1. Ethics

This study was conducted in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki. Approval from the Western Sydney Area Health Service Research Ethics Committee, and consent from all participants was obtained.

2.2. Subjects

Patients admitted into hospital with acute myocardial infarction were recruited into the study. Acute myocardial infarction was defined on the basis of a serum troponin-T > 0.05 μg/L, with or without ST segment elevation. Whether the subject had a past history of diabetes mellitus or glucose intolerance did not affect eligibility. Participants were excluded if they were pregnant, on glucocorticoid therapy at the time of admission, or had mental or intellectual impairment.

Random glucose and cortisol levels were measured at the time of admission. An additional blood sample was obtained for HbA1c assessment from participants who had known diabetes, or an admission blood glucose level (BGL) ≥7.8 mmol/L.

Age, gender, past or family history of diabetes, and usual diabetes therapy of the participants were recorded. Details of the myocardial infarct including cardiac troponin and creatinine kinase (CK) levels were also recorded.

Subjects who had an admission BGL ≥7.8 mmol/L but who were not previously known to have diabetes or glucose intolerance were asked to have their glucose metabolic status reassessed through a 75 g oral glucose tolerance test (OGTT) 3 months after discharge. Diagnosis of diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) was made according to World Health Organization GTT criteria.[9] Twenty three patients completed a OGTT, and a further 11 patients had only a single fasting BGL performed but not a full OGTT; a fasting BGL ≥7.0 mmol/L was classified as diagnostic of DM and a fasting BGL between 6.1 and 6.9 mmol/L was classified as IFG. The a priori definition of diabetes on follow-up was based on glucose parameters only, as Australia had not accepted an HbA1c for the diagnosis of diabetes at the time of commencement of the study.[10]

2.3. Assays

Cortisol was measured using a solid phase, competitive chemiluminescent enzyme immunoassay (IMMULITE® 2000 Immunoassay System, Siemens, Deerfield, IL, USA). BGL was measured using the hexokinase method (Roche Diagnostics, Indianapolis, IN, USA). HbA1c was measured using ion exchange high pressure liquid chromatography (VARIANT II Hemoglobin A_{1C} Program, BIORAD, Hercules, CA, USA). cTnT was measured using the electrochemiluminescence immunoassay (ECLIA) method that employs two monoclonal antibodies specifically directed against human cardiac troponin T (Elecsys Troponin T assay, Cobas-Roche Diagnostics, West Sussex, UK). Creatinine kinase measurements were based on rate of change in reflection density which is then converted to enzyme activity after a series of enzymatic reactions of CK (Vitros CK, Ortho-Clinical Diagnostics Inc., Rochester, NY, USA).

2.4. Statistical analyses

Results are presented as median with interquartile ranges, unless otherwise stated. The Chi square test was used to evaluate categorical variables and the Mann–Whitney test was used for continuous variables as most were not normally distributed. Spearman rank correlation was used to measure the degree of linear association between continuous variables, with r_s denoting the Spearman rank correlation coefficient. Logistic regression was used to analyse the association between bivariate groups and continuous variables. Multiple regression and backward stepwise multi-variable logistic regression were used to determine if associations were independent. *P* values of <0.05 were considered significant.

Based on the results of our previous retrospective study[8], it was estimated that a sample size of 35 participants with no previous history of abnormal glucose tolerance but with an admission BGL ≥7.8 mmol/L would be required to provide 80% power with 0.05 two-sided significance level to allow admission cortisol level to be utilized as a predictor of subsequent abnormal glucose tolerance status.

3. Results

3.1. Subjects with diabetes, stress hyperglycemia and normoglycemia

A total of 200 eligible patients consented to participate in the study (Fig. 1). There were 171 males and 29 females. Fifty eight patients (29% of the cohort, 47 males and 11 females) were known to have pre-existing diabetes/IGT (one male patient had IGT). Forty five patients had no past history of diabetes/IGT but had an admission BGL ≥7.8 mmol/L (22.5% of the entire cohort, 32% of those with no history of diabetes/IGT). This is the SH group (SHG). The remaining 97 patients (83 males and 14 females) all had an admission BGL <7.8 mmol/L, with no history of glucose intolerance.

Of the 45 patients in the SHG, 6 were diagnosed to have diabetes on clinical grounds (requiring medical therapy) during their hospital admission, and all but 5 of the remainder had follow-up testing of their glucometabolic status. Twenty three subjects had the 75 g OGTT at follow-up and the remaining 11 subjects only had a fasting BGL checked. Twenty subjects (50%) were newly diagnosed with diabetes/prediabetes (12 DM, 5 IFG, 2 IGT and 1 combined IFG/IGT) while the remaining 20 subjects were normal on follow-up. We grouped patients according to their final glucometabolic status (Fig. 1) defining those with normal glucose tolerance as Group 1 (N = 117), and those with diabetes/prediabetes as Group 2 (N = 78). The characteristics of the 2 groups are listed in Table 1.

3.2. Relationship between creatinine kinase and cortisol levels

There was a positive association between peak plasma CK level (with log transformation) and cortisol level in the entire cohort (r_s = 0.36, $p < 0.01$). This association remained on multiple regression with adjustment for gender, age, BMI and family history of diabetes ($p < 0.005$). The relationship also existed within Group 1 (r_s = 0.37, $p < 0.001$), and within Group 2 (r_s = 0.32, p = 0.009) (Fig. 2). There was also a correlation between the admission BGL and the peak CK level in subjects with normal glucose tolerance (r_s = 0.20, p = 0.03) but such an association was not found in those with diabetes/prediabetes.

3.3. Relationship between admission blood glucose and cortisol levels

There was a positive association between admission BGL and cortisol level in the entire cohort (r_s = 0.26, $p < 0.01$) that was lost on multiple regression (p = 0.13). However subgroup analysis indicated that there was a correlation between admission BGL and cortisol levels in Group 1 (r_s = 0.46, $p < 0.01$), but there was no association in Group 2 (Fig. 3). Amongst the subjects who had SH on admission but had normal glucose tolerance at follow-up (Group 1B), the same relationship was found between admission BGL and cortisol levels (r_s = 0.53, p = 0.03) but such

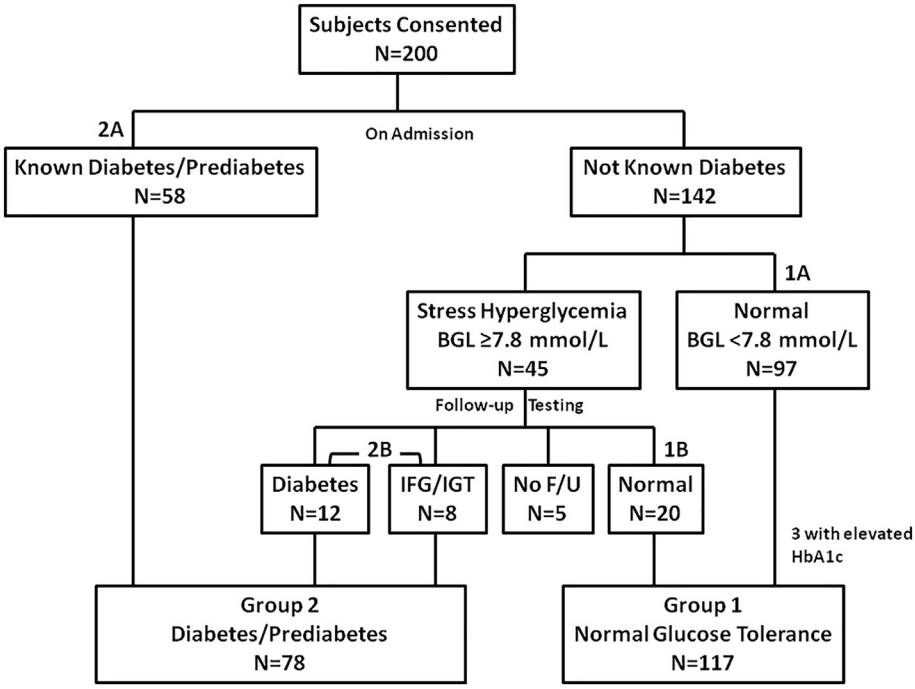

Fig. 1. Classification of subjects according to their final glucose tolerance status at follow-up. IFG = impaired fasting glucose; IGT = impaired glucose tolerance; BGL = blood glucose level.

an association was not found in those with SH but with newly diagnosed diabetes/prediabetes at follow-up (Group 2B).

3.4. Predictors of glucose intolerance in subjects with stress hyperglycemia

Amongst the subjects with SH, only the admission BGL (OR 1.5, 95% CI 1.03–2.0, $p = 0.03$) and HbA1c (OR 12.8, 95%CI 1.3–128.1, $p = 0.03$) were predictors for underlying glucose intolerance on univariate analysis. Cortisol levels were not predictive. Amongst the patients who had some form of hyperglycemia (Group 1B and Group 2), a positive family history of diabetes, admission BGL, as well as HbA1c level were predictors of abnormal glucose tolerance (Table 2). The association between cortisol levels and abnormal glucose tolerance did not reach significance ($p = 0.07$).

Multivariate analysis was also conducted within the patients with any form of hyperglycemia (Group 1B and Group 2). With backward stepwise multiple logistic regression analysis with cortisol, admission BGL, CK and family history in the model (but excluding HbA1c as this is now acceptable as a diagnostic test of diabetes), admission BGL remained a positive predictor (odds ratio 1.3, 95%CI 1.1–1.7, $p = 0.02$) and cortisol a negative predictor of abnormal glucose tolerance (OR 0.998, 95%CI 0.995–0.9998, $p = 0.03$).

3.5. Reclassification of subjects using HbA1c to diagnose diabetes

There were 3 subjects who did not have pre-existing diabetes/IGT nor an admission glucose level ≥ 7.8 mmol/L, but who had an HbA1c in the diabetic range (≥6.5%, 48 mmol/mol). These subjects were

Table 1
Subject characteristics according to final glucometabolic status (expressed as percentage of cohort or median and interquartile range).

	Diabetes/Prediabetes (Group 2, N = 78)	Normal glucose status (Group 1, N = 117)	*p* value
Known diabetes/prediabetes at admission	58	0	
Age (years)	60.5 (52.8 to 67.3)	59.0 (51 to 68)	0.72
Gender (male)	65 (83.3%)	102 (87.2%)	0.53
Family history of diabetes	42 (53.8%)	25 (21.4%)	<0.01
Admission BGL (mmol/L)	11.35 (8.3 to 15.8)	6.70 (5.8 to 7.6)	<0.01
Peak creatinine kinase (U/L)	548.5 (195.8 to 2418.0)	680.0 (250.0 to 1440.0)	0.65
cTnT (μg/L)	1.62 (0.3 to 4.4)	1.30 (0.4 to 3.4)	0.85
Cortisol (nmol/L)	605.5 (371.3 to 956.6)	657.0 (422.0 to 861.0)	0.97
HbA1c (%)	7.8 (6.5 to 9.6)	5.6 (5.2 to 5.8)	<0.01
HbA1c (mmol/mol)	63 (48 to 96)	38 (33 to 40)	<0.01
BMI (kg/m^2)	28.7 (26.5 to 32.4)	27.9 (25.5 to 30.2)	0.11
Waist circumference (cm)	102.8 (95.0 to 114.0)	100.8 (94.0 to 107.9)	0.04

BGL = blood glucose level; cTnT = plasma cardiac troponin-T; BMI = body mass index.

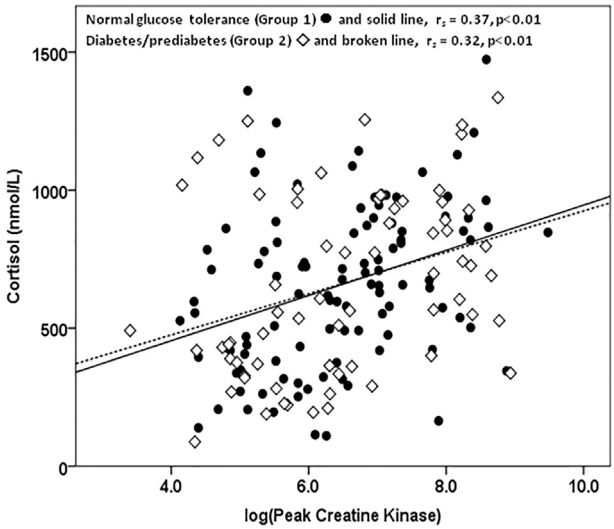

Fig. 2. Relationship between admission plasma cortisol and peak CK levels in patients with normal glucose tolerance (Group 1), and patients with diabetes/prediabetes (Group 2).

classified as non-diabetic in accordance with the a priori protocol, in the above analyses. Reclassifying these 3 subjects as having diabetes did not materially alter the major findings of the study. However, in the normal glucose subjects (Group 1), the relationship between admission BGL and peak CK fell out of significance ($r_s = 0.16$, $p = 0.1$) and amongst the subjects with SH, the admission BGL no longer predicted underlying glucose intolerance (OR 1.4, 95%CI 0.99–1.9, $p = 0.06$). Conversely, on backward stepwise multiple logistic regression, admission glucose remained predictive of glucose intolerance amongst subjects with any form of hyperglycemia (OR 1.3, 95%CI 1.01–1.6, $p = 0.046$), but cortisol fell out of the model (OR 1.0, 95%CI 0.99–1.0, $p = 0.06$).

4. Discussion

Our study found that amongst subjects suffering an acute myocardial infarction, 32% of those who were not known to have glucose intolerance, had SH. This concords with the literature where SH has been described in 30–90% of hospitalized patients.[2] The importance of SH is that it reflects either an underlying predisposition to diabetes

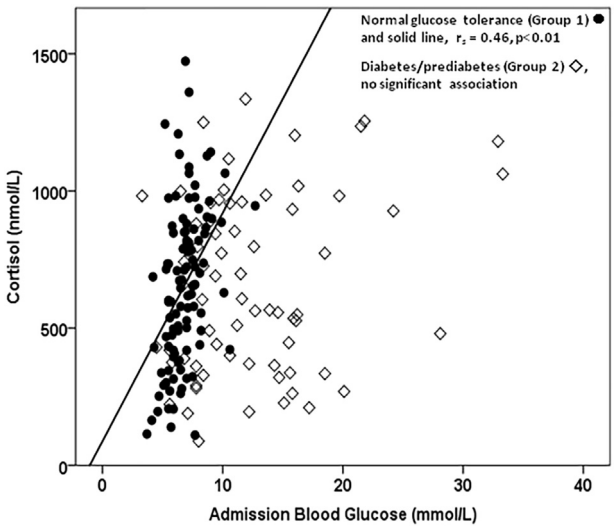

Fig. 3. Relationship between admission plasma cortisol and blood glucose levels in patients with normal glucose tolerance (Group 1) and patients with diabetes/prediabetes (Group 2).

Table 2
Predictors of abnormal glucose tolerance in patients with any form of hyperglycemia (Groups 1B, 2A and 2B).

Variable	Odds ratio	95% CI	*p* value
Age	0.98	0.94–1.03	0.39
Gender (female)	3.80	0.47–30.95	0.21
Family history of diabetes	3.46	1.13–10.57	0.03
Admission BGL	1.22	1.04–1.43	0.02
Peak creatinine kinase	1.00	1.00–1.00	0.91
Cardiac troponin-T	1.04	0.92–1.18	0.54
Cortisol	0.998	0.996–1.00	0.07
HbA1c	16.9	3.10–92.43	<0.01
BMI	0.98	0.89–1.07	0.63

(unmasked by the stress of illness), or is a marker of an extreme stress response and therefore indicates severe acute pathology.[8]

The key finding of the current study is that there are 2 different but overlapping groups of patients with SH (Fig. 4). The relationship between the degree of hyperglycemia and the severity of stress holds true only amongst those whose hyperglycemia is due to severe illness. This group has more severe disease, and are less likely to have underlying glucose intolerance. Their hallmark is an elevated serum cortisol. The second group has hyperglycemia due to an exacerbation of underlying glucose intolerance by even a moderately severe illness. This group has a better prognosis, but are likely to have diabetes on subsequent testing. In effect, they either had undiagnosed diabetes, or a degree of glucose intolerance which can be pushed over the edge by a modest degree of stress. Their cortisol levels are less elevated, and there is no relationship between the cortisol level with the severity of hyperglycemia. The level of hyperglycemia is mainly dictated by the severity of underlying abnormal glucose tolerance, rather than the severity of illness.

There is an abundance of literature that there is increased mortality with hyperglycemia, and that this relationship is stronger amongst hyperglycemic subjects who did not have known diabetes. This has been demonstrated in myocardial infarction,[11,12] intensive care,[13] patients requiring TPN,[14] general hospital patients,[3,15] and a range of other hospital situations. Whether treatment of SH improves outcomes remains unclear, with some studies showing benefit,[16–18] but others failing to demonstrate this[19,20] or even worse outcomes.[21]

The high rate of persistent hyperglycemia or subsequent diabetes amongst people with SH is also well described. The incidence of diabetes has been reported to be 8–68%,[8,22,23] with the wide range likely to be due to differences in population and study methodology. In the

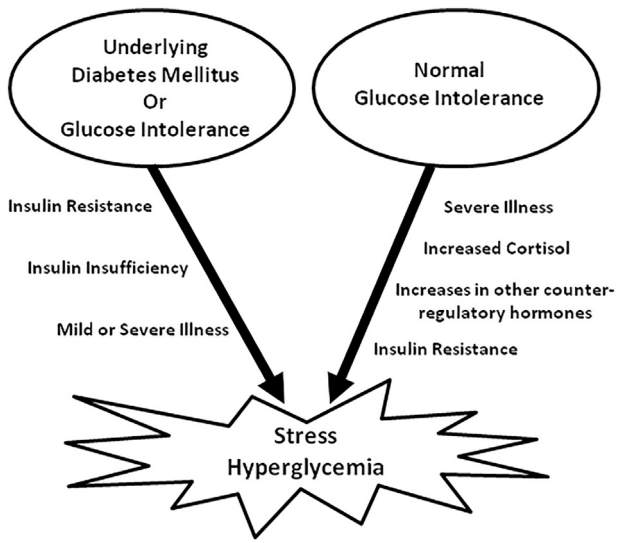

Fig. 4. Pathways to the development of stress hyperglycemia.

current study persistent hyperglycemia was also very high, with 50% of subjects who had SH demonstrating glucose intolerance on follow-up testing. The incidence of diabetes was 30%. We confirmed our earlier finding that the severity of hyperglycemia is a predictor of underlying glucose intolerance, but failed to repeat the finding that cortisol is a negative predictor. The relationship fell short of reaching significance ($p = 0.07$) but it is possible that a larger sample size may have demonstrated a significant relationship.

The development of SH has been attributed to the stress response with an elevation of cytokines such as tumour necrosis factor-α and interleukin-1, and release of counter-regulatory hormones such as glucagon, catecholamines and cortisol.[1] Activation of the hypothalamic-pituitary-adrenal (HPA) axis has been demonstrated in settings of acute medical stress.[24,25] The degree of HPA axis activation is in general proportionate to the severity of stress.[26] There is also increased insulin resistance and glucose production secondary to enhanced gluconeogenesis and glycogenolysis. The degree of hyperglycemia and insulin resistance has been reported to be directly proportional to the severity of the stress response.[1]

With respect to acute coronary syndromes, there are older studies that have shown that plasma cortisol is increased in patients with myocardial infarction,[27,28] and that the cortisol level was higher in those who have developed complications such as cardiogenic shock, or who died compared to those with uncomplicated infarcts.[5,29] One study which showed that endogenous steroid production is increased in patients with myocardial infarction and that the steroid levels correlated with serum cardiac enzyme changes, suggesting the severity of myocardial necrosis governed the magnitude of adrenocortical response.[30] Our study has confirmed the correlation between peak plasma CK and cortisol levels amongst people suffering myocardial infarction, with the relationship being present in both the normal glucose tolerance and diabetes/prediabetes subgroups. This finding is not surprising, as a higher CK should indicate a larger infarct and therefore a greater degree of stress.

The relationship between SH and complications following myocardial infarction has also been demonstrated in a post-hoc analysis of the HI-5 Study, a randomised controlled trial of tight glucose control in myocardial infarction.[31] In this study, the stress hyperglycemia ratio (mean glucose level in first 24 h/average glucose level in previous 3 months as estimated from glycosylated hemoglobin), was associated with a complicated myocardial infarct, death, congestive cardiac failure, arrhythmia, and cardiogenic shock. It is unclear if this is a superior measure to cortisol in the assessment of SH, but it may be more practical than cortisol in that the glycosylated hemoglobin should be routinely measured for patients with hyperglycemia. Unfortunately, we did not have a standardised process for measurement of glucose levels in the 24 h after myocardial infarction in the current study, so are unable to calculate the stress hyperglycemia ratio.

There are several limitations to our study. First, we grouped patients with pre-existing diabetes/prediabetes together with those who have newly diagnosed diabetes/prediabetes (Group 2A and 2B) at follow-up testing as having abnormal glucose status (Group 2) for a number of our analyses. The subjects with known diabetes were largely treated and this may have attenuated the degree of hyperglycemia. As already outlined, our sample size is relatively modest and this may account for the failure of the inverse relationship between cortisol and ongoing glucose intolerance to reach significance. Third, peak CK level has been used to arbitrarily define illness severity as this correlates with infarct size.[32] Peak CK level is influenced by treatment such as percutaneous coronary intervention and its timing. CK-MB would have been more specific for assessing myocardial damage, however with the advent of troponin testing, our hospital no longer routinely measured CK-MB and therefore this data was not available. Cortisol was also used as a surrogate measure of the severity of stress arising from the illness. There are other factors which influence serum cortisol including diurnal variation, psychological stress, and changes in binding proteins. People with diabetes have been noted to have higher cortisol levels than non-diabetics which if anything, reduced our study's ability to discriminate between underlying diabetes and SH on the basis of cortisol levels.[33] It also remains possible that subjects with SH who had normal glucose tolerance on follow-up testing have more subtle levels of insulin resistance or insulin deficiency that we were unable to detect, and will develop impaired glucose tolerance in future years. Another limitation is that there were some subjects who had only a fasting BG after discharge. There is a possibility that their diabetes classification would be different had they had a GTT. Finally, although we regarded subjects with an admission BG <7.8 mmol/L as having normal glucose tolerance, if these subjects had a follow-up GTT it is possible that some would have abnormal glucose tolerance. In a study where community subjects had a random BG and then a follow-up GTT, 8% of those with a random BG <7.6 mmol/L had abnormal glucose tolerance.[34] Given that the subjects in our study were stressed with myocardial infarction, it is unlikely that a dramatically greater percentage than this of our normal glucose tolerance group were misclassified.

5. Conclusion

Our study provides data regarding the dual pathophysiology of SH amongst patients with myocardial infarction. There are those who have normal glucose metabolism but a marked stress response to their acute illness, and those who have underlying glucose intolerance who develop hyperglycemia even in the presence of milder illness. Elevated cortisol is a marker of the former, and it may be more accurate to define this group as having genuine SH, as the name would suggest. However, serum cortisol is of insufficient specificity to be used as a clinical tool to differentiate the two forms of SH. Ultimately, “genuine stress hyperglycemia” needs to be determined by exclusion, through the measurement of HbA1c and/or follow-up glucose testing. With the high incidence of underlying glucose intolerance amongst people with SH, such testing should be routinely performed.

Conflict of interest

The authors have no conflicts of interest.

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Datasets

The datasets generated and/or analysed during the current study are not publicly available due to the presence of identifiable data, but deidentified data are available from the corresponding author on reasonable request.

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