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Cardiac damage associated with stress hyperglycaemia and acute coronary syndrome changes according to level of presenting blood glucose

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ABSTRACT

Objective: To determine the prevalence of stress hyperglycaemia in people presenting with acute coronary syndrome (ACS), and the relationships between admission glucose and cardiac damage, cardiovascular mortality and morbidity.
Methods: In a prospective observational study people presenting with ACS at the Gold Coast Hospital had their admission glucose (AG) level tested to determine stress hyperglycaemia. A range of measurements supplemented this data including troponin levels, category of ACS and major adverse coronary events (MACEs) were obtained through hospital records and patient follow-up post-discharge.
Results: One hundred eighty-eight participants were recruited. The prevalence of stress hyperglycaemia in ACS was 44% with 31% having a previous diagnosis of type 2 diabetes and 7.7% had undiagnosed diabetes. The stress hyperglycaemic group had a significantly higher median troponin levels compared to participants with normal blood glucose levels on admission ($p < 0.05$) however the highest presenting glucose group (>15 mmol/L) had troponin levels similar to people presenting with normal blood glucose levels and ACS ($p > 0.05$).
Conclusions: Cardiac necrosis as measured by troponin levels is significantly increased in people with ACS and stress hyperglycaemia. This study found that one in four participants presenting with ACS and an admission glucose of >7.0 had no previous diagnosis for diabetes.
Practice implication: Consistently ordering HbA1C testing on patients with high AG can enable earlier diagnosis and treatment of diabetes.

1. Introduction

Stress hyperglycaemia is high blood glucose that occurs during illness. The term is usually applied to people without previous known history of diabetes. According to the American Diabetes Association (ADA [1]) normal fasting blood glucose levels are less than 5.6 mmol/L or less than 7.8 mmol/L 2 h value following an oral glucose tolerance test. Increased glucose levels that occur during stress are the result of sympathetic nervous system activation causing raised production of catecholamines, cytokines and cortisol that stimulate glucose release from the liver and cause insulin resistance [2].

Stress hyperglycaemia occurs in 5–30% of people presenting with a range of critical illnesses including myocardial infarctions, sepsis and trauma and it is associated with deleterious outcomes [3]. Several studies have reported increased in-hospital and long term mortality rates for people who present with an acute myocardial infarction (AMI) and stress hyperglycaemia, regardless of a history of diabetes [4,5]. These studies show that hyperglycaemia, more than diabetes, is associated with a poor prognosis of AMI. Furthermore, elevated admission blood glucose levels appear to have greater influence than prior long-term abnormal glucose metabolism in predicting mortality in people with suspected acute coronary syndrome (ACS) [6,7].

In some cases of stress hyperglycaemia, type 2 diabetes (type 2 DM) or impaired glucose tolerance (IGT) has not been detected. In this cohort elevated glucose could be a marker of existing insulin resistance and/or pancreatic beta-cell failure. Undiagnosed type 2 DM has been reported to occur in 5% of people diagnosed with acute coronary syndrome (ACS) [8]. The level of glycosylated haemoglobin (HbA1c) in people with myocardial infarction reflects the average blood glucose level within a period of time up to 120 previous days and has been used to distinguish people who had only stress hyperglycaemia during acute infarction from those who had diabetes [9]. So far in the setting of ACS, the predictive role of serum level of HbA1c as an independent predictor of mortality is in dispute [9].

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ACS covers a spectrum of clinical presentations including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NonSTEMI) and unstable angina. In terms of pathology, ACS is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery [10]. Stress hyperglycaemia increases death rates in all groups of people diagnosed with ACS including STEMIs and Non-STEMIs [7].

In this project we will determine the prevalence of stress hyperglycaemia in people diagnosed with ACS, the extent of cardiac damage in relation to the admission glucose, as well as the relationship between admission glucose, cardiovascular mortality and morbidity.

2. Subjects and methods

2.1. Participants

People presenting with ACS between January 1, 2012 and June 30, 2013 at the Gold Coast Hospital, Southport Queensland were enrolled in this study. There were no interventions other than non-routine testing for diabetes for patients with high admission glucose. This project had human ethics approval from Queensland Health and Griffith University.

2.2. Inclusion and Exclusion Criteria

Participants were eligible for this study if they had retrosternal chest pain at rest for more than 20 min and a positive troponin, or ST segment depression on their electrocardiogram without an increase in troponin (classified as unstable angina). Participants with ST segment elevation of more than 1 mm in two contiguous leads were classified as STEMI, while participants without significant ST elevation but with positive troponin levels were categorized as NonSTEMI. Participants diagnosed with severe heart failure or end stage chronic kidney diseases were excluded from this study.

2.3. Variable measurement

The following variables were measured and recorded for each participant: Age, sex, smoking, creatinine, admission glucose level (AG), body mass index (BMI), hypertension (HTN), type 2 diabetes mellitus (Type 2 DM), high density lipoprotein (HDL), tropinin (TnI), low density lipoprotein (LDL), glycosylated haemoglobin (HbA1c), haemoglobin (Hb), and obstructive sleep apnoea (OSA). Participants were stratified into four groups according to their admission blood glucose level (AG): Group 1 (normal): AG < 7 mmol/L, Group 2: AG 7–10 mmol/L, Group 3: AG 10–15 mmol/L and Group 4: AG > 15 mmol/L. Stress hyperglycaemia was defined as AG levels of >7 mmol/L (groups 2, 3, & 4). A level of HbA1c of more than 6.5% (48 mmol/mol) was considered high and indicative of type 2 DM even if the patient had no previous diagnosis of type 2 DM. Major adverse coronary events (MACEs) was defined as any significant arrhythmias (supraventricular tachycardia (SVT), atrial fibrillation (AF), ventricular tachycardia (VT), or ventricular fibrillation (VF)), pulmonary oedema, hypotension (if SBP < 90 mm Hg), or cardiogenic shock. MACE within the first week was defined as MACE occurring prior to discharge or within seven days of hospital admission, whichever was earlier.

Cardiac damage was assessed through two proxy measurements: maximum troponin level and the extent of coronary arterial blockages. Maximum troponin was analysed as a continuous variable and then as a categorical variable with the following cut-offs: low = max Tn1 < 1.0; moderate = max Tn1 1–10; high = max Tn1 > 10. Arterial blockage was categorized as follows: none = normal angiogram; mild = no arteries with >60% blockage; level 1 = only one artery with >60% blockage; level 2 = two arteries with >60% blockage; level 3 = three or more arteries with >60% blockage. Participants without angiograms had this variable set to missing. Participants with ACS were subdivided into two groups: participants with STEMI and participants with NSTEMI/UA. All point estimates were analysed separately for these two groups, as well as for all participants with ACS combined. The variable ACS type was tested for significance in all analyses.

2.4. Data collection methods

Participants were screened using daily admission lists from the cardiology wards. Eligible participants were approached to provide informed consent. Following patient consent, data was collected from the electronic medical record and pathology result system using the data collection form.

Serum levels of the following parameters were requested if not already ordered: admission blood glucose level (AG), glycosylated haemoglobin (HbA1c), LDL cholesterol, TnI, Hb and serum creatinine.

The first ECG was reviewed to determine type of ACS and area of infarct (anterior, anterolateral, inferior and lateral). Angiographic findings were obtained from the procedure report. Follow-up data on MACE following discharge was collected at approximately three and six months post-discharge through telephone follow-up.

2.5. Data analysis

The extracted data of the participants was entered and analysed using the Statistical Package for Social Sciences program (SPSS version 15.0). Point estimates for prevalence rates were presented with 95% confidence intervals. The relationship between AG and the cardiac damage proxy variables was assessed through categorical 4 by x tables using the chi-square test, with a p-value of <0.05 considered statistically significant. Different distributions of xx, xx and xx by AG category using ANOVA. The non-parametric Mann–Whitney test was used to evaluate the statistical significance of differences in median values or of the non-normally distributed variables xx and xx. In addition, correlations were computed to identify individual variables that are significantly associated with AG as a continuous variable. Tn1 level was considered as a continuous variable and a categorical variable to determine if Tn1 release was associated with AG.

A linear regression model was created with AG as the continuous dependent variable. Any individual variables that were significantly associated with AG were tested in a multivariate model using a backwards stepwise method and a p-value of >0.1 as the cut-off for inclusion. To determine the relationship between AG and MACE, the incidence of MACE was ascertained for each of the four AG categories at the three MACE time points. Chi-square for trend statistics was calculated to determine if there was an increasing trend towards greater MACE with increasing AG at any of the three time points. In a second comparison, AG was categorized dichotomously as normal or hyperglycaemic. The incidence of MACE for these two categories was reported at each time point as point estimate with 95% confidence intervals. Statistically significant differences between the two categories were then assessed by the chi-square test.

3. Results

3.1. Participant characteristics

One hundred eighty-eight people (188) were recruited and had admission blood glucose levels measured. Of these, 71% were men and 63% were diagnosed as NonSTEMIs (Table 1). The average age of the group was 66 years ± 12.4 (SD), ranging from 32 to 94 years. There were 83 participants with admission glucose of >7.0, representing 44% of the entire sample (Table 2). Thus, the prevalence of stress hyperglycaemia in participants presenting with ACS in this sample was 44% (95% confidence intervals for the proportion = 37.2%, 51.3%) by mid-p exact methods. Of these participants with stress hyperglycaemia, 26