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Alpha$_{2A}$ Adrenergic Receptor Genetic Variation Contributes to Hyperglycemia after Myocardial Infarction

Abiodun Adefurin, MBChB, MSc[1], **Charles Vanderbilt, MD**[1], **Chimalum Okafor, MD**[1], **Vivian Kawai, MD, MPH**[1], **Chun Li, PhD**[2], **Anushi Shah, MSc**[3], **Wei-Qi Wei, MD, PhD**[3], **Daniel Kurnik, MD**[1,4,5], **C. Michael Stein, MBChB**[1]

[1]Departments of Medicine and Pharmacology, Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[2]Department of Epidemiology and Biostatistics, Institute for Computational Biology, Case Western Reserve University, Cleveland, Ohio

[3]Department of Biomedical Informatics, Vanderbilt University, Nashville, Tennessee, USA

[4]Clinical Pharmacology Unit, Rambam Medical Center, Haifa, Israel

[5]Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

Abstract

Background—Acute myocardial infarction (AMI) is frequently associated with transient hyperglycemia even in patients without pre-existing diabetes. Acute stress can lead to increased blood glucose through the effect of catecholamines on alpha$_{2A}$-adrenergic receptors (α_{2A}-ARs) present in pancreatic islet β-cells. Variation in the gene (*ADRA2A*) that encodes the α_{2A}-AR affects insulin release and glucose control and may play a particularly important role during times of stress.

Methods—We performed a retrospective cohort study using de-identified electronic medical records linked to a DNA repository in 521 Caucasians and 55 African-American non-diabetic patients with AMI. We examined the association between admission blood glucose concentrations and ten selected *ADRA2A* SNPs in Caucasians.

Results—Three *ADRA2A* SNPS were associated with stress-induced hyperglycemia in Caucasians. Individuals homozygous for the rs10885122 variant (n=9) had a 23% lower admission glucose (geometric mean [95% CI], 99 [83 – 118] mg/dl) compared with non-carriers (121 [118–125] mg/dl; n=401; P = 0.001). Admission glucose was 14% higher in rs1800544 variant homozygotes (134 [119–150] mg/dl; n=36) compared to non-carriers (118 [115–121] mg/dl; n=290, P=0.046). Furthermore, homozygotes of the rs553668 variant (n = 13) had a 13% higher glucose (133 [110–160] mg/dl) compared to non-carriers (118 [115–122] mg/dl; n=366; P = 0.056). Haplotypes including these *ADRA2A* SNPs were associated with higher admission glucose levels.

Address for correspondence: Daniel Kurnik, Division of Clinical Pharmacology, 542 RRB, Vanderbilt University School of Medicine, Nashville, TN 37232, USA. Phone: +1-615-936-3420, **Fax:** +1-615-936-2746. daniel.kurnik@vanderbilt.edu.

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Conclusions—Three *ADRA2A* genetic variants are associated with blood glucose and stress-induced hyperglycemia after AMI in Caucasians.

Keywords

Stress; Glucose; Alpha adrenergic receptors

Introduction

Acute serious illnesses, including myocardial infarction, are frequently associated with transient hyperglycemia even in patients without pre-existing diabetes (1). Such stress-induced hyperglycemia is an independent predictor of mortality in the setting of myocardial infarction, stroke, and other serious illnesses (2–5). For example, mortality after myocardial infarction is increased 4-fold in patients with stress-induced hyperglycemia, even after adjusting for other prognostic factors (6). Interestingly, the mortality risk associated with stress-induced hyperglycemia is consistently greater in patients without pre-existing diabetes than in diabetics (6–8).

Stress-induced hyperglycemia is associated with the severity of the underlying acute illness, but no other risk factor has been identified consistently, and it is unclear why some patients develop hyperglycemia and others do not (6, 9). The mechanisms underlying hyperglycemia are thought to include insulin resistance mediated in part through stress-induced sympathetic activation and catecholamine release (10). Catecholamines, among their other actions, act on postsynaptic alpha$_{2A}$-adrenergic receptors (α_{2A}-ARs) of pancreatic islet β-cells to inhibit insulin secretion and thus increase blood glucose during stress (10). There is substantial variation in the gene (*ADRA2A*) that encodes the α_{2A}-AR, and recent studies indicate that this genetic variability affects insulin release and glucose control (11–13). A relatively common *ADRA2A* variant (rs553668), present in approximately 15% of Caucasians and 25% of African-Americans, was associated with increased expression of *ADRA2A* messenger RNA and thus with greater α_{2A}-AR density on pancreatic islet β-cells, and also with decreased insulin secretion and higher glucose levels in response to a glucose load (11). Furthermore, *in vitro* studies using pancreatic islet cells from rs553668 carriers showed that the reduced secretion of insulin in response to glucose was normalized by pharmacological α_{2A}-AR antagonists (11, 14). In keeping with these findings, the rs553668 variant was associated with increased risk of diabetes in several large population studies (11, 15, 16). However, there is no information regarding the effect of rs553668 or other *ADRA2A* variants on glucose control under conditions of stress, a time when catecholamine concentrations are increased and the effects of α_{2A}-ARs on insulin regulation are likely to be most important.

Therefore, we examined the hypothesis that rs553668 and other *ADRA2A* variants are associated with the risk of stress-induced hyperglycemia after acute myocardial infarction in non-diabetic patients.

METHODS

Setting

We performed a retrospective cohort study using the Vanderbilt de-identified electronic medical record (EMR) database that is linked to the Vanderbilt DNA repository (BioVU).(17) BioVU contains approximately 180,000 DNA samples linked to de-identified EMRs; details about the recruitment, sample acquisition and storage, and data handling have been described previously.(17) Approval for the present study was obtained from the Vanderbilt Institutional Review Board.

Study Cohort

We identified Caucasian and African-American patients admitted to the Vanderbilt University Medical Center with a diagnosis of acute myocardial infarction (AMI) who had at least one blood glucose level measured at admission and who had a DNA sample available in BioVU. We excluded patients who had an AMI after a medical procedure and those admitted for other medical reasons and subsequently had an AMI during the hospital stay. We excluded patients with pre-existing diabetes, defined as having a hemoglobin A_{1C} level of > 6.5% at admission or during hospitalization or a previous history of diabetes mellitus, as determined from medical history and the use of antidiabetic medications.

Phenotyping

Patients fulfilled the third universal definition of myocardial infarction with a rise or fall of a cardiac biomarker (troponin I or troponin T >0.05 ng/ml, CKMB > 6 ng/ml or CKMB ratio >3%) and with at least one of the following: symptoms of ischemia, new or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block; development of pathological Q waves in the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or identification of an intracoronary thrombus by angiography.(18)

We identified patients with AMI in the de-identified EMR using strategies validated in large epidemiological studies.(19, 20) This involved the presence of ICD-9 code 410, excluding 410.x2 (readmission after AMI), on at least two consecutive days to identify potential cases, followed by manual review of the medical records to identify true cases meeting the criteria for AMI. Glucose measurements recorded in the EMR after the onset of signs and symptoms of AMI were extracted. We converted whole blood glucose measurements obtained from capillary samples to plasma glucose values by multiplying by a factor of 1.15, as previously described.(19) Covariates were extracted by both manual chart review and bioinformatic approaches.

Outcomes

The primary outcome was the first glucose concentration recorded after onset of signs and symptoms of AMI, termed ‘admission glucose’.

Genotyping

We genotyped nine *ADRA2A* tagSNPs previously described and one additional *ADRA2A* variant (rs10885122) that has been associated with diabetes mellitus or related traits in at least two genome wide association studies.(13, 21, 22) Genotyping was performed by the Center for Human Genetics Research at Vanderbilt University Medical Center according to standard protocols using the Sequenom platform. Two SNPs (rs2484516 and rs1800035) did not pool well in the Sequenom platform and were genotyped using TaqMan assays. For quality control, we examined genotyping call rates and calculated Hardy-Weinberg equilibrium (HWE) of genotype distributions.

Statistical Analysis

Baseline demographics were described using mean and standard deviation for continuous variables and frequencies and percentages for categorical variables and were compared between the two ethnic groups using independent sample t-tests and chi square tests, or non-parametric tests when the statistical assumptions were not met. Blood glucose levels were not normally distributed and were therefore log-transformed for analyses and expressed as geometric means with 95% confidence intervals (CIs). For all genetic analyses, we assumed an additive genetic model, coding the genotypes according to the number of variant alleles (0–2). In single-variant analyses, we used linear regression analyses to examine the association of admission glucose as dependent continuous variable with genotypes of each SNP, with and without adjustment for the following covariates: age, sex, BMI, peak CKMB, ST elevation, in-hospital use of diuretics, in-hospital defibrillation, and, for analyses of the combined cohort, ethnicity. In sensitivity analyses, we categorized the outcome variable (admission glucose) into a dichotomous variable (admission hyperglycemia yes/no) using cut-off values (associated with therapeutic and prognostic thresholds) of 140 mg/dl(19, 23) and assessed the association between admission hyperglycemia with each *ADRA2A* variant (before and after adjustment for covariates) using logistic regression analyses.

We defined haplotype families in each ethnic group using the 10 *ADRA2A* SNPs by expectation-minimization algorithms implemented using EM algorithm with the haplo.stats program. Furthermore, we assessed the association of each haplotype with admission glucose, with and without adjustment for covariates.

The primary analyses were performed in Caucasians; only exploratory analyses were performed in the African American group because of the small sample size. Statistical analyses were performed using R software (www.R-project.org) and SPSS (v. 21, IBM® SPSS® Inc., Chicago, IL). All analyses were two-tailed, and a P-value < 0.05 was considered significant.

RESULTS

Baseline Demographics

We identified 1586 potential cases of AMI based on ICD-9 code criteria, of whom 576 cases (521 Caucasian, 55 African-American) met the study criteria after manual EMR review (Figure 1). Cases were predominantly Caucasian males (Table 1 and Supplementary Table

1). Among the 521 Caucasian cases, the admission glucose ranged from 60 – 568 mg/dl (median (IQR); 113 mg/dl (100 – 138 mg/dl). 122 Caucasians (23%) had admission glucose > 140 mg/dL. In 32 patients (6.1%), stress-induced hyperglycemia was treated with insulin at some stage of the hospitalization.

Genotyping

Minor allele frequencies for the 10 *ADRA2A* variants (Supplementary Table S2) were in the expected range, and all genotypes conformed to Hardy-Weinberg equilibrium in each ethnic group. No Caucasians carried the rs34303217 variant.

ADRA2A Genotypes and Admission Glucose

Of the ten *ADRA2A* variants, three were associated with glucose levels at the time of hospital admission in Caucasians in single-variant analyses (Table 2). The strongest association was found with rs10885122: carriers of the T allele had lower admission blood glucose (β= −0.035; 95% CI, −0.056 to −0.14; adjusted P=0.001, Table 2, Supplementary Table 3) compared to non-carriers. The 9 subjects homozygous for the T allele had a 23% lower geometric mean admission glucose compared with the 401 subjects homozygous for the G allele (P = 0.001), and heterozygotes had intermediate values (Figure 2).

Two additional variants had a weaker association with admission glucose in Caucasians. rs553668 was associated with higher admission glucose (β=0.019; 95% CI, 0.001 to 0.038; adjusted P=0.056). Homozygotes (n = 13) had a 13% higher n admission glucose (133 mg/dl) compared with the 366 non-carriers (118 mg/dl; Table 2). Additionally, rs1800544 was associated with a higher admission glucose (β=0.016; 95% CI, 0.001 to 0.033; adjusted P=0.046). Admission glucose was 14% higher in variant homozygotes (134 mg/dl; n=36) compared to non-carriers (118 mg/dl; n=290; Table 2).

Multiple linear regression models that included covariates either with or without genotype information for all three significant *ADRA2A* SNPs in the Caucasian cohort revealed that adding genetic information improved the percentage of variability explained (adjusted R^2) from 7.0% to 9.5%. Other covariates associated with higher admission glucose included peak CK-MB (P=0.002), ST elevation (P=0.038), and need for defibrillation (P=0.009). In this model, rs10885122 was the only *ADRA2A* SNP significantly associated with admission glucose (P = 0.001).

In sensitivity analyses with admission glucose categorized as a dichotomous variable (≥ 140 mg/dl (n=122) compared to <140 mg/dl (n=399), only rs10885122 was significantly associated with admission glucose ≥ 140 mg/dl. Of patients homozygous for the G allele, 26% had an admission glucose greater than 140 mg/dl, compared with 11% of homozygous carriers of the T allele (P = 0.015). After adjusting for covariates, the G allele remained significantly associated with admission glucose > 140 mg/dL (OR=2.30; 95% CI, 1.71 to 3.11; P = 0.006). The two other *ADRA2A* variants were not associated with admission glucose ≥ 140 mg/dl before or after adjusting for covariates (all P > 0.31).

Among the African American subgroup (n = 55), none of the ten ADRA2A variants was significantly associated with admission glucose levels except for rs1800545, which

showed a trend to association with glucose levels but with no gene-dose-effect (P = 0.041, Supplementary Table S3).

ADRA2A Haplotypes and Admission Glucose

Thirteen haplotypes were derived in the Caucasian group and 8 in African-Americans, accounting for 99.6% and 80% of the populations, respectively (Supplementary Table 4). Haplotype 4, prevalent in 10% of Caucasians, included the variant alleles for rs1800544, rs553668 and the major G allele for rs10885122 (associated with higher admission glucose) was the only haplotype significantly associated with higher admission blood glucose (P = 0.040). Among African-Americans, haplotype 6 (prevalent in 7% of African Americans and including rs1800544, rs1800545 and rs10885122 variants) was significantly associated with higher admission blood glucose (P = 0.011; Supplementary Table 4B).

DISCUSSION

This is the first study of the genetic contribution of adrenergic receptor variants to stress-induced hyperglycemia. Examining the association of ten selected *ADRA2A* variants with initial blood glucose levels following an AMI in non-diabetic patients, we found that rs10885122, rs553668, and rs1800544 were associated with stress-induced hyperglycemia in Caucasians.

The increased sympathetic drive following an acute event such as an AMI results in release of stress hormones, including catecholamines. Catecholamines activate post-synaptic α_{2A}-ARs on pancreatic islet β-cells and inhibit insulin release; these actions facilitate an increase in blood glucose levels as part of the fight-or-flight response. Recently, several genetic variants in *ADRA2A* have been associated with impaired glucose regulation,(15, 21, 22) confirming the relevance of *ADRA2A* as a candidate gene for the regulation of glucose homeostasis. We have extended these findings and identified three *ADRA2A* variants associated with blood glucose levels in patients after AMI.

The strongest association with blood glucose concentrations was that of rs10885122. GG homozygotes had glucose levels on admission to hospital that was 23 mg/dL (geometric mean) higher than that of TT homozygotes, and heterozygotes had intermediate values. The G-allele of rs10885122 (approximate allele frequency in Caucasians, 88%) has been associated with impaired fasting glucose in two large GWAS studies.(13, 21, 22) This SNP is located in the intergenic region between the genes *TCF7L2* and *ADRA2A*. *TCF7L2*, positioned 1.6 Mbp upstream of rs10885122, encodes transcription factor 7-like 2, which has been consistently linked to diabetes mellitus and related traits.(24, 25) Thus, it is unclear whether rs10885122 has a causal association with blood glucose regulation or is only in linkage disequilibrium with a causal variant in either *TCF7L2* or *ADRA2A*.

Two additional variants, rs553668 and rs1800544, were also associated with admission glucose. The rs553668 variant, formerly identified as the *DraI* restriction fragment length polymorphism, was identified as a marker for type 2 DM, increased fasting glucose, and decreased insulin levels in a number of previous studies.(11, 15, 26) The gain-of-function T-allele of this SNP, located in the 3-′UTR of *ADRA2A*, was associated with higher mRNA

and receptor expression and enhanced α_{2A}-AR activity in different physiological pathways.(27–29) In human pancreatic islet β-cells from T-allele carriers, membrane docking of the insulin vesicles was reduced, and carriers thus had reduced insulin secretion and increased glucose levels.(11) Thus, our finding that patients homozygous for the T-allele had higher admission glucose levels compared to non-carriers is in keeping with findings from previous studies identifying the rs553668 T-allele as a marker for impaired glucose regulation.

The rs1800544 variant, also known as the C1291G polymorphism, was associated with diabetes-related traits such as fasting glucose in one previous study.(30) Moreover, it has been associated with other α_{2A}-AR-related phenotypes suggesting a gain-of-function action such as schizophrenia, weight gain during antipsychotic medication use, body fat accumulation, and vascular reactivity to stress.(31–34) The variant is in the promoter region of the gene, and it may exert its effects by influencing gene expression.(35) In keeping with previous findings related to glucose regulation phenotypes,(31–34) we found that the G allele was associated with higher admission glucose in Caucasians ($P = 0.046$) with a similar trend among African-American subjects.

Our findings may have implications for clinical practice. Stress-induced hyperglycemia is associated with increased mortality following cardiovascular events.(6) However, achieving stricter hyperglycemic control using insulin has not consistently achieved mortality benefits, suggesting that in such patients stress-induced hyperglycemia may be a marker of a detrimental enhanced adrenergic stimulation rather than representing the causal pathophysiological mechanism of increased mortality.(6, 8) Conceptually, inhibition of genetically defined enhanced α_{2A}-AR pathways has been shown to reduce hyperglycemia: a previous study demonstrated improved insulin secretion using the non-selective α_2-AR antagonist, yohimbine, in diabetic patients treated according to their rs553668 genotype.(36) It would be interesting to consider inhibition of the α_{2A}-AR pathway for the prevention or treatment of stress-induced hyperglycemia and its associated morbidity and mortality, particularly for individuals with genetic risk markers. However, there is no selective α_{2A}-AR antagonist available for clinical use; moreover, considering that α_2-AR antagonists such as yohimbine can increase blood pressure and sympathetic activity it would be challenging to conduct this type of study in acutely ill patients.(37)

Our study had several limitations. First, this was a retrospective study using a de-identified electronic medical records system. Thus, we could not measure the plasma insulin levels at the time of AMI to assess their relationship with the genetic variants studied. The direct effect of α_{2A}-ARs is to inhibit insulin secretion and thus increase glucose levels. However, blood glucose regulation also involves other pathways including other stress hormones such as cortisol, as well as glucose transporters and other factors that could affect stress-induced hyperglycemia. Second, given the complex phenotype and the hypothesis-driven approach based on known biology, we did not replicate our findings in a separate cohort. However, our findings reproduce the established biological effect of rs553668 and other *ADRA2A* variants previously associated with impaired glucose homeostasis. Third, due to the small size of the African-American sample, we were unable to adequately examine the genetic determinants of stress-induced hyperglycemia in this group. This likely accounts for the lack of statistically significant associations with most of the *ADRA2A* variants in the

African-American group. Fourth, in this retrospective study, we did not have data on glucose levels before AMI admission, and we therefore could not assess whether *ADRA2A* variants were associated with blood glucose specifically just under stress conditions or also at baseline. Last, we only studied stress-induced hyperglycemia following AMI. Stress-induced hyperglycemia also occurs following other acute conditions such as stroke, sepsis, and other serious illness.(2–5) It is unclear if our results can be generalized to hyperglycemia following other disease conditions. However, adrenergic activation is a feature common to all these conditions, and given our understanding of how the α_{2A}-AR pathway is relevant to the pathophysiology of stress-induced hyperglycemia, similar associations with *ADRA2A* variants may be expected.

In conclusion, our findings suggest that three *ADRA2A* genetic variants, known to be associated with impaired glucose regulation in population studies, are associated with blood glucose concentrations and stress-induced hyperglycemia after AMI in Caucasians. Future studies assessing the prognostic value of these variants on morbidity and mortality and their association with other adrenergic phenotypes in the setting of AMI, as well as other clinical conditions resulting in stress-induced hyperglycemia, will be of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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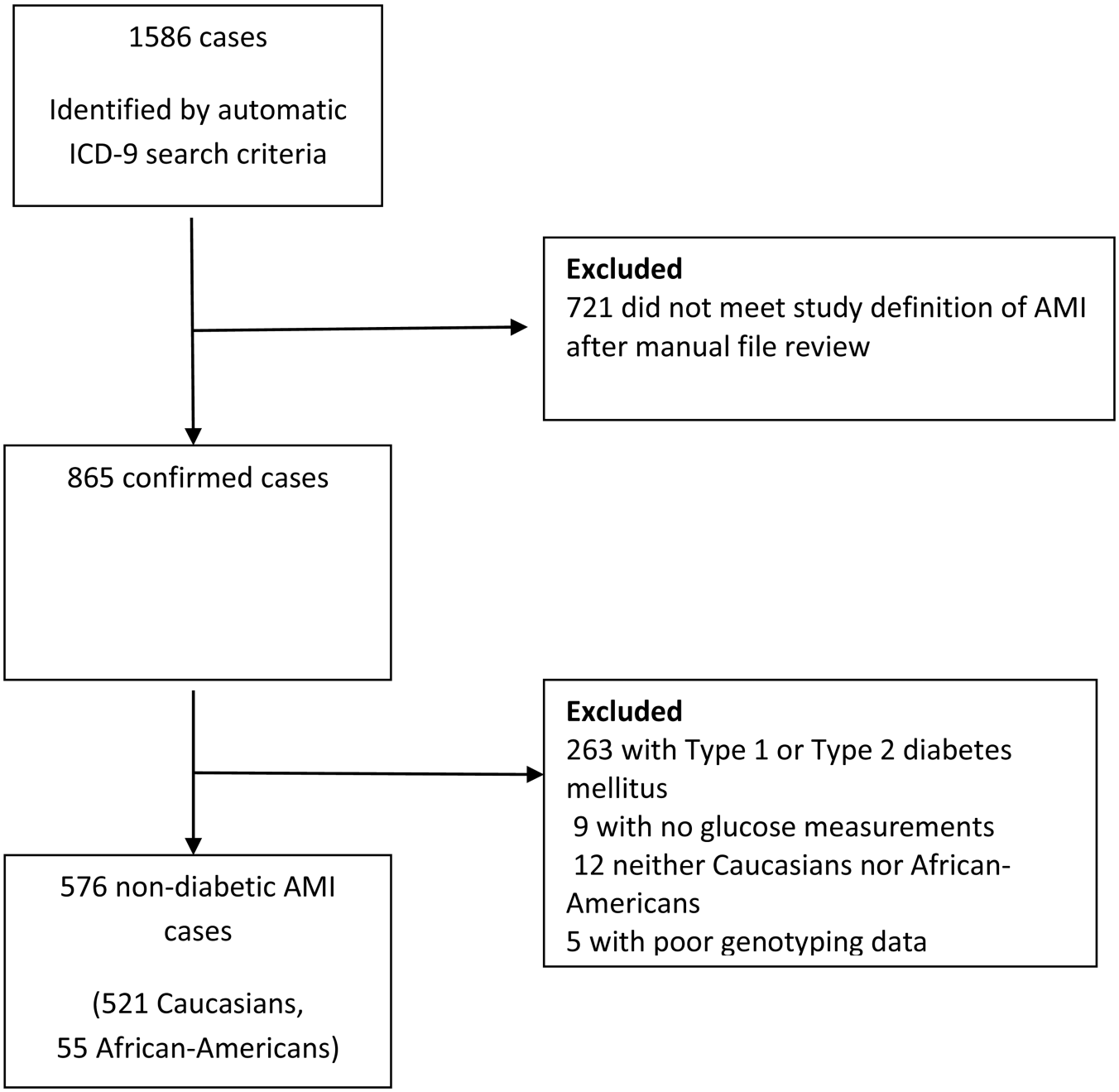

Figure 1.
Schematic diagram of selection of 576 AMI cases for the study

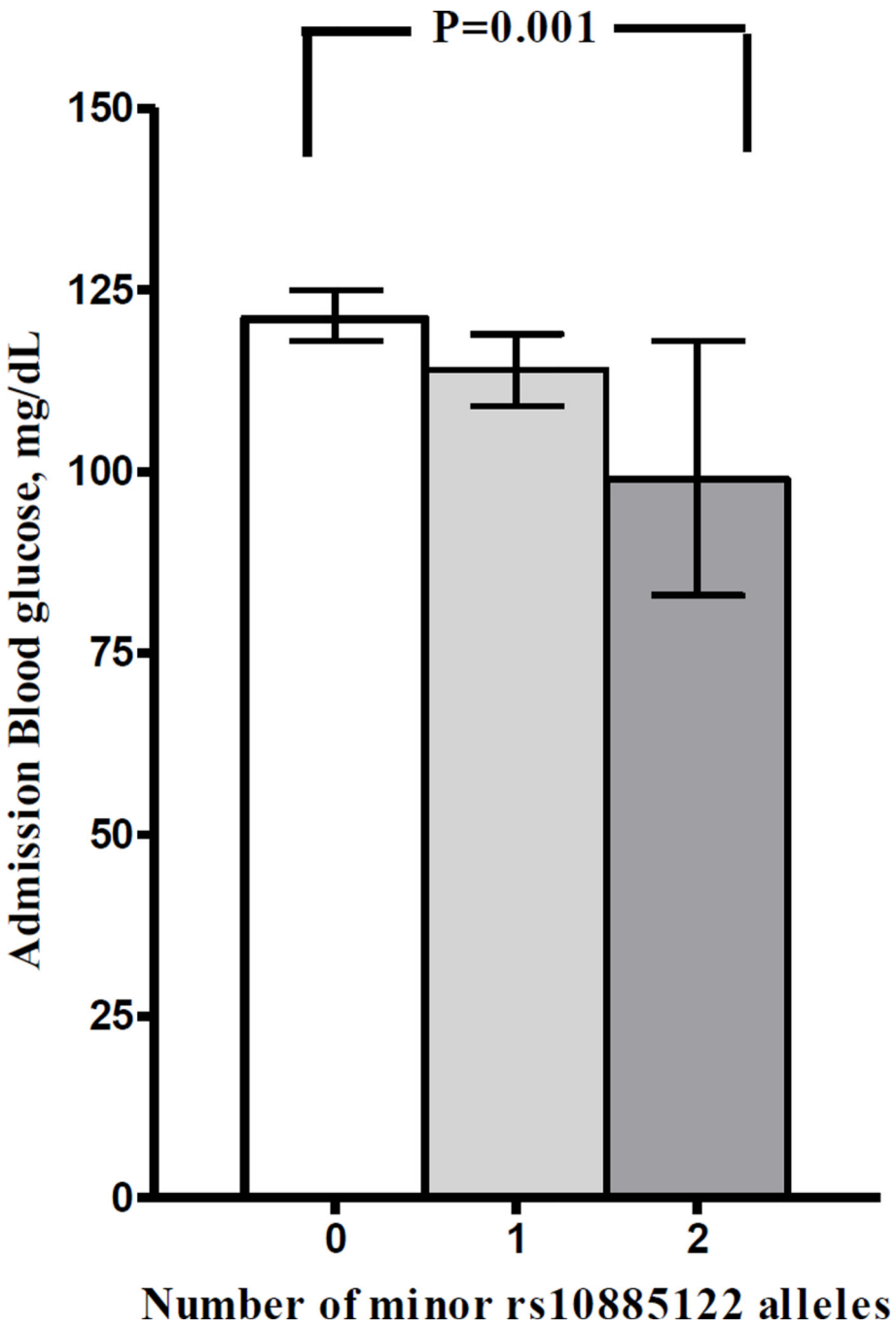

Figure 2.
rs10885122 genotype in Caucasians and its association with admission glucose following acute myocardial infarction.

Table 1

Baseline demographics and characteristics of 521 Caucasian patients

Covariates	Caucasians n = 521
Age, years	63±14
Female sex, n (%)	178 (34.2)
BMI, kg/m^2 *	27±5
Previous history of AMI, n (%)	117 (22.5)
Previous history of PCI/CABG, n (%)	144 (27.6)
ST elevation, n (%)	209 (40.1)
In-hospital events	
In hospital ventricular tachycardia/fibrillation, n (%)	70 (13.4)
In hospital PCI, n (%)	372 (71.4)
In hospital CABG, n (%)	46 (8.8)
In hospital thrombolysis, n (%)	26 (5.0)
In hospital defibrillation, n (%)	38 (7.3)
In-hospital Chemistry/Hematology	
Creatinine, mg/dl	1.2±0.9
Peak troponin I, μg/l *	42.2±155.6
Peak troponin T, μg/l †	2.0±2.6
Peak CK-MB, U/L ‡	102.8±142.7
Medication Use In-hospital	
Diuretics, n (%)	222 (42.6)
Beta blockers, n (%)	464 (89.1)
ACE Inhibitors, n (%)	363 (69.7)
Statins, n (%)	443 (85.0)
Aspirin, n (%)	496 (95.2)

* 328 of 521 patients had troponin I values;

† 130 of 521 patients had troponin T values

‡ 510 of 521 patients had CKMB values.

Table 2

ADRA2A variants associated with admission blood glucose levels in Caucasian patients with acute myocardial infarction.

SNP	Caucasians			
		Glucose, mg/dl Geometric mean (95% CI)	P-value*, adjusted	
Number of variant alleles	0	1	2	
rs10885122	121 (118–125) N = 401	114 (109–119) N = 111	99 (83 –118) N = 9	**0.001**
rs553668	118 (115–122) N = 366	121 (116–127) N = 142	133 (110–160) N = 13	**0.056**
rs1800544	118 (115–121) N = 290	119 (114–123) N = 195	134 (119–150) N = 36	**0.046**

* P value adjusted for age, sex, BMI, peak CKMB, ST elevation, in-hospital use of diuretics, in-hospital defibrillation.