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All-cause Mortality of High-normal Random Blood Glucose using Basic Demographics

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Abstract

Background: The prevalence of diabetes has reached epidemic proportions both in the United States and worldwide. A recent World Health Organization (WHO) report has estimated the prevalence has quadrupled in just three decades and is directly responsible for the deaths of 1.5 million people worldwide. More than 80% of these deaths occur in low and middle income countries. The forecasted urban population in developing nations is expected to double by the year 2030, compared to the year 2000.

Methods: We utilized a limited teaching dataset from the Framingham Heart Study to examine the relationship between blood glucose levels and mortality using a Multivariate Cox proportional hazards model, adjusting for age, gender, body mass index and blood pressure. We divided glucose according to four categories, with normal reflecting conventional "intensive" control, high-normal reflecting a higher glucose level and moderate and severe elevations for further comparison of relative mortality.

Results: 3,270 subjects were followed for 20 years, of which 316 fell into a high normal blood glucose category and 2,885 subjects had a normal blood glucose. The relative risk of death in the high normal random blood glucose (RBG) group was 1.22 times that of those with a random normal blood glucose (95% CI: 1.021.45; pvalue = 0.030).

Discussion: A high normal random glucose level with limited covariates may prognosticate a greater risk of all-cause morbidity and mortality compared to low normal glucose levels. These findings may help to provide estimates of risk in low and middle-income countries, where there is limited access to healthcare and basic lab testing such as HgbA1c.

Keywords: Random glucose; Diabetes; Mortality; Survival analysis

Introduction

Type 2 diabetes mellitus (T2DM) is both a metabolic and vascular disorder, whose prevalence has reached epidemic proportions both in the United States and worldwide over the past twenty years. A recent World Health Organization (WHO) report has found the prevalence of T2DM has quadrupled in just three decades. Today, T2DM is the direct cause of 1.5 million deaths worldwide. More than 80% of these deaths occur in low and middle-income countries today, which is expected to see a doubling of its urban population in 2030 compared to the year 2000 [1].

T2DM is a well-established risk factor for cardiovascular disease as well as an independent risk factor for all-cause mortality. It is known to occur on a continuous spectrum of gradual, progressive insulin resistance. Once diagnosed, the patient must undergo lifelong monitoring and treatment in order to prevent sequelae such as renal failure, blindness, peripheral neuropathy and risk of limb amputation.

According to the American Diabetes Association, a person is diagnosed with diabetes if they meet any of the following plasma glucose criteria: a fasting plasma glucose>126 mg/dL (7.0 mmol/L), a plasma glucose>200 mg/dL (11.1 mmol/L) two hours after dissolving 75 g anhydrous glucose in dissolved water, a plasma glucose>200 mg/dL (11.1 mmol/L) with "classic" symptoms of hyperglycemia or hyperglycemic crisis and in recent years, a Hemoglobin A1c of >6.5% using a National Glycohemoglobin Standardized Program (NGSP) certified assay [2]. Once diagnosed, patients are started on either oral hypoglycemics or insulin to control their blood sugars.

There is evidence to support that elevated blood glucose levels in the absence of T2DM may portend poorer outcomes in patients with cardiovascular disease as was discovered by the DECODE Study Group [3].

Variables	Total	Normal	High normal	Moderately elevated	Severely elevated	P-value
(Glucose mg/dL)		(70-99)	(100-139)	(140-199)	(>200)	
	N = 3270	n=2885 (88.23)	n = 316 (9.66)	n = 33 (1.01)	n = 36 (1.10)	
Age (±sd), year	50 (8.68)	50 (8.7)	52 (8.5)	55 (8.9)	56 (6.6)	<0.0001
Gender						0.0992
Male	1445 (44.19)	1260 (43.67)	148 (46.84)	21 (63.64)	16 (44.44)	
Female	1825 (55.81)	1625 (56.33)	168 (53.16)	12 (36.36)	20 (55.56)	
BMI						0.0007
Normal Weight	1422 (44.02)	1293 (45.37)	114 (36.31)	7 (21.88)	8 (23.53)	
Overweight	1372 (42.48)	1196 (41.96)	145 (46.18)	15 (46.88)	16 (47.06)	
Obese	436 (13.5)	361 (12.67)	55 (17.52)	10 (31.25)	10 (29.41)	
Systolic Blood Pressure, mm Hg						<0.0001
<120	913 (27.95)	839 (29.1)	61 (19.3)	7 (21.88)	6 (17.14)	
120-139	1295 (39.65)	1151 (39.92)	123 (38.92)	11 (34.38)	10 (28.57)	
140-159	642 (19.66)	550 (19.08)	79 (25)	8 (25)	5 (14.29)	
>160	416 (12.74)	343 (11.9)	53 (16.77)	6 (18.75)	14 (40)	
Diastolic Blood Pressure, mm Hg						0.2437
<80	1253 (38.45)	1123 (39.05)	107 (34.08)	11 (33.33)	12 (33.33)	
80-89	1158 (35.53)	1021 (35.5)	115 (36.62)	13 (39.39)	9 (25)	
90-99	574 (17.61)	495 (17.21)	65 (20.7)	4 (12.12)	10 (27.78)	
>100	274 (8.41)	237 (8.24)	27 (8.6)	5 (15.15)	5 (13.89)	

Table 1: Baseline sample characteristics.

This increased risk may be the result of cellular changes, inducing pathologic tissue changes prior to the development of clinical symptoms [4]. Pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-alpha, are believed to play a role in stimulating gluconeogenesis, increasing peripheral blood glucose levels and resulting in increased insulin resistance in the liver and peripheral tissues [5] (Table 1).

The impact of elevated glucose levels may impact cardiovascular mortality through multiple means. As discussed by Santulli et al. alterations in glucose regulation may impact ionic channels such as the type 2 ryanodine receptor (RyR2), leading to a pro-arrhythmic state [6]. In patients with coronary artery disease (CAD), Marafella et al. suggested that glycemic control may regulate endothelial progenitor cell level and differentiation in conditions where there is acute myocardial damage such as ST-elevation myocardial infarction, thereby potentially impacting post-procedure prognosis after percutaneous coronary intervention [7].

Parameter	Estimate	Standard Error	Hazard Ratio	95% Confidence Interval	P-value
Age, year	0.092	0.0037	1.096	1.088 - 1.104	<0.0001
Female	-0.5256	0.05856	0.591	0.527 - 0.663	<0.0001
Glucose level					
High normal	0.39585	0.08929	1.486	1.247 - 1.77	<0.0001
Moderately elevated	1.20238	0.20269	3.328	2.237 - 4.951	<0.0001
Severely elevated	1.67043	0.17732	5.314	3.754 - 7.523	<0.0001
Normal	Reference group				
BMI					
Obese	0.52065	0.08545	1.683	1.424 - 1.99	<0.0001
Overweight	0.31469	0.06426	1.37	1.208 - 1.554	<0.0001
Normal Weight	Reference group				
Systolic Blood Pressure, mm Hg					
120-139	0.41075	0.08622	1.508	1.273 - 1.786	<0.0001
140-159	0.93508	0.09126	2.547	2.13 - 3.046	<0.0001
>160	1.51982	0.09285	4.571	3.811 - 5.484	<0.0001
<120	Reference group				
Diastolic Blood Pressure, mm Hg					
80-89	0.17309	0.07351	1.189	1.029 - 1.373	0.0185
90-99	0.65081	0.08064	1.917	1.637 - 2.245	<0.0001
>100	1.07274	0.09356	2.923	2.434 - 3.512	<0.0001
<80	Reference group				

Table 2: Bivariate Cox regression results.

The role of hyperglycemia as a stress factor for inflammation and apoptosis in atherosclerotic plaques may not come as a surprise. In

fact, as suggested by Balestrieri et al. T2DM may be a trigger for worse prognosis in atherosclerotic lesions [8]. The exact threshold glucose levels for these mechanisms, however, have not been defined (Table 2).

The Israel Diabetes Research Group found that higher fasting glucose levels, when controlled for several other covariates, may be an independent risk factor among men and may help to identify people who are at greatest risk for progressing towards T2DM [9]. The optimal window for defining the threshold glucose levels at risk for progression to T2DM is of great interest to prevent overt progression and reduce the morbidity and mortality risks associated with this disease [10] (Table 3).

Parameter	Estimate	Standard Error	Hazard Ratio	95% Confidence Interval	P - value
Age, year	0.0838	0.00397	1.087	1.079 - 1.096	<0.0001
Female	- 0.75055	0.06117	0.472	0.419 - 0.532	<0.0001
Glucose level					
High normal	0.19531	0.08989	1.216	1.019 - 1.45	0.0298
Moderately elevated	0.89922	0.20414	2.458	1.647 - 3.667	<0.0001
Severely elevated	1.15182	0.18211	3.164	2.214 - 4.521	<0.0001
Normal	Reference group				
BMI					
Obese	0.06858	0.09099	1.071	0.896 - 1.28	0.451
Overweight	-0.0942	0.06644	0.91	0.799 - 1.037	0.1563
Normal Weight	Reference group				
Systolic Blood Pressure, mm Hg					
120 - 139	0.22088	0.09195	1.247	1.041 - 1.493	0.0163
140 - 159	0.47621	0.11295	1.61	1.29 - 2.009	<0.0001
>160	0.80143	0.13484	2.229	1.711 - 2.903	<0.0001
<120	Reference group				
Diastolic Blood Pressure, mm Hg					
80 - 89	-0.05685	0.0808	0.945	0.806 - 1.107	0.4817
90 - 99	0.06481	0.10311	1.067	0.872 - 1.306	0.5296
>100	0.25236	0.13341	1.287	0.991 - 1.672	0.0586
<80	Reference group				

Table 3: Multivariate Cox regression results.

United States practice guidelines do not specify a formalized protocol guiding clinicians for measuring random plasma glucose measurements. This differs from the International Diabetes Federation, which advocates subsequent testing if a random plasma glucose > 100 mg/dL (>5.6 mmol/L) [2,4]. Given how measuring random glucose is simple, quick and inexpensive, our group set out to explore whether a higher glucose measurement in the normal reference range, which otherwise may not trigger clinical concern or intervention, may offer some prognostic value on stratifying the long-term mortality risk on patients. We hypothesize that since the pathophysiology of elevated glucose levels occurs on a continuous spectrum, higher normal glucose ranges will confer an increased morbidity and mortality compared to lower normal glucose levels. Our aim is to examine whether a high-normal glucose level may confer an increased risk of mortality, when adjusted for other covariates when only limited resources are available.

Research Design and Methods

Our group conducted a retrospective cohort analysis using a limited Framingham Cohort Study data in 2013 with permission from the Framingham Heart Study (FHS). We examined the relationship between our primary outcome variable, time to all-cause death, and the following selected explanatory variables from the dataset: age, body mass index (BMI), categorical systolic blood pressure (SBP) and categorical diastolic blood pressure (DBP) at baseline. These variables were chosen given their simplicity in obtaining measurements without sophisticated laboratory equipment or burdensome calculations. We explored this relationship using a Multivariate Cox proportionate hazards model.

Blood glucose levels were divided into four categories: normal (70-99 mg/dL), high-normal (100-139 mg/dL), moderately high (140-199 mg/dL) and severely high (>200 mg/dL). We chose to examine the relationship of our high-normal group and compare it to the approximate levels for intensive control, as reported by studies such as the NICE-SUGAR [11]. Age was treated as a continuous variable in years, while gender was categorized as dichotomous, where coefficient for female gender = 1 and male gender = 0. BMI was classified as a categorical variable as follows: normal weight (BMI: 18-25 kg/m^2), overweight (BMI: 25-30 kg/m^2) and obese (BMI>30 kg/m^2). SBP was categorized according to the following: SBP<120, 120-139, 140-159 and >160 mmHg, while DBP was classified in four categories as well: <80, 80-89, 90-99 and >100 mmHg.

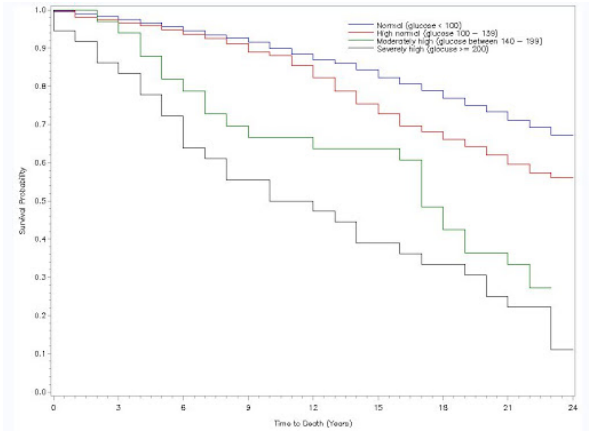

Figure 1: Statistical Analysis.

The categorical arrangements for blood pressure were based according to pre-hypertensive, Stage I and Stage II hypertensive measurements based on JNC-7. Reference groups for blood pressure were defined as SBP<120 and DBP<80 respectively. Our dataset

included total cholesterol values for each subject, but we excluded this as a covariate since we did not have lipoprotein breakdown values and would therefore inaccurately reflect a subject's true cardiovascular risk. We excluded subjects with a BMI<18.5 kg/m^2 or a blood sugar<70 mg/dL, since this would likely confer an independent significantly increased mortality. Statistical analysis was performed using SAS 9.3 (Figure 1).

Subjects were stratified according to pre-specified, categorized blood glucose levels, as well as age, gender, BMI, SBP and DBP. Means and standard deviation were reported for each blood glucose category. Means and standard deviations were reported using the PROC MEANS command. Pearson Chi-square tests of association were conducted for BMI, SBP and DBP, reported as categories. One-way analysis of variance (ANOVA) was used to analyze for statistical differences at $\alpha = 0.05$ (Figure 1).

Results

Baseline demographics are reported in Table 1. The overall mean age of the 3,270 patients included in our analysis was 50 + 8.68 years, with a statistically significant difference among the four blood glucose categories (p-value<0.0001). There were also statistically significant differences with respect to BMI differences among the four categories (p-value = 0.0007) and systolic blood pressure (p-value<0.0001), but not diastolic blood pressure. 55.81% of the population analyzed were female. There was n = 316 who were classified at study onset of having a high-normal blood sugar glucose (9.66%) and n = 2885 (88.23%) who were of normal blood glucose. Only 8 patients were classified as potentially having metabolic syndrome (total cholesterol>200 mg/dL, BMI>30 kg/m^2 and blood sugar glucose>200 mg/dL), insufficient for us to draw any statistical inference from the dataset.

We first tested association between our covariates and time-to-death using Bivariate Cox proportional hazards model (Table 2). All of our variables were noted to be associated with the outcome variable and were subsequently included in our multivariate Cox proportional hazards model. Coefficients for each model were reported with 95% confidence intervals and p-values, testing at a significance level of 0.05.

In the multivariate analysis, we found that subjects with a random blood sugar glucose>200 mg/dL had a 3.16 times greater risk of death compared to those with a normal blood sugarglucose, when controlled for our other covariates (95% CI: 2.214 - 4.521; p-value<0.0001). Consistent with previous findings, this was also observed among those classified as having moderately high blood glucose, where they had a 2.46 times greater risk of death (95% CI: 1.647-3.667; p-value<0.0001).

Our findings also found that, when controlled for these limited covariates, there was a statistically significantly elevated risk among the high-normal random blood glucose category. Those with a high normal blood sugar glucose had a 1.22 times risk of mortality compared to those with a normal random blood sugar glucose (95% CI: 1.02-1.45; p-value = 0.030).

We acknowledge some limitations of our conclusion from this limited dataset. While our intention was to evaluate the relationship using a random blood glucose, the reported blood glucose levels may actually reflect diabetics who are treated with oral hypoglycemics. The same can also be said for blood pressure as a one-time measurement. We did not distinguish between those who may truly be Stage I or II hypertensive, compared to simply elevated blood pressure or those with "white-coat" hypertension. Among patients with heart failure, high-normal glucose levels may impact the prognosis in patients with heart failure, compared to preserved systolic function [12]. However, ejection fraction was not a reported variable in the teaching dataset and therefore, we could not analyse the impact of systolic dysfunction on outcomes. However, whether the blood sugars are fasting or random, there is evidence to suggest similarly that there exists a gradient along random blood sugar levels and cardiovascular disease risk [11]. These individuals are likely to be at risk for developing pre-diabetes, which confers a risk of progression to frank diabetes. Among those with T2DM, this data confirms that metabolic alterations due to hyperglycemia may impact the prognosis among T2DM patients with normotensive blood pressure [12]. Among patients with heart failure, high-normal glucose levels may impact the prognosis in patients with heart failure, compared to preserved systolic function [13].

T2DM itself may predispose patients to the development of a pro-arrhythmic state. Previous studies, as reported by Rizzo et al. have noted an association between autonomic dysfunction and brief episodes of atrial fibrillation among diabetics [13]. In this study, the authors suggest T2DM may induce autonomic dysfunction. It is likely that the development of autonomic dysfunction occurs on a spectrum of gradual glucose intolerance and that high-normal glucose individuals may have structural cellular changes which contribute to the pathophysiology of autonomic dysfunction before the diagnosis of T2DM is made. As suggested by Santuli and discussed earlier, the impact of higher glucose levels on ionic channels is likely to contribute to the development of pro-arrhythmic states [6]. Marafella et al. showed that subclinical episodes of atrial fibrillation occurred more frequently and correlated with an increased risk of silent cerebral infarcts (defined by magnetic resonance imaging) and stroke in diabetic patients, independently of duration of diabetes and target organ damage [14]. These findings may impact the prognosis in patients who are thought to be "low-risk" diabetics. Recent evidence has suggested the presence of a 'diabetic cardiomyopathy,' whose mechanisms may be multifactorial and include changes in calcium regulation, inflammatory cytokines and endothelial dysfunction [15].

Our results support that there exists a gradient along random blood sugar levels and However, in a real-life clinical setting regardless of other co-variates, these findings do suggest that a high-normal random blood glucose may be a marker for concern for cardiovascular risk. This may clinicians and provide clinicians a broader temporal window for earlier and more aggressive action in this population and reduce morbidity and mortality. We believe that the practical value of our findings lies in the simplicity of using a fingerstick blood glucose, in addition to basic blood pressure and demographic values to prognosticate risk, without the need for technologically sophisticated machinery or laboratory analyses. In the general population, T2DM is often undiagnosed and lipid profiles are often not known among a vast majority of patients. Populations with limited resources- especially among the low and middle-income nations forecasted to have the greatest share of deaths due to T2DM, may benefit from increased emphasis on primary and secondary means of prevention. This may take place through increased counselling of patients with lifestyle modification or initiation of pharmacotherapy in a population with high-normal blood glucose levels. Patients at an increased risk of developing T2DM may therefore benefit from such early meaningful interventions- especially since these patients benefit more from treatments which reduce the risk of CAD [16].

The optimal window for those at risk of developing T2DM is not yet defined. The first challenge remains to operationalize the pre-disease

state, to define those who stand at an increased risk of mortality. Once this population is identified, the challenge remains to select the appropriate treatment, whether it is lifestyle modification or pharmacotherapy. Our data suggests that patients with high normal blood glucose are already likely to have subclinical pathological abnormalities that can contribute to long term cardiovascular risk.

Further validation of the predictive value of our model against models which also adjust for congestive heart failure, lipid and diabetes status will be clinically useful. A comparable predictive value may lead to a subsequent incremental cost-effectiveness ratio workup against a more resource-intensive workup, which may further shape public health policy through enhancing preventive health programs. The advantage of our model is the ease of the availability to measure the covariates in these subjects, as well as the cross-sectional assessment of each subject with limited resources. Earlier identification of at-risk patients may spur greater action in the outpatient setting. These practices may be further incentivized by health care reforms reimbursement models, aimed at preventing hospitalization to incentivize reducing what is perceived to be a preventable inpatient hospitalization admission, the role of primary and secondary prevention will take on an even greater role in the future.

Our results found that when controlled for age, gender, BMI, SBP and DBP, there is an increased risk of mortality in the high-normal blood glucose category, compared to normal blood sugars, as well as a statistically significant increase in relative risk in 20-plus year follow-up for mortality. These results are consistent with 20-year follow-up to assess mortality among middle-aged, non-diabetic men of three separate European cohort studies: the Whitehall Study, Paris Prospective Study and the Helsinki Policeman Study. In these studies, subjects in the top 20% of a nondiabetic 2 hour glucose level was found to have a statistically significant higher risk of all-cause mortality compared to the lower 80% of these distributions [17].

Our results validate the idea that over long periods of time, the clinically significant damage of blood glucose indeed occurs on a spectrum and may begin as early as in higher normal blood sugar levels. T2DM may modulate other co-morbid conditions as part of a metabolic syndrome, which itself has been identified as an independent risk factor for arrhythmias even among patients with structurally normal hearts [18]. We have shown that using one's age, gender, BMI and blood pressure, in conjunction with a random plasma glucose level, may offer some insight into their cardiovascular morbidity and mortality. The consistency of these results, when compared against other similar and validated studies, demonstrate a potential avenue for many countries, which may not have the health care infrastructure to develop their own specific guidelines or where it is simply not cost-effective for clinicians and patients to follow them [2]. As the worldwide prevalence of T2DM increases, the importance of preventing this chronic condition will take an even more paramount role.

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Authors' contributions

SS wrote the manuscript and participated in the design of the study. JT designed, performed statistical analysis and contributed to writing of the manuscript. GI contributed to the background, discussion and the writing of the manuscript. SA helped design the tables, figures and the final editing of the manuscript. AA and FA designed the tables and figures and contributed to the editing of the manuscript. MK reviewed and edited the manuscript. AK generated the research idea and contributed to the background and discussion.

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