Impact of Glycated Hemoglobin Level on Severity of Coronary Artery Disease in Non-Diabetic Patients

Thesis Submitted for Partial Fulfillment of Master Degree in Cardiology

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Dedication and Acknowledgments

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Abstract

Background: Glycated hemoglobin values reflect two to three months average endogenous exposure to glucose including postprandial spikes in blood glucose level and have low intra-individual variability particularly in non-diabetic patients. Elevated hemoglobin A1C is regarded as an independent risk factor for CAD in patients with or without DM, The purpose of this study is to determine the correlation between the level of Glycated hemoglobin (HbA1c), and the severity of coronary artery disease in non-diabetic patients.

Study design and methods: The study included four hundred and eight patients referred to coronary angiography in two tertiary centers. All patients were subjected to complete medical history, physical examination and full labs including HbA1c. Transthoracic echocardiogram and coronary angiography were done andthe Gensini score was calculated.Normally distributed continuous variables will be represented as mean ±SD, or as the percentage of the sample. Comparison between high and low risk groups was doneusing two-tailed unpaired student *t* test for continuous variables and thePearson's chi-square test for categorical variables.

Results: two hundred and ninety two patients (71.6%) high risk group and 28.4% were low risk group. High risk group had HbA1c(HbA1c 5.7 – 6.4%) mg% with mean HbA1cof 6.1± 0.3.The mean Gensini score was 39.9± 34.9.The level of HbA1c was positively correlated with Gensini score (r=0.243, P<0.05,) and RWMSI (r=0.103, p=0.038) and negatively correlated with LVEF(r= -0.146, p=0.003).

Key words: Non-diabetic patients - Coronary artery disease - Cardiovascular diseases - Glycated hemoglobin.

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List of Abbreviations

Abbreviations	**Meaning**
2-h OGTT	2 hours oral glucose tolerance test
ACC	American College of Cardiology
ACR	albumin-to-Creatinine ratio
ACS	acute coronary syndrome
ADA	American Diabetes Association
ADAG	A1C-Derived Average Glucose
ALL	Average length lesion
ARIC	Atherosclerosis Risk in Communities
AUC	area under the curve
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	Coronary artery disease
CGM	continuous glucose monitoring
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular Disease
DBP	diastolic blood pressure
DCCT	The Diabetes Control and Complications Trial
DM	Diabetes mellitus
eAG	estimated average glucose
Echo	Echocardiography
EEM	external elastic membrane
EF	Ejection fraction
EPIC	European Prospective Investigation of Cancer
FBG	fasting plasma glucose
FBS	Fasting blood glucose
FDR	First degree relative
Fig	Figure
FRS	Framingham Risk Score
GFR	Glomular filtration rate
HbA1c	Glycated haemoglobin
HbF	Fetal hemoglobin
HbS	hemoglobin S
HDL	high-density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HPFS	Health Professionals Follow-Up Study
HR	hazard ratios
hs-CRP	high sensitivity C-reactive protein

HTN	Hypertension
IDL	intermediate-density lipoprotein
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IMT	Intima media thickness
IVUS	Intravascular ultrasound
JNC	Joint of National Committee
LAD	Left anterior descending artery
LCX	Left circumflex artery
LDL	low-density lipoprotein
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MDCT	multi-detector computed tomography
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MVD	multivessel disease
N	Number
NDR	National Diabetes Register
NEFAs	Nonesterified fatty acids
NGSP	National Glycohemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NSTEMI	Non ST segment elevation myocardial infarction
NWAHS	The North West Adelaide Health Study
OGTT	oral glucose tolerance test
OHAs	oral hypoglycemic agents
OR	odds ratio
P	P-value
PAI-1	plasminogen activator inhibitor
pCAP	premature coronary atherosclerotic patients
PCI	percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
PWV	pulse wave velocity
RCA	Right coronary artery
RR	remodeling ratio
RWMSI	Regional wall motion score index
SBP	Systolic blood pressure
SD	Standard deviation
SDR	Second degree relative
SI	System International
SPSS	Statistical Package for the Social Sciences
STEMI	ST segment elevation myocardial infarction

SYNTAX	SYNergy between PCI with TAXUS™ and Cardiac Surgery
TC	total cholesterol
TG	triglyceride
US	united state
VLDL	very-low-density lipoprotein
Vs	versus
WC	waist circumference
WHO	World health Organization
WHtR	waist height ratio

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Introduction

Among the known risk factors for cardiovascular disease, diabetes mellitus (DM) ranks as one of the most potent. The excess risk for cardiovascular disease is two to eight folds higher in patients with diabetes mellitus compared to non diabetic individuals of similar age, sex and ethnicity [1], [2]. It has also been recognized that high normal fasting blood glucose and increasing hemoglobin A1C levels in individuals without diabetes mellitus are risk factors for cardiovascular events and subclinical atherosclerosis [3, 4].

Glycated hemoglobin values reflect two to three months average endogenous exposure to glucose including postprandial spikes in blood glucose level and have low intra-individual variability particularly in non-diabetic patients [5, 6.] New clinical practice recommendation from the American Diabetes Association advocates the use of hemoglobin A1c in diagnosis of diabetes mellitus largely on the basis of the established association between Glycated hemoglobin and microvascular disease.[7, 8, 9]

Elevated hemoglobin A1C is regarded as an independent risk factor for Coronary artery disease (CAD) in patients with or without DM, whereas levels of hemoglobin A1c less than 7% deemed appropriate for reducing risk of vascular complications.[10]

The level of hemoglobin A1c has been correlated with number of vessels significantly diseased at time of coronary angiography[11, 12]. Moreover, it has been found that the prevalence of elevated hemoglobin A1c levels in patients undergoing coronary artery bypass grafting is high[13]. Thus; the level of hemoglobin A1c may be correlated with the severity of coronary artery disease innon diabetic individuals.

Aim of the work

The aim of this work was to assess the relationship between the level of HbA1c and the severity of CAD, assessed by the Gensini score, among non-diabetic patients referred to coronary angiography as indicated clinically.

Chapter 1

Glycated Hemoglobin

There has been long-standing interest in the use of HbA1c values for screening and identification of impaired glucose tolerance (IGT) and diabetes[14].HbA1c values were not previously recommended to diagnose diabetes because of variation in HbA1c assays. However, the National Glycohemoglobin Standardization Program (NGSP) has standardized more than 99 percent of the assays used in the United States to The Diabetes Control and Complications Trial (DCCT) standard. A strict quality control program has improved precision and accuracy of assays in the US and many international assays.

An International Expert Committee issued a consensus report in June 2009, recommending that an HbA1c level ≥6.5 percent be used to diagnose diabetes and the ADA affirmed this decision[15]. The diagnosis should be confirmed with a repeat HbA1c. In making the recommendation, the report noted several technical advantages of the HbA1c assay over glucose testing, increased patient convenience (since there is no special preparation or timing required for the HbA1c test), and the correlation of HbA1c levels with retinopathy. The report also noted that if an HbA1c test is either unavailable or uninterpretable, for example owing to rapid red cell turnover with anemia, the previous diagnostic methods and criteria, using glucose testing, should be used.

HbA1c, FPG, and OGTT as PREDICTORS OF DIABETES MELLITUS

Although the natural history of IFG (impaired fasting glucose) and IGT is variable, approximately 25 percent of subjects with either will progress to diabetes over three to five years [16]. Subjects with additional diabetes risk factors, including obesity and family history, are more likely to develop diabetes.

HbA1c values may also be used to predict the incidence of type 2 diabetes. As an example, in a prospective cohort study of 26,563 women followed for 10 years, baseline HbA1c level was an independent predictor of type 2 diabetes, even at levels considered to be within the normal range[17]. In those individuals with baseline HbA1c in the highest quintile (HbA1c >5.22), the adjusted relative risk of diabetes was 8.2, 95% CI 6.0 to 11.1

HbA1c criteria for identifying patients with impaired glucose regulation were derived using data from NHANES 2005 to 2006 [7]. Compared with other cut points, an HbA1c cut point of 5.7 percent had the best sensitivity (39%) and specificity (91 %) for identifying cases of IFG (FPG ≥100 mg/dL [5.6 mmol/L]).

Although most of the high risk groups have been defined categorically (e.g. IFG or IGT), the risk for developing diabetes follows a continuum across the entire spectrum of subdiabetic glycemic values. Higher fasting or (2 hours oral glucose tolerance test) 2-h OGTT glucose values or higher HbA1c values convey higher risk than lower values.

ESTIMATION OF MEAN BLOOD GLUCOSE

It has been known since the 1970s that glucose can attach to many proteins via a non-enzymatic, post-translational process [18]. This occurs in two stages:

- A reversible reaction leads to the formation of an aldimine (or Schiff base).
- This is followed by an Amadori rearrangement to form an irreversible ketoamine.

A transient elevation in blood glucose concentration can lead to the formation of a large quantity of aldimines. This reaction reverses if the concentration returns to normal. However, formation of the ketoamine is irreversible because glucose remains permanently attached to the protein until it is metabolized.

HbA1c

The most widely used clinical test is measurement of HbA1c. Hemoglobin formed in new red blood cells enters the circulation with minimal glucose attached. However, red cells are freely permeable to glucose. As a result, glucose becomes irreversibly attached to hemoglobin at a rate dependent upon the prevailing blood glucose concentration. Approximately one percent of erythrocytes are destroyed every day, while an equal number of new ones are formed. Thus, the average amount of HbA1c changes in a dynamic way and indicates the mean blood glucose concentration over the life span of the red cell [19,20]. Although the HbA1c reflects mean blood glucose over the entire 120 day life span of the red blood cell, it correlates best with mean blood glucose over the previous 8 to 12 weeks.

This relationship has been demonstrated in several studies that have calculated average glucose on the basis of frequently measured, usually capillary, glucose levels [21,22]. As examples:

- DCCT estimated the mean blood glucose concentrations derived from seven measurements a day (before and 90 minutes after each of the three major meals, and before bedtime), performed once every three months, and compared the average glucose concentration with HbA1c values in patients with type 1 diabetes [21]. A relatively strong correlation was noted, and HbA1c values could be translated into a comparable average glucose level.
- A much smaller study captured average glucose by using continuous glucose monitoring (CGM) over three months in 25 participants (type 1 and type 2 diabetics and non-diabetic subjects) and compared the calculated average glucose levels to the HbA1c at three months [23].
- A large international study (A1C-Derived Average Glucose, or ADAG study) calculated average glucose levels in 507 subjects (268 type 1, 159 type 2, and 80 non-diabetic), using similar methods (CGM) as the study described above, and established a reliable regression equation that can be used to translate HbA1c results into an estimated average glucose value.[24]

Studies suggest that HbA1c values may also be helpful in the diagnosis of impaired glucose tolerance or overt diabetes mellitus, being simpler to perform and to repeat than the oral glucose tolerance test.

Assay

In the past, the results of the DCCT could not be extrapolated widely because of differences in methodology and a lack of standardization among laboratories[25]. The NGSP has standardized more than 99 percent of the assays used in the United States to the DCCT standard[26]. A strict quality control program has improved precision and accuracy of assays in the US and many international assays.

In addition, a new reference method has been established that will provide for even more reliable worldwide standardization of all HbA1c assays[27]. With this new reference system, HbA1c results will be reported globally in SI (Systeme International) units (mmol/mol) and derived NGSP units (the same values as reported currently as percent of total hemoglobin) using a master equation.

The estimated average glucose (eAG) (mg/dL or mmol/L)

It is a more relevant term for patients who self-monitor blood glucose. If there are differences in the eAG derived from the HbA1c result and the meter-calculated average glucose, further exploration is required. As an example:

- If the eAG is higher than the patient's meter calculated average glucose, it is possible that fingerstick testing is not being performed at times when the blood glucose is highest, e.g. after meals.
- If the eAG is lower than the meter average, a patient may be having undetected periods of low blood glucose, most often nocturnal hypoglycemia. In such cases, the timing of fingerstick blood glucose monitoring requires adjustment.

Sources of error

Although the international standardization of the HbA1c assay has decreased potential technical errors in interpreting HbA1c results, there are other biological and patient-specific factors that may cause misleading results.[28]

- HbA1c values are influenced by red cell survival. Thus, falsely high values in relation to a mean blood glucose values can be obtained when *red cell turnover is low*, resulting in a disproportionate number of older red cells. This problem can occur in patients with iron, vitamin B12, or folate deficiency anemia.
- On the other hand, *rapid red cell turnover* leads to a greater proportion of younger red cells and falsely low HbA1c values. Examples include patients with hemolysis and those treated for iron, vitamin B12, or folate deficiency and patients treated with erythropoietin.[29,30] Depending upon the methodology, the values may be high in patients with *abnormal hemoglobins* (such as HbF and HbS).[31] However, many methods for measuring HbA1c are no longer affected by hemoglobin variants.

- HbA1c values may be falsely elevated or decreased in those with *chronic kidney disease*. False elevations may be due in part to analytical interference from carbamylated hemoglobin formed in the presence of elevated concentrations of urea, leading to false elevations in the HbA1c level with some assays. False decreases in measured HbA1c may occur with hemodialysis and altered red cell turnover, especially in the setting of erythropoietin treatment.