Introduction

Ischemic Heart Disease, also known as Coronary Artery Disease, is a condition that affects the supply of blood to the heart. The blood vessels are narrowed or blocked due to the deposition of cholesterol on their walls. This reduces the supply of oxygen and nutrients to the heart muscles, which is essential for proper functioning of the heart. This may eventually result in a portion of the heart being suddenly deprived of its blood supply leading to the death of that area of heart tissue, resulting in a heart attack.

As the heart is the pump that supplies oxygenated blood to the various organs, any defect in the heart immediately affects the supply of oxygen to the vital organs like the brain, kidneys, liver, etc. This leads to the death of tissue within these organs and their eventual failure. Ischemic Heart Disease is the most common cause of death in many countries around the world ***(Mitchell et al 2007).***

The HbA1C test is a common blood test used to diagnose type 1 and type 2 diabetes and then to gauge how well you're managing your diabetes. The A1C test goes by many other names, including glycated hemoglobin, glycosylated hemoglobin, hemoglobin A1C and HbA1c.

The HbA1C test result reflects your average blood sugar level for the past two to three months. Specifically, the A1C test measures what percentage of your hemoglobin a protein in red blood cells that carries oxygen — is coated

with sugar (glycated). The higher your A1C level, the poorer your blood sugar control and the higher your risk of diabetes complications ***(Malkani, 2011).***

A 2010 clinical practice guideline from the American Diabetes Association recommends that physicians exclusively use the HbA1c assay to detect diabetes. The guidelines recommend a cutoff of 6.5% or greater for diagnosis.

HbA1c is significantly associated with the complexity of coronary lesions. This association is even observed in non-diabetic adults. A higher HbA1c value is an independent predictor of the prevalence of complex coronary lesions ***(Ikeda et al., 2012).***

Aim of the Work

To study the correlation of HbA1c to the severity of premature coronary artery disease among non diabetic patients and trying to get cutoff point of HbA1c for determining the probability and severity of coronary artery disease.

Chapter (1): Coronary Artery Disease

Coronary heart disease is the most common cause of death in the United States (US) and Europe ***(European Heart Network, 2008, 2012), (US National Center 2010, 2012).*** Acute coronary syndrome (ACS), a common complication of coronary heart disease, is associated with more than 2.5 million hospitalizations worldwide each year ***(Grech & Ramsdale, 2003).*** ACS describes clinical disorders ranging from ST-elevation myocardial infarction (STEMI) to non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) ***(Overbaugh, 2009).*** It is estimated that a myocardial infarction (MI) occurs every 34 seconds in the US, and that one person dies each minute from a major coronary event ***(Roger et al., 2011).***

Most cases of ACS are caused by rupture of an atherosclerotic plaque in a coronary artery, resulting in the formation of a thrombus ***(Mackman, 2008).*** When plaques erode or rupture, the resulting thrombus restricts the flow of blood to the heart muscle ***(Overbaugh, 2009; Hansson, 2005).*** A prolonged lack of blood supply resulting in necrosis of heart muscle tissue is defined as an MI ***(Hansson, 2005).***

Plaque rupture results in exposure of the contents of the plaque and subendothelial fibres to the blood, leading to the activation of platelets, which in turn adhere to

subendothelial structures. Aggregation of additional platelets causes the thrombus to grow. At the same time, the coagulation cascade is activated, resulting in the production of thrombin, which stimulates further platelet recruitment and aggregation. Thrombin also catalyses the generation of fibrin, which forms the main protein component of the thrombus ***(Mackman, 2008).***

Diagnosis of ACS

Patients with ACS typically present with acute chest pain. The main methods used to confirm a diagnosis of ACS and to distinguish between the three types of ACS are as follows*: **(Hamm et al., 2011)***

- Electrocardiogram (ECG) - UA and NSTEMI are associated with ST depression / transient elevation and/or T-wave changes; persistent ST elevation is characteristic of STEMI.
- Cardiac troponins - elevated as a result of myocardial damage; can be used to distinguish UA from NSTEMI ***(Hamm et al., 2011).***

Acute phase treatment of ACS

- Acute phase treatment of ACS includes a combination of anti-ischaemic and antithrombotic agents, with coronary reperfusion achieved using fibrinolysis and/or revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) ***(Overbaugh, 2009).***

- During an ACS event, platelets become activated and thrombin is generated, leading to potentially life threatening coronary artery occlusion. Antiplatelet and anticoagulant agents are routinely used during the acute phase of ACS treatment, for example**: *(Ault et al, 1999; Merlini et al, 1994).***
- Antiplatelets - acetylsalicylic acid (ASA), P2Y inhibitors (e.g. clopidogrel, ticagrelor, prasugrel)
- Anticoagulants - unfractionated heparin, low molecular weight heparins, bivalirudin, fondaparinux ***(Pearte et al., 2006).***

Chapter (2): Glycated Hemoglobin

Glycated hemoglobin (*hemoglobin A1c, HbA_{1c}, A1C,* or *Hb_{1c}*; sometimes also **HbA1c**) is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement.

In diabetes mellitus, higher amounts of glycated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy. Monitoring HbA_{1c} in type 1 diabetic patients may improve outcomes ***(Larsen ML, Horder M &Mogensen EF, 1990).***

Hemoglobin A1c was first separated from other forms of hemoglobin by Huisman and Meyering in 1958 using a chromatographic column ***(Huisman TH,et al., 1958).*** It was first characterized as a glycoprotein by Bookchin and Gallop in 1968. Its increase in diabetes was first described in 1969 by Samuel Rahbar *et al,* ***(Rahbar S et al., 1969).*** The reactions leading to its formation were

characterized by Bunn and his coworkers in 1975 ***(Bunn et al., 1975).*** The use of hemoglobin A1c for monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Anthony Cerami, Ronald Koenig and coworkers ***(Koenig et al., 1976).***

Principle

Glycation of proteins is a frequent occurrence, but in the case of hemoglobin, a nonenzymatic reaction occurs between glucose and the N-end of the beta chain. This forms a Schiff base which is itself converted to 1-deoxyfructose. This rearrangement is known as Amadori rearrangement.

When blood glucose levels are high, glucose molecules attach to the hemoglobin in red blood cells. The longer hyperglycemia occurs in blood, the more glucose binds to hemoglobin in the red blood cells and the higher the glycated hemoglobin.

Glucose levels are intermittently raised in portal vessels carrying absorbed glucose to the liver for regulation. Passing red cells will have increased glycation after sugary food intake.

Once a hemoglobin molecule is glycated, it remains that way. A buildup of glycated hemoglobin within the red cell, therefore, reflects the average level of glucose to which the cell has been exposed during its life-cycle.

Measuring glycated hemoglobin assesses the effectiveness of therapy by monitoring long-term serum glucose regulation. The HbA_{1c} level is proportional to average blood glucose concentration over the previous four weeks to three months. Some researchers state that the major proportion of its value is weighted toward the most recent 2 to 4 weeks ***(Michigan,* 2007).** This is also supported by the data from actual practice showing that HbA1c level improved significantly already after 20 days since glucose-lowering treatment intensification ***(Sidorenkov et al., 2011).***

The approximate mapping between HbA_{1c} values given in DCCT percentage (%) and eAG (estimated average glucose) measurements is given by the following *equation* ***(Nathan et al., 2008).***

eAG (mg/dl) = 28.7 × A1C - 46.7

eAG (mmol/l) = 1.59 × A1C - 2.59

Table (1): Data in parentheses are 95% confidence intervals

HbA_{1c}		eAG (estimated average glucose)	
(%)	(mmol/mol)	(mmol/L)	(mg/dL)
5	31	5.4 (4.2–6.7)	97 (76–120)
6	42	7.0 (5.5–8.5)	126 (100–152)
7	53	8.6 (6.8–10.3)	154 (123–185)
8	64	10.2 (8.1–12.1)	183 (147–217)
9	75	11.8 (9.4–13.9)	212 (170–249)
10	86	13.4 (10.7–15.7)	240 (193–282)
11	97	14.9 (12.0–17.5)	269 (217–314)
12	108	16.5 (13.3–19.3)	298 (240–347)
13	119	18.1 (15–21)	326 (260–380)
14	130	19.7 (16–23)	355 (290–410)
15	140	21.3 (17–25)	384 (310–440)
16	151	22.9 (19–26)	413 (330–480)
17	162	24.5 (20–28)	441 (460–510)
18	173	26.1 (21–30)	470 (380–540)
19	184	27.7 (23–32)	499 (410–570)

The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c ≥ 48 mmol/mol (≥6.5 DCCT %) as another criterion for the diagnosis of diabetes ***(Executive summary: Standards of medical care in diabetes-2010).***

Indications and use

Glycated hemoglobin testing is recommended for both (a) checking the blood sugar control in people who might be pre-diabetic and (b) monitoring blood sugar control in patients with more elevated levels, termed diabetes mellitus. There is a significant proportion of people who are unaware of their elevated HbA_{1c} level before they have blood lab work ***(Walid et al., 2010).*** For a single blood sample, it provides far more revealing information on glycemic behavior than a fasting blood sugar value. However, fasting blood sugar tests are crucial in making treatment decisions. The American Diabetes Association guidelines are similar to others in advising that the glycated hemoglobin test be performed at least two times a year in patients with diabetes that are meeting treatment goals (and that have stable glycemic control) and quarterly in patients with diabetes whose therapy has changed or that are not meeting glycemic goals ***(American Diabetes Association, 2007).***

Glycated hemoglobin measurement is not appropriate where there has been a change in diet or treatment within 6 weeks. Likewise, the test assumes a normal red blood cell aging process and mix of hemoglobin subtypes (predominantly HbA in normal adults). Hence, people with recent blood loss, hemolytic anemia, or genetic differences in the hemoglobin molecule (hemoglobinopathy) such as sickle-cell disease and other conditions, as well as those that have donated blood recently, are not suitable for this test.

Due to glycated hemoglobin's variability (as shown in the table above), additional measures should be checked in patients at or near recommended goals. People with hemoglobin A1C values at 64 mmol/mol or less should be provided additional testing to determine whether the HbA_{1c} values are due to averaging out high blood glucose (hyperglycemia) with low blood glucose (hypoglycemia) or the HbA_{1c} is more reflective of an elevated blood glucose that does not vary much throughout the day. Devices such as continuous blood glucose monitoring allow people with diabetes to determine their blood glucose levels on a continuous basis, testing every few minutes. Continuous use of blood glucose monitors is becoming more common, and the devices are covered by many health insurance plans but not by Medicare in the United States. The supplies tend to be expensive, since the sensors must be changed at least weekly. Another test that is useful in determining if HbA_{1c} values are due to wide variations of blood glucose throughout the day is 1,5 Anhydroglucitol, also known as GlycoMark. GlycoMark reflects only the times that the person experiences hyperglycemia above 180 mg/dL over a two-week period.

Concentrations of hemoglobin A1 (HbA1) are increased, both in diabetic patients and in patients with renal failure, when measured by ion-exchange chromatography. The thiobarbituric acid method (a chemical method specific for the detection of glycation) shows that patients with renal failure have values for glycated hemoglobin similar to those observed in normal

subjects, suggesting that the high values in these patients are a result of binding of something other than glucose to hemoglobin ***(http:// www.clinchem.org / cgi / reprint / 30 / 3 / 485.pdf. clinchem.com. Retrieved 2009-08-31).***

Chapter (3): HbA1c and Cardiovascular Disease

In Absence of Diabetes Mellitus

Whether HbA1c is related to incident macrovascular disease independent of other risk factors in people without diabetes is uncertain. In a community sample an increased risk of incident CHD and stroke ***(Selvin et al., 2005)*** was found in people without diabetes with an elevated HbA1c. However, this has not been a consistent finding. Selvin et al. reported that HbA1c was not associated with prevalent CVD in a community sample with diabetes despite an association with carotid IMT ***(Selvin et al., 2005),*** although one report showed that HbA1c was associated with severity of coronary atherosclerosis in selected men undergoing coronary *angiography* ***(Sasso et al., 2004).*** Others have found no independent relationship in women between HbA1c and CHD after adjustment for age and smoking ***(Blake et al, 2004; Lawlor et al, 2007),*** although some have found the opposite, reporting an association between HbA1c and CHD in women but not men ***(Park et al., 1996),*** or an increased risk in women only at an HbA1c of ≥6% ***(Khaw et al., 2004).*** A recent study reported an association with fasting insulin but not with markers of altered insulin secretion, such as HbA1c in older women ***(Lawlor et al., 2007).*** These authors concluded that, "the overall evidence, while scant, does not suggest a strong association between HbA1c and CHD or all CVDs in non-diabetic women".

The risk of CHD in people with diabetes is greater in women than men ***(Huxley et al, 2006).*** Studies in women examining these associations in people without diabetes are scarce. In a meta-analysis of 20 studies examining the association of glucose and cardiovascular events 94% of the subjects studied were men ***(Coutinho et al., 1999).*** A meta regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years ***(Justin RR et al., 2013).*** Representation of women in a more recent meta-analysis had increased to only 17%. Furthermore, some of these studies did not fully adjust for concomitant cardiac risk factors or did not exclude those who developed diabetes during follow-up, and the relevance of some of these results may be limited because baseline data were collected up to 20 years ago, with major changes to treatment and risk factor prevalence, particularly obesity, over that time ***(Park et al., 1996).*** The most recent large study in women found no association between HbA1c and CHD and stroke. Recently, IFG was reported to be an independent predictor of CVD mortality in an Australian population sample, after adjustment for traditional risk factors. However, this study was limited by differences between responders and non-responders and relatively low follow-up rates, indicating that the cohort may not have been fully representative of Australian adults. Therefore, confirmation of the association of HbA1c and incident macrovascular disease independent of concomitant cardiac risk factors in a recent, representative population cohort of people without diabetes is important.