

*Original Article*

## HbA1C as predictive marker for diabetic complication

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### Abstract

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The aim of this study was to find the correlation between HbA1c with FBS and establish a conversion equation between them, and also to examine the relationship between glycohemoglobin (HbA1c) and age and gender difference as well. Finally, try to set up diagnostic criteria related to early diabetes and to detect pre-diabetes. This was a cross-sectional study done in diabetic hospital, Tripoli. There were 100 cases enrolled during period study. All fasting blood sugar (FBS) and HbA1c data of each case were collected for study. The study target is to prove if we can rely on HbA1c values to assess the diabetic complication and consequently used it as to assess their usefulness in monitoring the glycemic control in diabetic patient and predictive biomarker to prevent the diabetic complications.

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### 1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The aim of the present study was to find the correlation between HbA1c with FBS, so as to assess their usefulness in monitoring the glycemic control in Diabetic patient.

Diabetes causes about 5% of all deaths globally each year. The relatively ineffective

insulin in this condition results in hyperglycemia. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. (1) The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with

diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.

The diabetes mellitus in urban population in developing countries is projected to double between 2000 and 2030. According to the latest World Health Organization (WHO) report, India has 31.7 million diabetic subjects, and the number is expected to increase to a staggering 79.4 million by 2030. (2) Glycemic control is an important aspect in managing diabetes in order to prevent acute or chronic complications of diabetes mellitus. Many randomized, prospective clinical trials in type 1 and 2 diabetes have clearly shown that achieving glycemic control or reducing hyperglycemia significantly decrease the micro vascular complications of diabetes. Each 1% reduction in hemoglobin A1c was associated with a 37% decrease in risk for micro vascular complications and a 21% decrease in the risk of any end point or death related to diabetes. (3, 4) The most commonly used assay to measure chronic hyperglycemia is HbA1c test. However, it is not available in resource poor settings due to its high cost. In some clinical situations that affect red cell life span or hemoglobinopathies, laboratory assessment using the A1C test may provide unreliable information. There are many reports showing the acceptable correlation between hemoglobin A1c level and fasting blood glucose (FBS) level (5)

HbA1c (Glycated Haemoglobin) a long term indicator of diabetic control. HbA1c can therefore be described as a long term indicator of diabetic control unlike blood glucose which is only a short term indicator of diabetic control. It is therefore a more

reliable indicator of glycaemic control than the blood glucose.

Determination of HbA1c is a great importance in the long term care of the diabetic patient and as such it is recommended that HbA1c levels are monitored every three to four months. In patients who have recently changed their therapy or in those who have gestational diabetes it may be beneficial to measure HbA1c levels more frequently, at two to four weeks intervals. Patient understanding of HbA1c is poor, especially among type 2 diabetes patient's , so strategies to engage patient's to know and interpret their HbA1c values should be encouraged within routine clinical practice. (6) This may be the main reason that will determine if HbA1c will be globally expressed as an estimated average glucose.

The most common forms of diabetes are termed type 1 and type 2. Type 1 diabetes was previously called insulin-dependent diabetes or juvenile diabetes while type 2 diabetes was formerly known as non-insulin-dependent diabetes or adult-onset diabetes. The older terminology was often confusing since both insulin-dependent and non-insulin-dependent diabetic individuals may take insulin as part of their management regimen. The difference is that type 1 patients are truly dependent on insulin therapy whereas type 2 patients may benefit from insulin therapy but are not dependent on it for survival. The new classification system minimizes this confusion because it is based on the rather than on the treatment (4).

Type 1 diabetes accounts for about 5% of all diagnosed cases of diabetes.

Type 1 is first diagnosed in children and young adults . Risk factors for type 1 diabetes can be autoimmune, genetic, or environmental. As far , there are no known ways to prevent type 1 diabetes (7).

### **The aims of this study:**

- 1- To establish an appropriate conversion equation between HbA1C and FBS.
- 2- Identifying fasting blood glucose and HbA1C to set up diagnostic criteria related to early diabetes or a screening method for pre-diabetes detection.

### **Material and Methods**

One hundred fasting blood samples collected In fluoride and K3- EDTA tubes in Diabetic hospital- Tripoli . HbA1c Samples will analyzed with Fully automated biochemistry instrument(Integra 400 from Roche) while

### **Test principle**

Total Hb and HbA1c concentrations are determined after hemolysis of the Anticoagulated whole blood specimen. Total Hb is measured colorimetrically. HbA1c is determined immunoturbidimetrically. The ratio of both concentrations yields the final percent HbA1c result [HbA1c (%)].The anticoagulated whole blood specimen is hemolyzed automatically on COBAS INTEGRA systems with HbA1c Hemolysis Reagent in the predilution cuvette. Erythrocytes are lysed by low osmotic pressure. The released Hb is proteolytically degraded by pepsin, to make the  $\beta$ -N-

Type 2 diabetes accounts for about 95% of diagnosed diabetes in adults. Several studies have shown that healthy eating and regular physical activity, used with medication if prescribed, can help control health complication from type 2 diabetes or can prevent or delay the onset of type 2 diabetes (7).

- 3- To examine the relationship between HbA1C and age and gender difference as well.
- 4- To achieving out good glycemic control as to reduce the morbidity and mortality due to various complications of diabetes mellitus.

fasting blood glucose done by glucose analyzer .Quality assurance will strictly followed throughout the procedures to Guarantee the reliability of the results The kit used is Hemoglobin A1C *Whole Blood Application - Standardized according to IFCC*

terminal structures more accessible for the immunoassay. Additionally, the heme portions are oxidized for the Hb assay. Total Hb is determined on COBAS INTEGRA systems in the hemolysate using a cyanide-free colorimetric method based on the formation of a brownish-green chromospheres (alkaline hematin D-575)in alkaline detergent solution.<sup>10</sup>

The color intensity is proportional to the Hb concentration in the sample and is determined by monitoring the increase in absorbance at 552 nm. The test result is

calculated using a fixed factor determined from the primary calibrator chlorohemin.<sup>11</sup>

HbA1c is measured on COBAS INTEGRA systems using monoclonal antibodies attached to latex particles. Remaining free antibodies are agglutinated with a synthetic polymer carrying multiple copies of the  $\beta$ -N-terminal structure of HbA1c. The change in turbidity is inversely related to the amount of bound glycopeptides and is measured inversely related to the amount of bound glycopeptides and is measured turbidimetrically at 552 nm.

A synthetic polypeptide comprising the N-terminal structure of HbA1c is used for calibration.<sup>12</sup>

The final result is expressed as percent HbA1c and is calculated from the HbA1c/Hb ratio as follows:

Protocol 1 (according to IFCC, not applicable for US customers):

$$\text{HbA1c (\%)} = \text{HbA1c/Hb} \times 100$$

Protocol 2 (according to DCCT/NGSP):

## Results

A total of 100 blood samples were evaluated in this study which done in diabetic hospital, Tripoli - Libya. A fasting blood sugar and HbA1c data for each sample were collected for study. There was significant relationship between HbA1c and diabetic complications especially in the elevated HbA1c P value is 0.031 less than 0.05 the rate of complication is augmented, on the other word, this correlation is the main target of the research

$$\text{HbA1c (\%)} = (\text{HbA1c/Hb}) \times 87.6 + 2.27$$

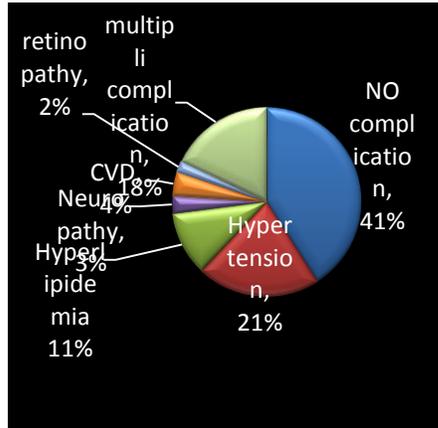
Expected values

Protocol 1 (acc. to IFCC, not applicable for US customers):2.9-4.2% HbA1c<sup>19</sup>

Protocol 2 (acc. to DCCT/NGSP) 4.8-5.9% HbA1c.<sup>(8)</sup>

HbA1c levels above the established reference range are an indication of Hyperglycemia during the preceding 2 to 3 months or longer. HbA1c levels may reach 20% or higher in poorly controlled diabetes. Therapeutic action is suggested at levels above 8%. Diabetes patients with HbA1c levels below 7% meet the goal of the American Diabetes Association. HbA1c levels below the established reference range may indicate recent episodes of hypoglycemia, the presence of Hb variants, or shortened lifetime of erythrocytes. Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

study. Also there is strong relation in concern of gender and HbA1c, especially in female it may due to the prevalence of



uncontrolled diabetes or other reasons such as hormonal disturbance or any other reason need to be study.

Corresponding to the age related to complications P value 0.001 significant < 0.05 mainly in the old ages.

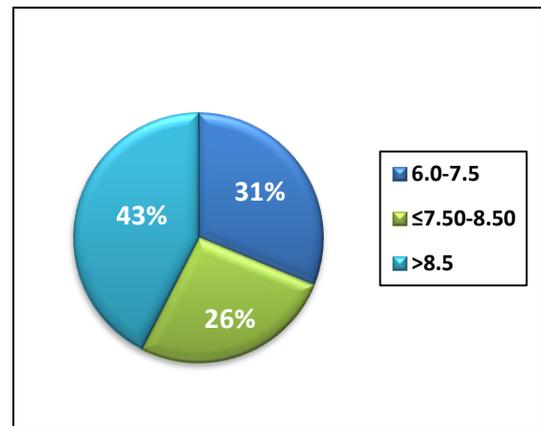
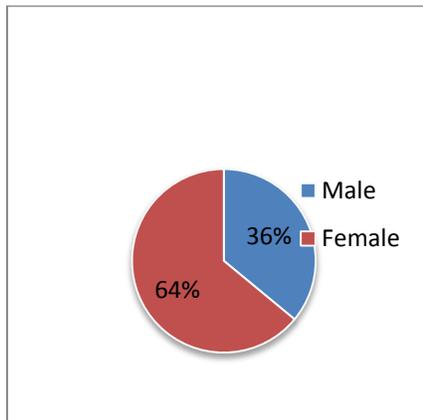


Fig. 10 distribution of HbA1c % over three groups

Fig. 9The percent's of male to the female involved in data analysis

Fig. 11The figure shows the percentage of complication which is 59% of the diabetic

patients who have different disease related to diabetic complication and 41% have no complication.

### Discussion:

Diabetes mellitus is a chronic illness that requires continuing medical care, patient education, and support to prevent acute complications and to reduce the risk of long-term complications. Control of blood glucose in patients with diabetes can be

assessed by several methods. These include assessment of glycated hemoglobin (HbA1c), fasting blood sugar (FBS). The gold standard for assessment of glycaemic control at follow up is the glycated haemoglobin level. (20)

High concentrations of glucose can increase the glycation of common proteins such as HbA1c, formed through the non-enzymatic attachment of glucose to haemoglobin, which is commonly considered to reflect the integrated mean glucose level over the previous 8–12 weeks, the time period being dictated by the 120-day lifespan of the erythrocyte. The concentration of HbA1c predicts diabetes complications because it reflects more harmful glycation sequelae of diabetes, such as retinopathy and nephropathy, which are understood to be due to harmful advanced glycation end products. (21, 22, 23)

A large number of medical conditions are associated with alterations in the HbA1c values. Hematological conditions such as the presence of hemoglobin variants, iron deficiency, and hemolytic anemia, the presence of carbamylated hemoglobin in uremia, a variety of systemic conditions, including certain forms of dyslipidemia, malignancies, and liver cirrhosis, various

### Conclusion:

In conclusion, FBS sounds more reliable to separate diabetic from non diabetic subjects than HbA1c. In case of being interested in using HbA1c in screening, the conventional cutoff points of 6% is an acceptable threshold for differentiate of diabetics from non-diabetics. (26)

HbA1c remains the gold standard in the assessment of glycemic control with availability of standardized methods. The limitation of resource or cost should not be the barrier to provide the good medical care. However in resource poor settings & in conditions with limitations for using HbA1c, FBS can be used to monitor the

medications, and finally, pregnancy are among the factors that influence the HbA1c measurement. (24,25).

There are many reports showing the acceptable correlation between hemoglobin A1c levels and fasting blood glucose levels. In our study, we found that there was significant correlation between FBS with HbA1c levels.

Fully automated clinical biochemistry instrument (Integra 400 and blood glucose analyzer used to investigate HbA1c and FBS, among the 100 cases, there were 62% females and 38% males. Only less than 91% of all cases had HbA1c higher than 6, as shown in Table (3), Item 1. Furthermore, 6 of the study samples had serum glucose values < 126 mg/dl and more than 12% of all cases had fasting glucose < 110, as shown in Table (3), Item 2, more than 86% of all cases had FBS > 110 mg/dl and their HbA1c > 6%, interaction of 2 events, in Item 3, Table (3) and over 93% of all cases, their FBS > 110 mg/dl and HbA1c > 6 % in Table (3), Item 4.

glycemic control. The diabetic patients needs to be regarding the importance of achieving good glycemic control to monitor and achieve Hba1c < 7% so as to reduce the morbidity & mortality due to various complications of diabetes mellitus. HbA1c (Glycated Haemoglobin) a long term indicator of diabetic control. HbA1c can therefore be described as a long term indicator of diabetic control unlike blood glucose which is only a short term indicator of diabetic control. It is therefore a more reliable indicator of glycaemic control than the blood glucose.

Determination of HbA1c is a great importance in the long term care of the diabetic patient and as such it is recommended that HbA1c levels are monitored every three to four months. In patients who have recently changed their therapy or in those who have gestational diabetes it may be beneficial to measure HbA1c levels more frequently, at two to four weeks intervals.

Patient understanding of HbA1c is poor, especially among type 2 diabetes patient's

so strategies to engage patient's to know and interpret their HbA1c values should be encouraged within routine clinical practice.(27) This may be the main reason that will determine if HbA1c will be globally expressed as an estimated average glucose .The advantage of glycosylated hemoglobin or hemoglobin A1c is that the test is not affected by food intake just before the test.

### **Disclaimer**

The article has not been previously presented or published, and is not part of a thesis project.

### **Conflict of Interest**

There are no financial, personal, or professional conflicts of interest to declare.

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