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HbA1c-Glycated Hemoglobin: Perfect Tool to Curb the Diabetes

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Editorial

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Editorial

Millions saw the apple fall but Newton asked Why...!!

Bernard Baruch has very well said this quote as these questions are the basis of science and knowledge. Medical science is not different from it too. In routine day to day practice of medicine we come across with lot many emerging diagnostic techniques and newer modalities. After period of time, all the pros and cons of these techniques could be possible.

Diabetes is not a disease but a syndrome, which virtually involve all parts of the body. Incidence of diabetes is increasing constantly as the stress factor, diet and the life style of common people have been grossly changed in the present scenario. According to International Diabetes Federation- South East Asia (IDF-SEA) region data, 425 million people have diabetes in the world and 82 million people in the SEA Region; by 2045 this will rise to 151 million. There were over 72 million cases of diabetes in India in 2017 [1]. Therefore the world need good diagnostic tool for diabetes mellitus (DM) which is not only helpful in early diagnosis of the disease but also has significant role in evaluation of maintenance of therapy and progression of disease so that complications associated with the disease could be anticipated in time. In 2011 the WHO advocated the use of HbA1c for the diagnosis of type 2 DM and in 2012 UK guidance followed suit [2,3].

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-hour plasma glucose (2-h PG) value after a 75 gram oral glucose tolerance test (OGTT) or HbA1C criteria [4,5]. It is recommended by American Diabetes Association (ADA) that the HbA1C test should be performed by the certified methods from the National Glycohemoglobin Standardization Program (NGSP). These methods should be standardized to the Diabetes Control and Complications Trial (DCCT) reference assay. The HbA1C has several advantages compared with the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and illness [6].

Normal adult hemoglobin consists predominantly of HbA (97%), HbA2 (2.5%) and HbF (0.5%). HbA1 amounts approximately 6% of total HbA, which is further fractionated to HbA1a1, HbA1a2, HbA1b and HbA1c. These fractions are defined by their electrophoretic and chromatographic properties. HbA1c (~5% of total HbA) is the most abundant of these fractions. HbA1c is formed by glycation of the N-terminal valine of the beta chain of hemoglobin where glucose ultimately forms aldimine (Schiff base) before undergoing an Amadori rearrangement to form a more stable ketoamine. All this is a non-enzymatic reaction occurring within red blood

cells constantly and resulting in an increased negative charge of the molecule. The more glucose is present in the blood stream during the lifetime of the red blood cells, the higher the concentration of HbA1c.

The HbA1c is typically performed every three monthly with the notion that the concentration of glycated hemoglobin changes with the life span of the red blood cells which is approximately 120 days. It is therefore used as a clinical tool for monitoring of glycemic control in people with diabetes [7,8]. But in our opinion, this tool should be used on monthly basis to assess its trend as we have noticed significant changes in its value with oral hypoglycemic drugs in established Type 2DM patients.

Analytical methods of HbA1c include high-performance liquid chromatography (HPLC), affinity chromatography, immunoassay, enzymatic assays and capillary electrophoresis. Most commonly HPLC methods (Tosoh, Bio-Rad, and ARKRAY/Menarini) are being used in all over the world. For diagnosis of the diabetes mellitus, the ADA criteria for HbA1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay [6]. A person without diabetes with his/her HbA1c test level ranging between 4% to 5.6% is considered normal; between 5.7% to 6.4% indicates a high risk of diabetes or pre-diabetes.

Although the HbA1c estimation helps a lot in diagnosis and evaluation of the adequate treatment patient, some limitations associated with its estimation are as follows:

Factors that Interfere with HbA1c Measurement: Genetic variants (e.g. HbS trait, HbC trait), elevated fetal hemoglobin (HbF) and chemically modified derivatives of hemoglobin (e.g. carbamylated Hb in patients with renal failure) can affect the accuracy of HbA1c measurements. The effects vary depending on the specific Hb variant or derivative and the specific HbA1c method [9]. When selecting an assay method, laboratories should take into consideration characteristics of the patient population served, (e.g. high prevalence of hemoglobinopathies or renal failure).

Factors that affect interpretation of HbA1c Results: Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, hemolytic anemia) will falsely lower HbA1c test results regardless of the assay method used [10]. HbA1c results from patients with HbSS, HbCC, and HbSC must be interpreted with caution given the pathological processes, including anemia, increased red cell turnover, and transfusion requirements, that adversely impact HbA1c as a marker of long-term glycemic control. Alternative forms of testing such as glycated serum protein or glycated albumin should be considered for these patients.

In developing countries like India, iron deficiency anemia is a major health issue particularly in females. It is associated with higher HbA1c and higher fructosamine [11]. Alternative measures of glycemic assessment (e.g., glucose monitoring) must be used in the presence of significant iron deficiency anemia, at least until the iron deficiency has been successfully treated.

The role of HbA1c estimation in diabetic subjects with renal disease is not very established. Few studies suggest HbA1c underestimates glycemic control in diabetic patients on dialysis and that glycated albumin is a more authentic indicator of glycemic control [12,13]. Further studies are needed to clarify the role of HbA1c in diabetic patients with chronic renal failure.

In 2014, the WHO estimated the global prevalence of DM to be 9% amongst adults over 18 years and predicted it to be the 7th most common cause of death by 2030. Approximately 90% of all cases of diabetes are type 2 DM. majority cases of DM amongst adults are estimated to be undiagnosed, the detection of the condition and adequate glycemic control is crucial to managing the course of the disease as treatment and therapies need to be adjusted in order to minimize micro- and macrovascular complications including nephropathy, neuropathy and retinopathy. HbA1c proved to be a good diagnostic tool with few limitations to diagnose frank diabetes and to alert pre-diabetes conditions. It helps in monitoring the different treatment modalities.

HbA1c testing in most part of the world is commonly recommended once in a three month. Even after extensive review of literature, Canadian agency recommended that HbA1c testing is typically done twice yearly in well controlled patients and four times yearly in poorly controlled individuals [14]. But we noticed that if it is carried out on monthly basis, an early peak and troughs of the HbA1c levels can be easily detected and by that we can accordingly increase or decrease the anti-diabetic treatment. Thereby, we can avoid unnecessary delay of two months of effective treatment that in turn saves patients from further complications of diabetes which can otherwise be avoidable. Thus, to the best of our knowledge, first time in world literature, we strongly recommend monthly estimation of HbA1c in individuals who have established DM and their baseline HbA1c is

above 7% with or without overt complication. We also recommend more research data to come forward to further enlighten the issue..

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