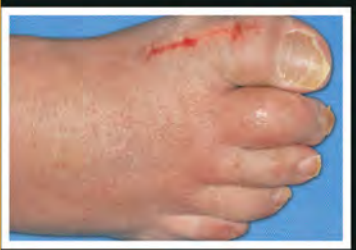
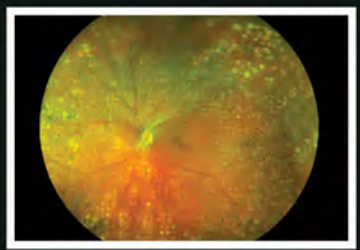


Clinical Atlas of DIABETES MELLITUS

Arturo R Rolla • Sanjay Agarwal

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Contents

CHAPTER 4

Monitoring Glycemic Control: Focus on Alternate Markers of Glycemia

Anjali Amit Bhatt, Manish M Bothale, AG Unnikrishnan

INTRODUCTION

One of the most important pillars of effective diabetes management is monitoring of diabetes to assess the glycemic control. The major of treatment of diabetes is to prevent the occurrence and to slow down the rate of progression of debilitating microvascular complications like retinopathy, nephropathy and neuropathy. Significant, though a lesser degree of association also exists between glycemic control and macrovascular complications like myocardial infarction and cerebrovascular accidents in patients with diabetes.[1,2] Glycosylated hemoglobin (HbA1c) is currently the most effective, reproducible and evidence-based glycemic monitoring tool and has also been shown to correlate with the risk of developing diabetes related vascular as well as non-vascular complications. In situations where validity of HbA1c is questioned, end products of glycation of other biomolecules like fructosamine, glycated albumin and 1,5-anhydroglucitol (1,5-AG) may be considered as markers of glycemic control. This chapter will focus on HbA1c, 1,5-AG and similar markers, and will not cover continuous glucose monitoring and self-monitoring of blood glucose.

EVIDENCE FOR UTILITY OF HbA1c—MEAN PLASMA GLUCOSE AND VASCULAR COMPLICATIONS OF DIABETES

Though the concept of HbA1c is known since 1960s,[3] the first major evidence of utility of HbA1c came from DCCT (Diabetes Control and Complications Trial).[4,5] Firstly, the 6 ½ years' follow-up of 1500 odd patients made it possible to relate 25,000 odd readings of self-monitoring of blood glucose with serial reports of HbA1c.[6] This analysis found a linear relationship between mean plasma glucose and HbA1c. The relationship, controversially described by the equation —"Mean plasma glucose (mg/dL) = (35.6 × HbA1c) - 77.3"—is still utilized by clinicians and other healthcare providers to explain the meaning of HbA1c value to patients with diabetes. Some reports have questioned this linearity of the relationship, which is also thought to change according to absolute value of HbA1c. In other words, the same equation may not be applicable to HbA1c of 7% as well as 11%.[6] Additionally HbA1c loses its linearity in patients who

have extreme excursions in glucose levels with recurrent hypoglycemia and hyperglycemia. However, currently the evidence in favor of utility of HbA1c as an important predictor of mean plasma glucose is stronger than the evidence otherwise.[7]

Secondly, DCCT[5] also cemented the utility of HbA1c which was further agreed upon by results of UKPDS[8] trial in predicting microvascular complications in patients with type 1 and type 2 diabetes respectively. Indeed on long-term follow-up it was shown that achieving a lower HbA1c during initial period after diagnosis also translates in better long-term outcomes irrespective of subsequent glycemic status – a phenomenon termed as 'metabolic memory or legacy effect.'[9]

Later, three landmark trials ACCORD,[10] ADVANCE[11] and VADT[12] confirmed the beneficial effect of lowering of HbA1c on reduction in onset as well as progression of microvascular complications. But these landmark trials also showed no significant reduction in CVD outcomes with stricter targets of HbA1c.

METHODOLOGICAL CONSIDERATIONS

In the initial phases of discovery using ion-exchange chromatography, five sub-fractions of normal adult hemoglobin (HbA) were demonstrated namely HbA1a, HbA1b, HbA1c, HbA1d and HbA1e based the order of elution.[13] Later, combination of demonstration of a simple biochemical concept of elevated glycosylation product of hemoglobin and a genuine clinical demand led to use of a variety of analytic principles for the measurement of HbA1c. Most notably ion-exchange high-performance liquid chromatography systems are utilized to separate these fractions based on their charge difference. But methods like affinity chromatography and immunochemical methods which identify difference in molecular structure are becoming widely available. It is mandatory to standardize the test results according to the International Federation of Clinical Chemistry (IFCC) Reference Measurement Procedure (RMP) in harmony with the efforts of the National Glycohemoglobin Standardization Program (NGSP).[14]

As the average lifespan of RBC is 120 days, HbA1c logically represents mean glucose levels over the preceding three months. But practically, recent glycemia influences the result largely. It is shown that in a patient with stable glycemic control, HbA1c values have 50% contribution from the glycemic status in the month prior to sampling, 25% in the month before that, and the remaining 25% from the earlier month.[15]

LIMITATIONS IN USE OF HbA1c

Conditions Interfering with Formation of HbA1c

As discussed earlier the normal form of hemoglobin on high performance liquid chromatography (HPLC) is Hemoglobin A (HbA). A glycated product of HbA is recorded on HPLC as HbA1c. People with abnormal hemoglobin, which is different from HbA logically, have an abnormal glycated product. A classical example of this condition is sickle cell anemia in which patients have HbS hemoglobin, which form HbS1c. A similar process occurs in patients with HbC and so on. The proportion of abnormal glycated product to HbA1c depends on severity of the disease but is difficult to predict in a given individual. With advances in the analyzers, it is now possible to

detect the non-glycated portion of the abnormal fractions of hemoglobin but it is still difficult to predict HbA1c had it not been a patient with abnormal hemoglobin.[16] Another advantage of the advanced glycosylated hemoglobin analyzers is their ability to account for fetal hemoglobin (Hb) which may persist in few subjects even in adulthood and may interfere with HbA1c formation.

Being a chromatographic representation of hemoglobin, HbA1c values are directly affected by red blood cells (RBCs) survival. In conditions resulting in decreased turnover of RBCs, HbA1c can be falsely elevated losing its relationship with mean blood glucose concentrations. Classical example of this condition is anemia due to deficiency of iron, vitamin B_{12} or folic acid. Conversely, with excellerated hematopoiesis HbA1c values can be lower than that estimated from mean plasma glucose. This condition includes anemia due to blood loss, hemolytic anemia, hyperdynamic circulation like pregnancy, or patients recovering from nutrient deficiency anemia.[17]

Conditions Interfering with the Interpretation of HbA1c

Apart from the glycemic variability making HbA1c difficult to correlate with mean plasma glucose, some health conditions make use of HbA1c less reliable as a marker of glycemic control. HbA1c is less useful as a marker of glycemic control and as a tool for diagnosis of diabetes during pregnancy.

HbA1c values may be unpredictable in various phases of chronic kidney disease including those on dialysis due to multiple factors like iron deficiency, hemolysis, altered RBC survival. Methodologically carbamylated hemoglobin formed by compounding of hemoglobin by urea-derived isocyanate which is difficult to distinguish from HbA1c.[18] Liver disease and chronic malaria have also shown to cause a falsely lowered HbA1c level. Drugs, which cause hemolysis, may theoretically interfere with interpretation of HbA1c, e.g. aspirin but this effect does not seem to be clinically relevant.

Some studies have suggested a racial and ethnic effect on A1c[19] but, the evidence is not strong enough to result in change in recommendations of different interpretations of A1c in different ethnic populations.

RECOMMENDATIONS FOR CLINICAL USE OF HbA1c

Currently, it is recommended to perform HbA1c in all patients with diabetes as an initial assessment and as well as a part of continued monitoring. Measurement should be done every three months to evaluate whether glycemic targets are reached or not. The frequency may change on clinical scenario, intensity of change in medications and choice of clinician as well as patient. Generally patients with unstable control of diabetes require more frequent testing than those with stable control.[20]

The recommended target of HbA1c for most non-pregnant adults with no severe comorbidity is <7% (53 mmol/mol). The target may be higher (up to 8%) in patients with long-standing diabetes with established vascular complications (especially coronary artery disease), multiple associated comorbidities with a reduced life expectancy. The targets are higher in patients with tendency to develop hypoglycemia due to any reason. Antagonistically a stricter target may be recommended in newly detected, otherwise healthy and motivated young patient with availability of resource and support system.[20] HbA1c can be used to diagnose diabetes—a value

of more than or equal to 6.5% indicates diabetes, and a value that is between 5.7% and 6.4% is akin to prediabetes, indicating a high risk state of predisposition to diabetes.

ALTERNATIVE BIOMARKERS FOR ASSESSING GLYCEMIC CONTROL IN DIABETES

Due to the knowledge of certain conditions and specific population making HbA1c a less reliable test for assessment of diabetes, there has been increasing interest in developing non-traditional glycemic markers as alternatives to HbA1c. Three such most important biomarkers include fructosamine, glycated albumin, and 1,5-anhydroglucitol.[21,22] Recently evidence has shown those fructosamine and glycated albumin are strongly associated with fasting glucose.[23]

Fructosamine

Contemporary to binding of hemoglobin to glucose, binding of fructose to serum protein results in a ketoamine termed as Fructosamine. The term fructosamine includes end products of glycosylation of all proteins. Though, fructosamine assays are cheaper and easier they are less standardized than HbA1c assays. Fructosamine assays are useful as markers of recent short-term changes in glycemic status as they reflect mean plasma glucose over a period of previous two to three weeks due to much shorter half-life of albumin compared to RBCs. The higher within-subject variation and effect of change in serum protein (especially albumin) are the limitations in widespread utility of fructosamine.[24]

Glycated Albumin

It is the ratio of glycated albumin to total serum albumin. Unlike fructosamine, this product is not affected by serum albumin levels. The value of glycated albumin is approximately three times that of HbA1c. Similar to fructosamine, glycated albumin reflects glycemic control over preceding two to three weeks. Clinical utility of glycated albumin lies in monitoring for glucose control in patients with abnormal RBC lifespan or variant hemoglobin and conditions in which glycemia changes rapidly such as in fulminant type I DM. Limitations of this test include abnormal values in diseases that result in abnormal albumin metabolism including obesity.[25]

1,5-anhydroglucitol

The 1-deoxy form of glucose known as 1,5-anhydroglucitol. It is a dietary compound, which is reabsorbed by renal tubules in an euglycemic subject. A competitive fall in serum levels of Serum 1,5-anhydroglucitol suggests increase serum glucose to >180 mg/dL. Hence, lower serum 1,5-anhydroglucitol levels reflect high circulating glucose over the past 1 to 2 weeks.[26] This test is affected by alteration in renal hemodynamic as well as use of drugs altering the glucose excretion through kidney like SGLT-2 inhibitors. This test is not widely utilized.

CONCLUSION AND FUTURE DIRECTIONS

Monitoring of glycemic status is one of the most important aspects of continued diabetes care. Markers of glycemic control have shown a strong association with onset and progression of

microvascular complications and to a certain extent on macrovascular complications. Currently HbA1c is the most preferred method of evaluating long-term status of glycemic status in people with diabetes. In conditions and populations where HbA1c is less reliable, alternative tests like fructosamine, glycated albumin, and 1,5-anhydroglucitol. New research would focus on markers that are related to glucose, but more predictive of complications. It is known that HbA1c is formed by glycation of hemoglobin. It is well known that according to the glycation theory, some advanced glycation products may predict both glucose control and diabetes complications. N-1-(Deoxyfructosyl) valine (DFV) β-hemoglobin (β-Hb), commonly referred as HbA1c, is as mentioned above, a widely used marker of hyperglycemia—and is thought that it also indicates glycation to some extent. However, arguing that HbA1c is still not as advanced a glycation end product, researchers have tried to identify molecules in later stage of glycation, which may reflect hyperglycemia, but also improve accuracy in complication detection. Such carboxy-ethyl and carboxy-methyl variants of glycated hemoglobin have been recently discovered and may predict hyperglycemia and its complications to a better extent.[27] However, they are still under research and if clinical studies prove their relevance, the future may have another new tool to detect diabetes and its complications.[27]

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Clinical Atlas of DIABETES MELLITUS

The *Clinical Atlas of Diabetes Mellitus* is a must read book created with the idea of what is important for the physicians who take care of patients with diabetes. It is a practical and comprehensive manual without unnecessary research details.

Each chapter is comprehensively written by authorities from across the world with extensive clinical experience. Pictures, tables, flow diagrams and bullet points make its reading simple and direct.

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