REVIEW

Glycosylated Hemoglobin: The Importance in Management of Type 2 Diabetes

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Type 2 diabetes is a major public health problem with high and increasing prevalence, morbidity and mortality. The association between diabetes and microvascular and macrovascular complications is well known besides, tight glycemic control is a necessity. HbA_{1C} has clinically been used since 1980s as a gold standard for monitoring glycemic control and predicting of diabetic complications.

The present review article was prepared by computerized sources of literature searches 2000 - 2009.

The history of Hemoglobin A_{1C}, its assay techniques, optimal A_{1C} targets, its reliability in control of diabetic complications, limitations of test results and its importance in control of diabetes patients and their complications are discussed.

Key words: glycemic control, HbA_{1C}, type 2 Diabetes

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Diabetes is a major health concern at worldwide and despite increasing diagnostic techniques, knowledge about its effects on public health and complex complications in current life of diabetic patients, only modest progression has been achieved in glycemic control. On the other hand, hemoglobin A_{1C} (HbA_{1C}) is an important index of glycemic management (Brownlee & Hirsch, 2006). High levels of A_{1C} is associated with high risk of peripheral arterial diseases even among individuals without diabetes (with A_{1C} levels 5.3% - 6%).

Therefore, efforts to reduce the levels of A_{1C} may reduce the risk of these complications (Day & Bailey, 2007; Munter et al., 2005; Selvin et al., 2006). A trial on 2412 diabetic and nondiabetic patients with symptomatic chronic heart failure showed that the A_{1C} level is an independent progressive risk factor for cardiovascular death, hospitalization for heart failure, and total mortality (Gerstein et al., 2008; Qaseem et al., 2007). Another large study on 47904 persons confirms that A_{1C} levels are strongly associated with subsequent

mortality in both men and women without prior diabetes diagnosis (Brewer et al., 2008).

Glycosylated hemoglobin

Hemoglobin (Hb) is made up two globin dimmers each with a heme moiety. HbA comprises 97% of the total Hb and hemoglobin A_{1C} is an irreversible complex that forms when glucose binds to hemoglobin (Gallagher et al., 2009). HbA_{1C} constitutes about 60-80% of total glycated hemoglobin (Tran et al., 2004).

First 60 years ago it was shown by Allen that HbA contains three minor components; HbA_{1c}, $HbA_{1b,}$ and HbA_{1c} (or A_{1C}). A_{1C} is nonenzymatic glycated product of the hemoglobin beta-chain at the valine terminal residue. The number 1C represents the order of Hb detection on chromatography (Kahn & Fonseca, 2008; Tran et al., 2004). HbA_{1C} was first separated by Huisman and Meyring in 1958 and was identified as a glycoprotein by Bokchin and Gallop in 1968, but it was characterized as an unusual hemoglobin" in diabetic patients by Iranian scientist "Samuel Rahbar" in 1969 who noted that diabetes is clearly associated with an elevation in glycated hemoglobin.

The use of HbA_{1C} for control of blood sugar in diabetic patients was proposed by Cerami and Koenig in 1976 (Kahn & Fonseca, 2008; Tran et al., 2004). After clinical works in 1980s, it was introduced as a better index of diabetic control trials (Gallagher et al., 2009; Kahn & Fonseca., 2008).

An important change in diabetes care occurred in the 1970s and 1980s as two methods became available: self-monitoring of blood glucose (SMBG) and HbA_{1C} testing (A_{1C}). Regular SMBG has positive effect on improving glycemia particularly in testing the individuals treated with insulin. SMBG reflects the immediate plasma glucose levels, while HbA_{1C}

measures long-term glycemic control (Saudek et al., 2006).

HbA_{1C} assays and limitations

Standardization of A_{1C} measurement has been proposed in different countries to ensure accuracy in A_{1C} results (Gallagher et al., 2009).
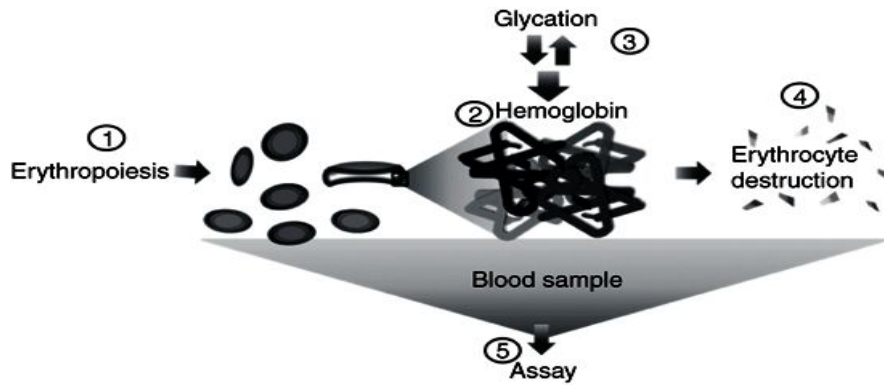
Assays for A_{1C} use technologies based on either charge differences high performance liquid chromatography (HPLC) or structure (boronate affinity or immunoassay combined with general chemistry) and newly techniques based on combined immunoassay and general chemistry (Bode et al., 2007).

In past decades, the trials such as DCCT (Diabetes Control and Complications Trial) and UKPDS (UK Prospective Diabetes Study) considered A_{1C} as the gold standard of diabetes care (Dailey, 2009; Gallagher et al., 2009; Saudek et al., 2006). Furthermore, the programs such as NGSP (National Glycohemoglobin Standardization Program) and associations such as AACC (American Association for Clinical Chemistry) (Kahn & Fonseca, 2004) have worked on standardization of A_{1C} values leading to present methods in measurement of $A_{1C.}$ Recently, NGSP-certifies rapid HbA_{1C} assays have become available, allowing office and home testing (Saudek et al., 2006).

Because A_{1C} is based on hemoglobin, quantities or qualitative variations in hemoglobin can affect the A_{1C} value and interpreting of results (Bloomgarden, 2008). These variations include the case of reduced total Hb or turnover of red blood cells that cause reduced level of A_{1C} even in the presence of high ambient plasma glucose (Tran et al., 2004) Generally, abnormal results of A_{1C} test may get with sickle-cell disease, glucose-6-phosphate dehydrogenase deficiency, B_{12} or folate deficiency,

alcoholism, chronic renal or liver disease, splenectomy or splenomegaly, chronic opiate use, large doses of aspirin, vitamin C and vitamin E supplements, creatin and drugs such as dapsone, ribavirine and so forth (Gallagher et al., 2009; Tran et al., 2004). Besides HbA of human erythrocytes contain other hemoglobins such as HbA_2 and fetal hemoglobin (HbF). Figure 1 questions remain about exact mechanisms of these abnormal situations (Gallagher et al., 2009; Goldstein et al., 2004; Saudeket al., 2006).

Factor influencing A_{1c}	Increased A_{1c}	Decreased A_{1c}	Variable change in A_{1c}
1. Erythropoiesis	Iron deficiency, vitamin B_{12} deficiency, decreased erythropoiesis	Administration of erythropoietin, iron or vitamin B_{12}; reticulocytosis, chronic liver disease	
2. Altered hemoglobin			Fetal hemoglobin, hemoglobinopathies, methemoglobin
3. Glycation	Alcoholism, chronic renal failure, decreased erythrocyte pH	Ingestion of aspirin, vitamin C, vitamin E; certain hemoglobinopathies, increased erythrocyte pH	Genetic determinants
4. Erythrocyte destruction	Increased erythrocyte lifespan: splenectomy	Decreased erythrocyte lifespan: hemoglobinopathies, splenomegaly, rheumatoid arthritis, drugs such as antiretrovirals, ribavirin, and dapsone	
5. Assays	Hyperbilirubinemia, carbamylated hemoglobin, alcoholism, large doses of aspirin, chronic opiate use	Hypertriglyceridemia	Hemoglobinopathies

Figure 1: Factors influencing A_{1C}

It seems that HbA_{1C} has negative correlation with age (El-Kebbi et al., 2003; Gilliland et al., 2002) and shift in the onset of diabetes to younger ages is notable. This difference may be the result of differences among age groups in treatment strategies

or poor control as well as visit frequency in older people (Gilliland et al., 2002).

Monitoring value and recommended ranges

A_{1C} is nonenzymatic glycated product of the hemoglobin beta-chain and it is normally present at low levels in circulating red cells because of the glycosylation reaction between Hb and circulating glucose, but in the presence of excess plasma glucose this glycation is increased, thus making the A_{1C} a useful index of glycemic control (Tran et al., 2004).

Average life span of erythrocytes is 117 days in men and 106 days in women. Because erythrocytes are freely permeable to glucose, the level of HbA_{1C} in a blood sample provides a glycemic history of the previous 120 days, therefore diabetic patients are recommended to be tested every 3 months (Gallagher et al., 2009; Goldstein et al., 2004; Smaldone, 2008).

"American Diabetic Association" (ADA) recommends measuring HbA_{1C} at least 2 times per year for patients who have met their therapeutic goals and quarterly for patients who have not met their glycemic goals or have changed their therapies (Dailey, 2009; Gallagher et al., 2009).

The normal range of HbA_{1C} test for nondiabetic people is between 4-6% (Goldstein et al., 2004). In diabetic patients the recommended value by "International Diabetes Federation" and "American College of Endocrinology" is below 6.5%, while acceptable level of ADA is below 7% in general but suggesting an A_{1C} level as close to normal (<6%) as possible without causing significant hypoglycemia in individual patients (Cefalu, 2008). The suggested target hemoglobin A_{1C} level by "American Association of Clinical Endocrinology" is $\leq$ 6.5%. Their guideline states that the normalization of blood glucose levels should be the goal, while the

guideline of "American Academy of Family Physicians" states that due to differences in patients' life expectancies and co-morbid conditions, a uniform target A_{1C} level for all patients with type 2 diabetes is inappropriate. The guideline of "American Geriatrics Society" suggests "individualized" A_{1C} levels for older persons. This organization accepts $\leq$ 7% level for relatively healthy adults with good functional status and 8% level for others with a life expectancy of less than 5 years or the risk of intensive glycemic control outweighs the benefit. Other organizations such as "Canadian Diabetes Association" and "Institute for Clinical Systems Improvement" recommend "individualized" goals for certain populations (Cefalu, 2008; Qaseem et al, 2007). It is difficult to achieve or maintain target A_{1C} levels and only about a third of diagnosed patients achieve that goal (Dailey, 2009; Kahn & Fonseca, 2008; Tran et al, 2004). In general, level of approximately 7% is confirmed in trials on high-risk populations, specially the use of aggressive pharmacological therapy is under consideration (Cefalu, 2008).

Epidemiologic studies suggest that each 1% increase in the A_{1C} value is associated with a 18% increase in the relative risk of cardiovascular diseases for patients with type 2 diabetes (Buse et al., 2007) and with 15% for type I diabetes (Selvin et al., 2004). In normoglycemic range, this risk has been estimated about 20-30% (Day & Bailey, 2007).

Meta-analysis of clinical trials shows that every 1% reduction in A_{1C}, lowers the risk of developing eye, kidney complications, and neuropathy by 40%. This reduction for myocardial infarction (MI) is 14% (Bode, 2007; Selvin, 2004).

The meta-analysis of observational studies indicates that the relationship of A_{1C} with cardiovascular diseases in diabetic persons is less

clear than microvascular diseases, thus further randomized trials is necessary (Cefalu, 2008; Selvin, 2004).

Some authors believe that optimal diabetes management involves adjunct control of fasting (FBS); preprandial, postprandial glucose (PPG) levels. A_{1C} can not be used to identify whether an abnormal glycemic level is primarily due to high FBS or high PPG levels. In fact, elevated A_{1C} signals a need for a change in therapy (not what type changes), whereas PPG is increasingly important as A_{1C} decreases toward target levels (Dailey, 2009; Day & Bailey, 2007; Shiraiwa et al., 2005). Continuously, A_{1C} is the gold standard for monitoring glycemic control and serves as an indicator for diabetic related diseases.

SUMMARY

HbA_{1C} measuring is consistently the best way for monitoring glycemic control over time and predicting of diabetic complications. Different organizations have different guidelines for glycemic control, but most of them accept a target A_{1C} level of approximately 7% with specific or "individualized" goal especially for older patients or in the presence of comorbid conditions. They state that although A_{1C} measures mean glycemic exposure during the preceding 2-3 months, it does not provide information about day-to-day changes in glucose levels. Regular SMBG is presented as an important adjunct to A_{1C}, because it can distinguish among fasting, preprandial, and postprandial hyperglycemia and can identify hypoglycemia and provide necessary changes in medication, food and activity choices. A_{1C} has good standardization in comparison with FBS and other parameters, although nonglycemic factors affecting A_{1C} should be taken into account (Bloomgarden, 2008).

Due to attention to recent advances in rapid A_{1C} assays allowing immediate feedback changes, and improving community-based public health interventions through nutrition and exercise programs (Goldhaber et al., 2003), better future for glycemic control of diabetic population will be imaginable.

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