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LEMBAR
HASIL PENILAIAN SEJAWAT SEBIDANG ATAU PEER REVIEW
KARYA ILMIAH : JURNAL ILMIAH

Judul Jurnal Ilmiah (Artikel : Glycated HEMOGLOBIN A1C AS A BIOMARKER PREDICTOR FOR DIABETES MELLITUS, CARDIOVASCULAR DISEASE AND INFLAMMATION

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Semarang, 11 September 2020
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Glycated HEMOGLOBIN A1C AS A BIOMARKER PREDICTOR FOR DIABETES MELLITUS, CARDIOVASCULAR DISEASE AND INFLAMMATION

by Indranila Kustarini Samsuria

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LITERATURE REVIEW

GLYCATED HEMOGLOBIN A1C AS A BIOMARKER PREDICTOR FOR DIABETES MELLITUS, CARDIOVASCULAR DISEASE AND INFLAMMATION

(Glikasi Hemoglobin A1c sebagai Petanda Biologis Peramal Diabetes Melitus Penyakit Kardiovaskular dan Inflamasi)

Indranila KS

ABSTRAK

Hemoglobin glikasi (HbA1c) telah diakui secara luas sebagai petanda biologis peramal untuk keparahan Diabetes Melitus (DM). Hemoglobin glikosilasi (HbA1c) adalah petanda biologis penting yang mencerminkan kepekatan glukosa plasma puasa dan postprandial selama 120 hari sebelumnya. Telah dianggap sebagai alat penting dalam diagnosis dan manajemen diabetes. Peningkatan kadar HbA1c berarti resistensi insulin jangka panjang dan konsekuensi berat adanya hiperglikemia, dislipidemia, hiperkoagulabilitas dan respons inflamasi. Terdapat hubungan positif antara HbA1c tinggi dan hasil yang buruk pada DM, penyakit kardiovaskular (CVD) dan inflamasi. HbA1c adalah petanda biologis peramal tidak hanya di DM, tetapi juga untuk CVD dan inflamasi.

Kata kunci: *HbA1c, petanda biologis, aspek molekuler, DM,CVD, inflamasi*

ABSTRACT

Glycated Hemoglobin A1c (HbA1c) has been widely recognized as a biomarker predictor for the severity of Diabetes Mellitus (DM). Glycated Hemoglobin (HbA1c) is a pivotal biomarker reflecting both fasting and postprandial plasma glucose concentration over the preceding 120 days. It has been regarded as an important tool in diabetes diagnosis and management. Elevated HbA1c levels probably mean longterm insulin resistance and severe consequences such as hyperglycemia, dyslipidemia, hypercoagulability, and inflammatory response. There is a positive relationship between elevated HbA1c and poor outcome not only in DM, but also Cardiovascular Disease (CVD) and inflammation. It is said that HbA1c is a biomarker predictor in several ways as molecular aspects through hyperglycemic environtment increasing apoptosis of polymorphonuclear leukocytes and production of inflammatory cytokines.

Key words: HbA1c, biomarker, molecular aspect, DM, CVD, inflammation

INTRODUCTION

Glycated Hemoglobin (HbA1c) was discovered in the late 1960s, as a biomarker of glycemic control it has gradually increased over the last four decades.[1] Glycated hemoglobin is used for monitoring of glucose control in diabetic patients and was proposed used in routine clinical laboratories around 1977.[2] Glycated haemoglobin (HbA1c) identifies the average of plasma glucose concentration and commonly used in the relation to diabetes.[3] HbA1c is formed when haemoglobin joined with glucose in the blood, this explains why HbA1c is differs from blood glucose levels for diagnosing diabetes.[4] Traditionally, HbA1c has been thought to represent average blood sugar levels for over a period of time. It is limited to an average lifespan of a red blood cell over the entire 120- days.[5] RBCs do not undergo lysis at the same time, so HbA1C is taken as a

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limited measure of 3 months.[6] The higher the HbA1c level in patients, the greater the risk of developing diabetes-related complications.[7] Measuring HbA1c can detect and predict the average level of glucose and the severity of CVD and inflammation.[8]

DISCUSSION

HbA1c and DM

Glycated hemoglobin is a long term control of glycaemia.[9] HbA1c and glucose are complementary information and both are used to assess and individual's glycemic status.[10] Red blood cells in the human body survive for 120 days before renewal and HbA1c will reflect the average blood glucose levels over that duration.[11] A prospective multinational study documented a linear relationship between HbA1c and mean blood glucose.[12] HbA1c target for people with diabetes to aim for 48 mmol/mol (6.5%) (see Table 1).[13]

Table 1. Diagnosis DM with prediabetes, normal and diabetes using HbA1c[13]

HbA1c	%	mmol/mol
Normal	Below 6.0%	Below 42 mmol/mol
Prediabetes	6.0% to 6.4%	42 to 47 mmol/mol
Diabetes	6.5% or over	48 mmol/mol or over

Glycated hemoglobin (HbA1c) is a long-term glycaemic control, lowering of HbA1c, by improving HbA1c by 1% (or 11 mmol/mol) for people with type 1 diabetes or type 2 diabetes, cuts the risk of microvascular complications Retinopathy; Neuropathy; Diabetic nephropathy by 25% and lowering the risk of macrovascular complication.[14] Research has also shown that people with type 2 diabetes who reduce their HbA1c level by 1% are: 19% less likely to suffer cataracts, 16% less likely to suffer heart failure, 43% less likely to suffer amputation or death due to peripheral vascular disease.[15] HbA1c is commonly used as a gold standard index of glycemic control in the clinical setting, it is recommended to bring HbA1c lower than 7.0% is order to prevent the development and progression of chronic diabetic complications.[16] HbA1c examination has been received to assess the results of the treatment and be able to assess disease control DM so as to prevent microvascular and macrovascular diabetes complications.[17] Higher amounts of glycated hemoglobin, indicate poorer control of blood glucose levels and have been associated with cardiovascular disease, nephropathy, neuropathy, retinopathy and inflammation.[18]

HbA1C and CVD

Diabetes is associated with increased in risk of cardiovascular disease. Several studies have demonstrated a positive relationship between elevated HbA1c and outcome in the Acute Coronary Syndrome (ACS), Acute Myocardial Infarction (AMI), heart failure, pancreatitis and even patients after coronary artery bypass surgery and Drug-Eluting Stent (DES) implantation with and without primary DM.[19]

Although consistent evidence have supported that optimal control of HbA1c at a target value, can confer to a lower incidence of microvascular complications, and the associations of high levels of HbA1c with macrovascular complications such as stable coronary disease remains controversial.[20] Previous studies have demonstrated a positive correlation of high HbA1c levels with severity of Coronary Artery Disease (CAD).[21] Others associated glycated hemoglobin as an intermediate glycaemic marker, a potent atherogenic protein and the risk of cardiovascular disease.[22] Intensive glycemic control has been shown to reduce the development of CVD as well as diabetic microangiopathy during long-term follow up in patients with both type1 and type 2 diabetes.[23]

Recent clinical trials aimed at reducing HbA1c levels in patients with DM type 2 have failed to show an additional benefit on CVD outcome.[24] Reducing HbA1c below the normal 6% would reduce the rate of cardiovascular events in Type 2 Diabetes.[25] HbA1c is used as a reliable tool for not only diagnosing DM but also identifying individuals at high risk of cardiovascular events with and without DM.[26] Cavalot *et al.*[27], indicate that CVD was associated with increased age, longer diabetes duration, higher HbA1c and fibrinogen in men.[27]

Hong *et al.* clearly suggest that high level of plasma HbA1c (>6.3%) is an independent predictor for presence and severity of CAD as well as the early outcome of patients with stable angina.[28] Another trial by ACCORD determined that reducing HbA_{1c} below 6.0% would reduce the rate of cardiovascular events.[29] Persistent elevations in blood sugar and HbA1c increase the risk of long-term vascular complications of diabetes such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy, gangrene and poor wound healing.[30]

Impaired lipid metabolism results from uncontrolled hyperglycemia has been implicated in cardiovascular complications, HbA1c is an useful biomarker for

identifying lipid profile, glycaemic control and risk of cardiovascular complication.[31]

HbA1c AND INFLAMMATION

Inflammation has been suggested to play a central role in developing atherosclerosis. Diabetes is known as a risk factor for atherosclerosis, also associated with increased level of sensitive markers of subclinical systemic inflammation.[32]

Wu *et al.*[33], shows elevated C-Reactive Protein (CRP) were associated with higher level of circulating HbA1c. Higher level of HbA1c was related to elevated inflammatory markers such as C-reactive protein (CRP), fibrinogen and white blood cell count, which were routinely available and well established predictors of future mortality. Therefore, it might provide meaningfully predictive value than either alone used.[33]

Hyperlipidemia was considered to be present in patients with fasting total cholesterol (TC) ≥200 mg/dL or triglyceride (TG) ≥150 mg/dL. The underlying hypothesis of the current results might consist that the high levels of HbA1c were not only associated with long-term disorder of glycolipid metabolism but also connected with low-grade systematic inflammation and atherosclerotic plaques progress.[34]

Association between HbA1c and fibrinogen level were also found in patients with non-insulin dependent diabetes and between HbA1c and white blood cell count.[35] Diabetic patients have increased level of markers of inflammation and have a relationship between this inflammation markers and HbA1c. HbA1c within the normal range indicate an early association between degree of glycemia, inflammation and atherosclerosis.[36] Some studies have demonstrated that when the glycated hemoglobin (HbA1c) is <8.0%, the proliferative function of CD4 T lymphocytes and their response to antigen is not impaired.[37]

HbA1c IN MOLECULAR ASPECT

Glycation of immunoglobulin occurs in patients with diabetes in proportion with the increase in HbA1c and this may harm the biological function of the antibodies. However, the clinical relevance of these observations are not clear, since the response of antibodies after vaccination and to common infections are adequate in patients with DM.[38]

Some studies have detected a deficiency of the C4 component in DM, reduction of C4 is probably associated with polymorphonuclear dysfunction and reduced cytokine responses.[39] Mononuclear cells and monocytes of diabetic people secrete less interleukin-1 (IL-1) and IL-6 in response to stimulation by lipopopysaccharides.[40] Others studies reported that the increase of glycation could inhibit the production of IL-10 by myeloid cells, as well as that of interferon gamma (IFN-γ) and Tumor Necrosis Factor (TNF-α) by T cells. Glycation would also reduce the expression of class I Major Histocompatibility Complex (MHC) on the surface of myeloid cells, impairing cell immunity.[41]

Hyperglycemia also decreased mobilization of polymorphonuclear leukocytes, chemotaxix, and phagocytic activity, block the antimicrobial function by inhibiting glucose-6-phosphate dehydrogenase (G6PD), increasing apoptosis of polymorphonuclear leukocytes and reducing polymorphonuclear leukocyte transmigration through the endothelium.[42]

INTERPRETATION OF RESULTS

Glycated hemoglobin (HbA1c) is formed by a nonenzymatic reaction occuring between glucose and the N-end of the beta chain. This forms a Schiff base which is converted to 1-deoxyfructose. This rearrangement is an example of an Amadori rearrangement.[43] When blood glucose levels are high, glucose molecules attach to the hemoglobin in red blood cells, the longer hyperglycemia occur in blood, the more glucose binds to hemoglobin in the red blood cells and the higher the glycated hemoglobin.[44]

Glycated hemoglobin within the red cell, 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 plasma glucose regulation.[45]

Laboratory results may differ depending on the analytical technique, the age of the subject, and biological variation among individuals. Two individuals with the same average blood sugar can have HbA1c values that differ by as much as 3 percentage points.[46]

Results can be unreliable in many circumstances as for example after blood loss, after surgery, blood transfusions, anemia, high erythrocyte turnover, chronic renal or liver disease, after administration of high-dose vitamin C, and erythropoetin treatment.[47]

A review of the UKPDS, Action to Control Cardiovascular Risk in Diabetes (ACCORD), ADVANCE and Veterans Affairs Diabetes Trials (VADT) estimated that the risks of the main complications of diabetes (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy and macrovascular disease) decreased by approximately 3% for every 1 mmol/mol decrease in HbA1c.[48]

REFERENCE RANGE

In healthy young people is about 30–33 mmol/mol (4.9–5.2 DCCT%).[49] Higher levels of HbA_{1c} are found in people with persistently elevated blood sugar, as in DMhttps://en.wikipedia.org/wiki/Diabetes_mellitus. While diabetic patient treatment goals vary, many include a target range of HbA1c values. A diabetic person with good glucose control has a HbA1c level that is close to or within the reference range.[50] The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the HbA1c ≥48 mmol/mol (≥6.5 DCCT%) as another criteria for the diagnosis of diabetes.[51] The International Diabetes Federation and the American College of Endocrinology recommend HbA1c values below 48 mmol/mol (6.5 DCCT%), while the American Diabetes Association recommends HbA1c below 53 mmol/mol (7.0 DCCT%) for most patients.[52] Lower-than-expected levels of HbA1c can be seen in people with shortened red blood cell lifespan, such as with glucose-6-phosphate dehydrogenase deficiency, sickle-cell disease, or any other condition causing premature red blood cell death.[53] Blood donation will result in rapid replacement of lost RBCs with newly formed red blood cells. Since these new RBCs have only existed for a short period of time, their presence will lead HbA1c to underestimate the actual average levels.[54]

There may also be distortions resulting from blood donation which occurr as long as two months before due to an abnormal synchronization of the age of the RBCs, resulting in an older than normal average blood cell life (resulting in an overestimate of actual average blood glucose levels).[57] Conversely, higher-than-expected levels can be seen in people with a longer red blood cell lifespan, such as with Vitamin B_{12} or folate deficiency.[58]

INDICATIONS

Glycated hemoglobin testing is recommended for both checking the blood sugar control in people who might be pre-diabetic and monitoring blood sugar control in patients with more elevated levels, termed diabetes mellitus.[59] A significant proportion of people who are unaware of their elevated HbA_{1c} level before they have blood lab work. For a single blood sample, it provides far more revealing information on glycemic behavior than a fasting blood sugar value.[60] 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 twice a year in patients with diabetes who are meeting treatment goals (and who have stable glycemic control) and quarterly in patients with diabetes whose therapy has changed or who are not meeting glycemic goals.[61]

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). 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.[62]

Due to glycated hemoglobin measurement is not appropriate where there has been a change in diet or treatment within 6 weeks. The test assumes a normal red blood cell aging process and mix hemoglobin subtype. People with recent blood loss, hemolytic anemia, or genetic differences in the hemoglobin molecule (hemoglobinopathy) such as sickle-cell disease, as well as those who donated blood recently, are not suitable for this test.[63]

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 of 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.[64] In autoimmune hemolytic anemia, concentrations of hemoglobin A1 (HbA1) are undetectable. Administration of prednisolone (PSL) will allow the HbA1 to be detected.[65]

CONCLUSION

Glycated Hemoglobin A1c is now standardized & traceable to IFCC methods HPLC-CE and HPLC-MS. A new unit (mmol/mol) is used as part of this standardization. The standardized test does not however test for iodine levels in the blood. Hypothyroidism or Iodine supplementation are known sources that artificially raise the A1c number. The Committee Report further states that, when HbA_{1c} testing cannot be done, the fasting and glucose tolerance tests be done. Diagnosis of diabetes during

pregnancy continues to require fasting and glucose tolerance measurements for gestational diabetes and not the glycated hemoglobin. That HbA1c in several studies have demonstrated a positive relationship between elevated HbA1c and poor outcome in CVD, DM, inflammation and others. The purpose of writing shows that HbA1c is as a biomarker of predicting DM, CVD and inflamation.

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