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Is HbA_{1c} the only choice? Alternative biomarkers for glycaemic control assessment

ABSTRACT

A rise in concentrations of glycated proteins occurs in diabetic patients; glycated hemoglobin is the most significant parameter, a 'gold standard' for glycaemic control. Other serum proteins also become glycated, i.a albumins and immunoglobulins. In practice, Fructosamine and glycated albumin are used. However, some conditions influence HbA_{1c} concentrations, hence the search for alternative biomarkers for glycaemia monitoring. Glycated albumin (GA) appears to be the most promising, as its assessment enables both faster detection of changes in glycaemia control in cases of poor metabolic discipline and documentation of glyceamic control improvement, after appropriate treatment is implemented. This may be important mostly in patients scheduled for surgical, cardiosurgical or orthopedic procedures, which are sometimes postponed because of inadequate glycaemia control. Monitoring GA in particular groups of patients (i.a during pregnancy, with renal insufficiency or haematologic comorbidities) reflects glycaemic control levels more accurately than HbA_{1c}. (Clin Diabetol 2017; 6, 4: 136–141)

Key words: diabetes, HbA_{1c}, glycated albumin

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Introduction

Despite the enormous medical progress in the past few years, treatment of diabetes still poses a great challenge. Striving for glycaemia normalization is fundamental to preventing and halting the progress of chronic macro- and microvascular complications of diabetes. Self-control remains a crucial element of an effective, multimodal treatment of diabetes; keeping track of blood glucose levels by the patient is its essential component. It is recommended to begin glycaemia monitoring as an element of self-control immediately at diagnosis for better understanding of the disease and preventing both hypoglycaemic and hyperglycaemic incidents, therefore limiting acute and chronic complications of diabetes.

Glycaemia monitoring should be a part of education and an instrument for adjusting treatment to previously set, optimal goals. Self-control ought to facilitate an effective participation in controlling and treating the condition, altering health related behaviors or changing the actual treatment plan in cooperation with a physician. A self-monitoring schedule depends on the type of treatment in use and is individually determined by the leading diabetologist. A rise in concentrations of glycated proteins occurs in diabetic patients, unlike in a diabetes free population; glycated hemoglobin is the most significant parameter used in everyday clinical practice, a 'gold standard' for glycaemic control.

Glycated hemoglobin (HbA_{1c})

Glycated hemoglobin is a measure of hemoglobin glycation in erythrocytes, expressed as a percentage of total hemoglobin concentration. It reflects exposition of erythrocytes to irreversible influence of glucose, with a time and concentration dependent effect. Since, in diabetic patients, glucose levels fluctuate within a wide range daily and on a day-to-day basis,

HbA_{1c} concentration is the best indicator of long term glycaemic control. Glycated hemoglobin is formed in a process of non-enzymatic glycation where glucose molecules bind to N-terminus amin groups of the β chain of hemoglobin. Erythrocyte cell membrane is permeable to glucose; therefore the amount of glycated hemoglobin inside reflects the mean concentration of blood glucose within an average erythrocyte lifespan, which is 2 to 3 months. Glycation is an irreversible process, so hemoglobin bound glucose remains inside the cell until the erythrocyte breaks down. HbA_{1c} blood concentration remains in proportion to erythrocyte lifespan and blood glucose levels. However, 50% of the pool reflects glycaemia levels from up to a month before the test, while the 60–120 day period before the test is represented by 25% of total HbA_{1c} value [1–3]. A sudden rise in glycaemia causes a fast change in HbA_{1c} within the first two months, with a stabilization period occurring later. A benchmark method of measuring glycated hemoglobin is high-performance liquid chromatography approved by the *National Glycohemoglobin Standarization Program* (NGSP) in the US [4, 5]. The result is expressed as a percent of HbA_{1c} in relation to total hemoglobin blood concentration. It is recommended for glycated hemoglobin measuring methods to be certified by NGSP. Despite being used for diagnosis of diabetes in i.a the US, in Poland HbA_{1c} measurements are only performed for glycaemia control monitoring (in accordance with the PTD recommendations) [6].

Nonetheless, HbA_{1c} which has been used in diabetology since 1976 [7] has its limitations due to sex, racial and ethnical differences. Taking into account age and body mass index (BMI) higher HbA_{1c} values were observed in black males (by 0.3%) and females (0.4%) than in Caucasian men and women without diabetes ($p < 0.05$) [8]. Further research comparing HbA_{1c} levels between ethnic and racial groups with type 2 diabetes showed higher values of HbA_{1c} in Afroamericans, Hispanic Americans and Asians/Asian-pacific islanders, than in patients of Caucasian origin [9]. Variables that may influence glycaemia such as age, sex, education, marital status, obesity (BMI and waist circumference), blood pressure, pre and post prandial glycaemia, β cells performance, insulin resistance and haematocrit levels were considered in multiple linear regression and a significantly higher values of HbA_{1c} were shown in Afroamericans, Hispanic Americans, Native Americans and Americans of Asian origin, than in patients of Caucasian origin [10].

Falsely elevated HbA_{1c} values are also observed in patients with vitamin B_{12}, folic acid and iron deficiency anemiae, in chronic kidney disease, hyperbilirubinemia, in patients using acetylsalicylic acid in large doses, opiate users, post splenectomy patients and those with abnormal erythrocyte structure (lower than usual erythrocyte pH, longer erythrocyte lifespan) [11–16]. Conversely, falsely decreased results are obtained from patients treated with iron preparations, vitamin B_{12}, folic acid, erythropoietin, vitamins C and E. Similar effects are reported in conditions with shortened erythrocyte lifespan — i.a massive blood loss, hemolytic anemias — and hemoglobinopathies, splenomegaly, chronic liver diseases, in chronic alcohol drinkers, patients with hypertriglyceridemia, rheumatoid arthritis and retroviral therapy subjects [11–16].

Fetal hemoglobin is the main hemoglobin during intrauterine development, with a 60 to 90% ratio present at birth. Within the first year of life, the HbF ratio decreases to values observed in adults, which is approximately 1%. An increase in HbF may occur in pathologic conditions, such as leukemia, anemia or thalasemia, or in hereditary persistence of fetal hemoglobin [17], with the latter resulting in values reaching up to 30%. This condition is asymptomatic and its presence may influence the results of HbA_{1c} tests. Depending on test modality, elevated HbF may falsely elevate or decrease the result, or have no effect on it at all [18]. Moreover, HbA_{1c} is not a good glycaemia control marker in children with neonatal diabetes because of the presence of fetal hemoglobin [19].

Falsely decreased HbA_{1c} values may occur in patients with diabetes and renal function disorders, which is due to reduced erythrocyte lifespan, using recombinant human erythropoietin or iron preparations treatment. Uremia alone, changes in blood pH or presence of carbamylated hemoglobin as well as the need of transfusion in patients with advanced kidney failure, result in a decrease in HbA_{1c} values, regardless of changes in glycaemia level [20–23].

Glycation of serum proteins

Other serum proteins also become glycated in diabetic patients, such as albumins and immunoglobulins. In practice, fructosamine and glycated albumin are used.

Fructosamine (isoglucosamine)

It is formed in a process of non-enzymatic glycation of carbonyl group of glucose with amino groups of circulating serum proteins, mainly albumins. Due to a shorter half-life of serum proteins compared to the erythrocyte lifespan, fructosamine concentration is a short term marker and enables retrospective assessment of glucose concentrations in 10–14 days or — as some authors claim — 21 days prior to the test

[24]. It provides an alternative when HbA_{1c} results cannot be trusted. It is also useful in monitoring patients with gestational diabetes, as it marks the dynamic of changes in glycaemia and glyceamia control within a short period of time. However, fructosamine is not a perfect marker — it is affected by conditions altering serum proteins concentrations, dysproteinemias. A false decrease in fructosamine may be related to lower protein or/and albumin level as a result of an increased protein loss with urine, e.g. nephrotic syndrome, abnormalities of protein absorption in the digestive tract e.g. malabsorption, or disturbance in protein production e.g. cirrhosis [25]. The test should not be performed, if the serum concentration of albumin is below 30 g/L. Fructosamine is used less frequently due to lower sensitivity, its dependence on blood protein concentrations and metabolism, hydration levels, bilirubin serum level or hemolysis [26].

Research in patients with chronic kidney disease — stage 3 and 4 — has shown a correlation between frutosamine levels and good glycaemia control in diabetic patients; however the estimated mean glucose level based on fructosamine was significantly undervalued [27]. Different research has shown a correlation — in hemodialysis patients — between fructosamine levels adjusted to actual albumin concentrations and glycaemia control similar to this of HbA_{1c} [28].

Glycated albumin (GA)

Glycated albumin is a fraction of total albumin content in blood serum. Albumin is the serum protein most susceptible to glycation. GA is a ketoamine similar to fructosamine and is a product of glucose and albumin bonding in a non-enzymatic oxidation reaction. Due to a short half-life of albumins — approx. 15 days — glycated albumin reflects a short period of glycaemic control (2–3 weeks) [29]. Its concentration is not connected with total albumin values and is nearly 3 times higher than HbA_{1c} percentage. The result is calculated based on the GA/albumin ratio. Glycation reduces the albumin antioxidative properties and its bonding abilities, which can have a negative effect on blood concentrations of medicaments in use [30]. A rise in GA concentration and advanced glycation end products alike affects the change of cell signal transduction pathways, activating inflammatory mediators and contributing to development of late diabetic complications. GA binds to specific endothelial proteins of vessels, inciting late complications progression [30].

Glycated albumin remains unchanged even when erythrocyte abnormalities or hemoglobinopathy. It is particularly useful in assessment of glycaemic control in patients with comorbidities such as anemia, bleeding, kidney failure, pregnancy, cirrhosis, neonatal diabetes. Also, in patients with rapid changes in glycaemia or unstable type 1 diabetes. Glycated albumin shows better correlation with postprandial glycaemia and daily glucose level fluctuations in comparison to HbA_{1c}, reflecting a short period of glycaemic control [31].

Glycated albumin levels are measured by colorimetric, enzymatic, immunologic, chromatographic or electrochemical techniques [32]. The enzymatic method is most commonly used in clinical practice. A Luccica GA-L (Asahi Kasei Pharma) commercial test has only recently been introduced, using a biochemical analyzer [33]. Reference range for glycated albumin is 11.9–15.8%. It was determined by research conducted on diabetes free individuals with a normal oral glucose tolerance test result in American, Japanese and Italian population. No sex related differences were observed, although the results were higher in individuals of black origin [33].

Clinical relevance of GA

A research conducted on patients recently diagnosed with type 2 diabetes, who underwent intensive insulin therapy for 8 weeks, showed an insignificant decrease in HbA_{1c} — from 10.9% to 10.0% — while GA decreased from 35.5% to 25%. This suggests GA being a more adequate indicator of therapy effectiveness in a short period of time. Besides, a rise in GA provides a much faster record of worsening glycaemic control than HbA_{1c} [34].

Some data suggest that GA is an indicator more dependent on postprandial glycaemia than HbA_{1c}, which reflects mean glycaemia values in a specific time period [35]. A GA/HbA_{1c} ratio was also introduced and defined as an indicator of impaired insulin secretion but not insulin resistance. An increase in GA/HbA_{1c} ratio may be the result of an aggravated cell capacity in type 2 diabetic patients. A comparison of GA/HbA_{1c} levels in type 2 diabetes patients treated with insulin and oral hypoglycemic agents has shown higher values in the insulin using group [36]. A significantly higher GA/HbA_{1c} ratio has also been proven in patients with similar HbA_{1c} values, but with greater glycaemia fluctuation [35].

In pregnant women with pre-gestational diabetes, or in those who develop gestational diabetes, intensive glyceaemic control is particularly important. A two phase change in HbA_{1c} has been shown in healthy women during pregnancy; a decrease in HbA_{1c} in the first and third trimester and an increase in the second trimester [36, 37]. The cause of the second trimester increase in HbA_{1c} remains unknown. Perhaps it may be attributed to iron insufficiency, which occurs during pregnancy. Such phenomenon did not occur in case of

GA testing [39]. A rise in HbA_{1c} in the third trimester was also observed in pregnant, diabetic women, with GA concentrations remaining stable. This was tied to an increase in transferrin saturation and decrease in ferritin serum concentrations, which can be explained by progression of iron deficiency. Therefore, HbA_{1c} is not an adequate indicator for glycaemia control monitoring during pregnancy. Glycated albumin appears to be an appropriate one [39].

In patients with chronic liver diseases HbA_{1c} levels may be underestimated, whereas both fructosamine and glycated albumin levels may show a false increase, due to prolonged albumin half-life [40–42]. An indicator was proposed for glycaemia control monitoring in patients with diabetes and concomitant liver disease, described as a mean value of HbA_{1c} and GA [42].

In case of chronic kidney failure HbA_{1c} may be falsely increased — due to presence of carbaminohemoglobin — as well as falsely decreased, as a result of treating nephrogenous anemia with erythropoietin and iron preparations [43]. Much research has shown that GA may be a useful indicator of glycaemia control in hemodialysis patients. In cases of diabetic nephropathy with symptomatic proteinuria, GA values seem to be underestimated due to an increase in albumin metabolism [43, 44].

It has been shown that in comparison to HbA_{1c}, glycated albumin is significantly related to both microvascular complications such as kidney disease and retinopathy, and macrovascular complications such as pulse velocity and all cause mortality [45–47]. Also, when compared to HbA_{1c}, it appears to be a better marker for glycaemic control in patients with nephropathy and no symptomatic proteinuria. To date, there is no large prospective research confirming the influence of better glycaemic control — and therefore, decreased GA values — on mortality and micro/macroangiopathy reduction.

Elevated GA levels were also described as an independent risk factor of contrast induced nephropathy in patients with type 2 diabetes and impaired renal function, who underwent PCI procedures [48].

Medical conditions and illnesses were specified, in which measuring GA should be recommended, based on available data of GA utility for metabolic control of diabetes. These include: unstable glycaemia in type 1 diabetes patients, patients with dominating postprandial glycaemia, patients with hemolytic or iron-related anemia, patients who suffered blood loss, those treated with transfusions or iron preparations and patients with hemoglobinopathies. This also applies to patients with renal failure — especially requiring hemodialysis — cirrhosis and pregnant women with diabetes.

1,5-anhydroglucitol

While discussing glycaemia control markers, one should mention 1-deoxyglucose, a form of glucose known as 1,5-anhydroglucitol (1,5 AG), which naturally comes mostly from alimentation, with just a fraction being produced endogenously. It is easily filtered in the glomerulus and then reabsorbed in the proximal tubule. Blood serum concentration persists at 12–40 μq/mL [49]. 1.5 AG levels decrease after 24 hours of over 180 mg/dL hyperglycaemia, due to an increase in renal excretion. Its values increase with improved metabolic control of diabetes. Based on 1.5 AG levels, an assessment of metabolic control within a week prior to testing is made. Lower anhydrogluictol levels imply more frequent postprandial hyperglycaemic episodes, that exceed the renal threshold. In patients with kidney failure, its concentrations decrease due to worse reabsorption, regardless of glucose excretion. It is ascertained that 1.5 AG may be a useful glycaemia control marker in patients with type 2 diabetes and chronic kidney failure stage 1 to 3. It should not be used in patients with advanced kidney failure, liver diseases, renal glycosuria, malabsorption or in pregnant women. Limited significance and seldom use of the markers stems from, among others, the influence of dietary products on 1.5 AG serum levels [49, 50].

Summary

The markers for glycaemia monitoring alternative to HbA_{1c} presented above have many advantages, but also some meaningful restrictions. Glycated albumin seems to be the most promising one. Implementing glycated albumin measurements to everyday practice would facilitate faster detection of changes in glycaemia control in cases of poor metabolic discipline and documentation of glycaemic control improvement, after appropriate treatment is implemented. This may be of significance mostly in patients scheduled for surgical, cardiosurgical or orthopedic procedures, which are sometimes postponed because of inadequate glycaemia control. Monitoring GA in particular groups of patients (i.a during pregnancy, with renal insufficiency or haematologic comorbidities) reflects glycaemic control levels more accurately than HbA_{1c}. Reports confirming the correlation between GA concentrations and decreased occurrence of microvascular complications of diabetes give rise for further research and appear promising.

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