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Hba1c Level is Not Always a Reliable Parameter of Metabolic Control of Diabetes

In this issue of Clinical Diabetology, Chung K. and Huang N. [1] present an interesting case of 29-year-old female with undetectable glycated hemoglobin (HbA1c). This particular case is related to hemoglobinopathy; however, it may also bring into focus the limitations related to HbA1c assessment in clinical practice in general.

HbA1c was and is widely used for monitoring glycemic control in patients with diabetes, as it reflects average plasma glucose over the previous three months and corelates very well with the risk of diabetes complications [2]. As HbA1c estimation does not require any special preparation (such as fasting) and can be performed at any time of the day, it is widely recognized as a convenient and useful screening tool. HbA1c assessment has been also proposed for diagnosis of diabetes [3] and presently is endorsed by most international and national diabetes societies and WHO [4] also for this purpose. The current cut-off point for diagnosis of diabetes is an HbA1c of 6.5% (48 mmol/mol).

However, it should be mentioned that as glycated hemoglobin is formed by the non-enzymatic glycation of hemoglobin, the level of HbA1c depends on glucose concentration in the extracellular fluid in which the erythrocyte is located and on the time of exposure to hyperglycemia. As HbA1c is catabolized only after erythrocyte's death, its turnover is dependent on the erythrocytes' lifespan. Conditions that prolong the life of erythrocytes (e.g., aplastic anemia, iron deficiency anemia and after splenectomy) may lead to increased (prolonged) exposure of cells to glucose and to falsely high HbA1c results. On the other hand, conditions that shorten erythrocytes' life (hemolytic anemia, hemorrhagic anemia, kidney failure, treatment with erythropoietin, iron preparations or vitamin B12) may result in reduced exposure of cells to glucose and in falsely low HbA1c percentage.

Other hematologic conditions that alter hemoglobin A1c concentrations are hemoglobinopathies, which modify the composition and structure of hemoglobin. The main types of hemoglobinopathies are thalassemias and structural hemoglobin variants (abnormal hemoglobin). It should be noted that structural variants of hemoglobin are usually clinically silent and may be discovered incidentally for example during the HbA1c assessment [5], like in the case of a 29-year-old described by Chung K. and Huang N. [1].

Hemoglobinopathy may influcence HbA1c results for a variety of reasons [6]. It may alter glycation and interfere with the assay, causing results of HbA1c measurements falsely high or falsely low, depending on the variant, the method, and the specific assay used [7]. For example, in the case report published in this issue of Clinical Diabetology [1], with high HbE/HbA2 and HbF ratios, HbA1c was undetectable. Presence of the hemoglobin S variant may be, in contrary, associated with higher HbA1c concentration [4]. Therefore, an attention to hemoglobinopathy as the factor influencing HbA1c measurement is required, and, given the demographic changes in world population, not only in

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regions where the population of Hb variants is highly prevalent [8].

In addition to various hematological conditions, there are many other factors influencing HbA1c results. The first one is biological variability that may influence glycated hemoglobin level. Results of some studies suggest that genetic factor may play a significant role in the determination of HbA1c [9, 10], but clinical factors may also play a role. Chao et al. [11] found that age, weight, gender, fatty liver disease, blood lipids, and uric acid level were related to the increase in HbA1c level. Jansen et al. [12] have shown that age, gender, BMI, mean corpuscular hemoglobin concentration, current smoking and alcohol consumption were independent predictors of HbA1c, together explaining 26.2% of the variance in HbA1c. Diagnostic performance of HbA1c may be also influenced by the obesity class [13], by ethnicity [14] and by many medications (some of them quite commonly used) [15]. Interestingly, it seems that chronic kidney disease does not exert any significant influence on HbA1c level [16].

From the above-mentioned reason, and possibly other reasons, in clinical practice, one may encounter substantial differences between the expected and obtained HbA1c results but also discrepancies between HBa1c and blood glucose levels. Indeed, in spite of the fact that the correlation between HbA1c and average blood glucose (ABG) from 3 months is in most studies very good, the differences and discrepancies on an individual level may be quite substantial. For example, in patients with type 1 diabetes and ABG between 180 and 190 mg/dL, corresponding HbA1c value was between as low as 6% and almost 9% [17].

In patients with type 2 diabetes the discrepancies may be also pronounced. In spite of the fact that ADA guidelines suggest that the ABG value corresponding with HbA1c of 7% should be equal to 154 mg/dL, with the upper limit of the 95% CI of 185 mg/dL [18], the probability that HbA1c level exceeds 7% is higher than 90% only in patients with type 2 diabetes in whom ABG exceeds 200 mg/dL, and achieves 99% only in patients with ABG of 260 mg/dL [19].

In case of incompatibilities, it is often argued that their reason may be that patients do not measure blood glucose sufficiently often or do not record high or low glucose values in their diaries, and therefore the calculations may be biased. Although it may be true in many cases, physicians should be aware of possible limitations of the HbA1c test and in case of doubts and when it may be of clinical importance, they should consider the above-mentioned influencing factors. In some cases, a comparison of HbA1c with the results of other tests used to diagnose (fasting plasma glucose, oral glucose tolerance test) or to control diabetes (blood glucose, fructosamine, glycated albumin or plasma 1,5-anhydroglucitol levels) may be helpful and should be performed. The best emerging tool to check the reliability of HbA1c seems to be a continuous (or flash) glucose monitoring, as the Time-In-Range (TIR) and Time-Above-Range (TAR) values are easy to obtain and, as they are based on numerous glucose estimations, much more reliable that single or even multiple glucometer measurements. It should be noted, however, that only HbA1c has been validated in randomized controlled trials to predict diabetes-related complications [7] and long-term associations of these alternative biomarkers of glycemia with the risk of complications need to be confirmed [20].

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