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Editorial

The Influence of Iron Status in Hba1c Analysis

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Editorial

Glycohemoglobin (HbA1c) is the N-terminal (1-deoxyfructosyl) valineglycation product of hemoglobin Hb A_0.

Hba1c is an Extremely Remarkable Protein

It is produced as a post translational chemical modification (glycation) of a macromolecule (Hemoglobin) in one tissue (blood), and its clinical usefulness is the control of one single disease (Diabetes Mellitus).

Moreover, the HbA1c synthesis is not a common one, it is not a biosynthesis

Red cells lack active metabolism, there are neither contributions of membrane pumps nor enzymes.

The generation of HbA1c proceeds as if was done in an inert environment

There is neither regulating mechanism nor enzymes involved and glycation is governed by the average plasma glucose concentration during the red cell's lifespan.

HbA1c measurement provides the most important medium to long-term marker of time-averaged glycemic status. Its relationship to likely clinical outcome in diabetes mellitus has been convincingly demonstrated for both Type-I and Type-II in major clinical trials [1, 2].

For over two decades, measurement of HbA1c has been widely used as a mean to retrospectively evaluate long-term glycemic control in diabetic patients. The International Expert Committee published a report recommending that Type-2 diabetes be diagnosed when HbA1c ≥6.5% (48mmol/mol) [3], and more recently WHO sanctioned HbA1c for diagnosing Type-2 diabetes [4].

In the clinical setting, HbA1c values are regarded as virtually synonymous with glycemic control despite some ongoing limitations, not only related to methods of measurement. Different factors can influence the HbA1c synthesis so in certain states (physiologic and pathologic) the accuracy of glycemic control of individual patients based on HbA1c must be considered [5].

A normal erythrocyte progresses through several stages in the circulation, including a short period as a reticulocyte, a long periodas a mature RBC, and a terminal, senescent state most probably of short duration; in physiologic status erythropoiesis and eryptosis are well balanced [6].

Because of the long lifespan of erythrocytes, HbA1c levels reflect average plasma glucose concentration over a long-term period of time (2-3 months). However, HbA1clevels are not affected by blood glucose levels alone and every factor affecting the life span of erythrocytes, from erythropoiesis to eryptosis, can potentially affect the value of HbA1c, modifying the relationship with mean plasma glucose.

The different conditions are noted strange in daily practice

Including anemia (hemolytic and iron deficiency), hemoglobinopathies, acute and chronic blood loss, uremia have also been shown to affect HbA1c levels [7]. Hb disorders may invalidate the results of HbA1c, resulting in missed diagnosis, misdiagnosis or mismanagement of the patient. The presence of Hb variants is widely considered a potential source of error in HbA1c analysis, due to analytical, biochemical and biological aspects [8]. The analytical aspect deals with trueness and precision of the assay. The biochemical aspect deals with the question whether the glycation rate of variant Hb and HbA_0 is equal. The biological aspect is the erythrocyte lifespan, lees than normal for common Hb variants [9]. The influence of iron status and red cell survival are not so often considered in this way. HbA1c can be considered as a surrogate marker for red cell survival, sensitive for detection of mild hematologic disorders. Hemolysis becomes evident by the too low

HbA1c values irrespective to average blood glucose, the severity of hemolysis running in parallel with shortened survival. Iron deficiency anemia is the most common anemia around the world [10]. The influence of iron status on red cells dynamics, survival an eryptosis has been long ago recognized [11]. Although many forms of anemia are associated with lowering of HbA1c, iron deficiency has been shown to shift HbA1c upward independent of fasting glucose level. HbA1c levels were higher in patients with iron deficiency anemia and decreased significantly upon treatment with iron [12, 13].

Recently a systematic review on the effect of anemia and RBC abnormalities on HbA1c analysis [14] was published; the conclusion is that HbA1c is likely to be affected by iron deficiency and IDA with a spurious increase in HbA1c values, but the need for more evidence, especially in identifying the types and degrees of anemia, and iron deficiency without anemia was stated.

The recognition of the influence of the iron status of patients on HbA1c levels is crucially important when it is used in diagnosing diabetes and pre-diabetes state [15], and spurious high prevalence of pre-diabetes in iron deficient populations has been reported [16]. This fact supports the notion that iron deficiency contributes to an increased erythrocyte survival and a falsely elevated HbA1c in subjects with similar degrees of glycemia.

The exact mechanism through which iron deficiency anemia affects HbA1c levels still remains unclear, but new methodological approaches have explained previous concepts. According to Higgins and Mahadevan [17], the bone marrow production of fewer reticulocytes in IDA is counterbalanced by delayed clearance of old red cells by reticulo-endothelial cells; this delay allows body to maintain an stable total RBC population, an appearance of normality, although a negative iron balance is appearing.

Form this point of view, higher HbA1c in subjects with iron deficiency could be a consequence of the relative longer survival of the previously form erythrocytes, and the increased average age of circulating red cells leads to elevated HbA1c levels.

Diabetic patients are treated to keep their HbA1c levels below 7.0% (53mmol/mol) as it correlates with random plasma glucose levels of 7.0mmol/L. This goal is often not achieved and thus treatment regimen is often changed [18]. It is therefore important to consider iron deficiency when HbA1c levels do not correlate with clinical expectations and HbA1c concentrations in diabetic patients with iron deficiency anemia should be interpreted with caution and the possibility of a fictitious increment associated with iron deficiency.

This would suggest that primarily people with anemia who are close to the diagnostic threshold may require retesting or the use of another diagnostic method. Therefore, consideration should be given to performing glucose testing in patients, who have low Hb concentrations and an HbA1c concentration just below the diagnostic threshold for diagnostic purposes [19].

The use of HbA1c to diagnose pre-diabetes and diabetes in iron-deficient populations may lead to a spuriously exaggerated prevalence. These considerations must be taken into account when using HbA1c as a screening tool in nutritionally compromised populations.

References

1. The Diabetes Control and Complications Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329: 977-986.

2. UK Prospective Diabetes Study (UKPDS) Group, Intensive blood glucose control with sulphonylure as or insulin compared with conventional treatment and risk of complications in patients with Type-2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.

3. The International Expert Comitee, International Expert Commitee Report on the role of the A1c assay in the diagnosis of diabetes. Diabetes Care. 2009; 32: 1327-1334.

4. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. Geneva: WHO. 2011.

5. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of Hemoglobin A1c in the management of diabetes. J Diabetes 2009; 1: 9-17.

6. Cohen RM, Franco RS, Khera PK, Smith EP, Lindsell CJ, Ciraolo PJ, et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood 2008; 112: 4284-4291.

7. Cavagnolli G, Pimentel AL, Correa Freitas PA, Gross JI, Lins Camargo J. Factors affecting A1c in non-diabetic individuals: Review and meta-analysis. Clin Chim Acta. 2015: 445:107-114.

8. Reeve J, Blake L, Griffin D, O'Shea P. Incidental detection of Haemoglobin (Hb) variants during high performance liquid chromatography (HPLC) analysis of HbA1c: Is it time for a standardized approach to reporting? Ir J Med Sci. 2015; 184: 353-355.

9. Rhea JM, PhD, Molinaro R. Pathology Consultation on HbA1c Methods and Interferences. J Clin Pathol. 2014; 141: 5-16.

10. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global a1emia burden from 1990-2010. Blood. 2014; 123: 615-624.

11. Temperley IJ, Sharp AA. The life span of erythrocytes in iron-deficiency anaemia. J Clin Path. 1962; 15: 346-349.

12. El-Agouza I, Abu Shohla A, Sirdah M. The effect of iron deficiency anae¬mia on the levels of haemoglobin subtypes: possible consequences for clinical diagnosis. Clin Lab Haematol. 2002; 24: 285-289.

13. Coban E, Ozdogan M, Timuragaoglu A. Effect of iron deficiency anemia on the levels of hemoglobin A1c in nondiabetic patients. ActaHaematol. 2004; 112: 126-128.

14. English E, Idris I, Smith G, Dhatariya K, Kilpatrick ES, John WG. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c Analysis: A systematic review. Diabetologica. 2015; 58: 1409-1421.

15. Kilpatrick ES. HaemoglobinA1c in the diagnosis and monitoring of diabetes mellitus. J ClinPathol. 2008; 61: 977-982.

16. Hardikar PS, Joshi SM, Bhat DS, Raut DA, Katre PA, Lubree HG, et al. Spuriously high prevalence of prediabetes diagnosed by HbA1c in young indians partly explained by hematological factors and iron deficiency anemia. Diabetes Care 2012; 35:797-802.

17. Higgins JM, Mahadevan L. Physiological and pathological population dynamics of circulating human red blood cells. Proc Natl Acad Sci. USA. 2010; 107: 20587-20592.

18. ADA. Glycemic Targets. Diabetes Care. 2015; 38: S33-S40.

19. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab. 2008; 93: 2447-2453.

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