

Dear Editor,

Thank you and your reviewers very much for giving us a chance to revise our manuscript entitled “**Extraordinary Low Level of HbA1c due to Hemolytic Anemia**” for publication in “*Gazi Medical Journal*”. We also thank the Editorial board and the Reviewers for their crucial contributions.

We have reviewed all the valuable comments made by the Reviewers and revised the manuscript accordingly. You can find the final version of the manuscript in the attached file and please do not hesitate to make any further change according to the requirements of the journal.

Yours sincerely,

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Case Report

Extraordinary Low Level of HbA1c due to Hemolytic Anemia

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Abstract

HbA1c measurement gives us information about glycemic levels in patients with diabetes mellitus for the last 3 months. Some factors such as drugs, anemia (hemolytic anemia, hemoglobinopathies etc.), alcoholism, renal failure may affect HbA1c levels via decreasing erythrocyte survival. Herein, we report a very rare clinical presentation of a case of geriatric male patient with extraordinary low level of HbA1c (2.7%) being caused by immune hemolytic anemia associated with chronic lymphocytic leukemia.

Key words: Low level of HbA1c, hemolytic anemia, chronic lymphocytic leukemia

Introduction

Glycosylated hemoglobin consist with progressive, irreversible and non-enzymatic glycosylation of the HbA α - β chain (1). Thus glycosylation reaction occurs during the life span of erythrocytes depending on the blood glucose concentration and erythrocyte glucose exposure time. HbA1c (Glycohemoglobin) measurement gives us information about the last 3 months of glycemic levels in relation to erythrocyte survival (120 days).

Some factors such as drugs, anemia (hemolytic anemia, blood loss, sickle cell anemia, hemoglobinopathies, etc.), alcoholism, and chronic renal disease may affect HbA1c levels via decreasing erythrocyte survival (2-4).

Herein, we report a case of 80 year-old male with extraordinary low level of HbA1c causing by immune hemolytic anemia associated with chronic lymphocytic leukemia (CLL).

Case Report

An 80 year-old male patient admitted to our geriatric outpatient clinic due to worsening general weakness and fatigue in the last three months. The medical history of the patient consists of benign prostate hyperplasia, atrial fibrillation, essential tremor, and early stage CLL without treatment since 2 years. There was no history of alcoholism, renal failure, grossly blood loss anywhere. The physical examination at the admission was normal except pale conjunctiva. Patient was afebrile, normotensive, and with no signs of organomegaly.

Laboratory tests revealed that red blood cell count was $2.234 \times 10^{12}/L$ (normal range: $4-5.2 \times 10^{12}/L$), hemoglobin 8.38 g/dL (normal range: 14-18 g/dL), white blood cell $29.63 \times 10^3/\mu L$ (normal range: $4.5 - 11 \times 10^3/\mu L$), lymphocyte $20.82 \times 10^3/\mu L$ (normal range: $0.9 - 5.2 \times 10^3/\mu L$), erythrocyte sedimentation rate 77 mm/hr (normal range: 0-15 mm/hr), folic acid 3.09 ng/mL (normal range: 4.6-34.8 ng/mL), total bilirubin 2.84 mg/dL (normal range: 0.2-1.1 mg/dL), direct bilirubin 0.62 mg/dL (normal range: 0-0.5 mg/dL), aspartate aminotransferase 58 U/L (normal range: 0-40 U/L), fasting blood glucose 105 mg/dl (FBG) (normal range: 70-100 mg/dl). Renal function tests were in normal range.

Because he had impaired fasting glucose and diabetic symptoms such as xerostomia, polyuria, polydipsia and pollakiuria, FBG was repeated and found 93 mg/dL (normal range: 70-100 mg/dl), and HbA1c was performed and found 2.7% (normal range: 3.9-6%). He did not suffer from symptoms due to hypoglycemia or have any documented hypoglycemia attack before. Anisocytosis, polychromasia and 65% atypical lymphocyte predominance were seen in peripheral blood smear.

According to these findings, hemolytic anemia was suspected and to diagnose it hemolytic parameters were evaluated. Lactate dehydrogenase was 567 IU/L (normal range: 0-248 IU/L), reticulocytes count $178.23 \times 10^9/L$ (normal range: $22-139 \times 10^9/L$), percentage of reticulocyte 7.5% (normal range: 0.5-2.5%), haptoglobin <29 mg/dL (normal range: 30-200 mg/dL), and direct coombs Ig G was quite positive.

In light of these findings, diagnosis of immune hemolytic anemia due to CLL was done and the patient referred to the hematology department. After that, an oral corticosteroid (0.8 mg/kg/day methyl prednisolone) therapy was initiated.

Discussion

HbA1c measurement is commonly used in the diagnosis and follow-up of patients with diabetes mellitus. Available data indicates that hemoglobin glycosylation occur slowly and continues throughout the 120-day life span of erythrocytes (5). Independently of the measurement method, HbA1c level may decrease in cases with shortened life span of erythrocytes. Causes of rapid turnover of red cell such as hemolysis or anemia treated with iron, vitamin B12 and folate deficiency, and patients treated with erythropoietin lead to falsely low HbA1c values cause of greater rate of young red cells (6). Also, the presence of hemoglobin variants may cause interference in HbA1c results (2).

To the best of our knowledge, the lowest levels of HbA1c ever reported in Medline are 1.4% and 2.27% (7; 8) due to immune hemolytic anemia. In our case, the patient had complaint of some anemic and diabetic symptoms. We knew that the patient had CLL history. But, for the rule out of diabetes mellitus, FBG and HbA1c levels were measured. The level of HbA1c was extraordinary low with 2.7%. Also, he had anemia and increased level of indirect bilirubin. We thought he had hemolytic anemia according to these findings and we found demonstrative findings showing immune hemolytic anemia in his laboratory tests as increased level of reticulocyte, quite positivity of direct coombs, and decreased level of haptoglobin.

Conclusion

The clinician should be aware of the meaning of low level of HbA1c in patients with diabetes mellitus or suspected for diabetes to detect the common problems such as hemolysis.

Conflict of interest

There was no conflict of interest declared by the authors

References

1. Mcdonald MJ, Shapiro R, Bleichman M, Solway J, Bunn HF. Glycosylated minor components of human adult hemoglobin. Purification, identification, and partial structural analysis. *J Biol Chem* 1978; 253: 2327-32.
2. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. *Clin Chem* 2001; 47: 153-63.
3. Unnikrishnan R, Anjana RM, Jayashri R, Mohan V. Unexpectedly low HbA1c levels in two diabetes patients following dapsone use. *Indian J Endocrinol Metab* 2012; 16: 658-9.
4. Albright ES, Ovalle F, Bell DS. Artificially low hemoglobin A1c caused by use of dapsone. *Endocr Pract* 2002; 8: 370-2.
5. Fluckiger R, Woodtli T, Berger W. Quantitation of glycosylated hemoglobin by boronate affinity chromatography. *Diabetes* 1984; 33: 73-6.
6. Panzer S, Kronik G, Lechner K, Bettelheim P, Neumann E, Dudczak R. Glycosylated hemoglobins (GHb): an index of red cell survival. *Blood* 1982; 59: 1348-50.
7. Levitan EB, Liu S, Stampfer MJ, Cook NR, Rexrode KM, Ridker PM, Buring JE, Manson JE. HbA1c measured in stored erythrocytes and mortality rate among middle-aged and older women. *Diabetologia* 2008; 51: 267-75.
8. Wiener K. A falling HbA1c is not necessarily an indicator of improving diabetes control. *Ann Clin Biochem* 2001; 38: 406-7.