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CORRESPONDENCE

Causes of decreased HbA1c levels in a medical center laboratory in Taiwan

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Dear Editor,

We read with great interest the case report by Lai et al[1] in the February 2012 issue of the *Journal of the Formosan Medical Association*. The authors describe the clinical significance of "Falsely decreased HbA1c in a type 2 diabetic patient treated with dapsone". In order to investigate the prevalence of falsely low HbA1c in routine HbA1c measurement in a hospital laboratory, we reviewed the electronic records of HbA1c measurement during a 7-day period in March 2013.

In our laboratory we use boronate affinity chromatography to measure total glycated hemoglobin (GHb) with the Primus CLC 385 instrument (Primus® diagnostics Trinity Biotech Company, Berkeley Heights, NJ 07922, U.S.), and HbA1c value (reference range, 3.8–6.0%) is converted from total GHb (by equation: HbA1c = 0.56 × GHb + 2.1). We retrieved 3264 HbA1c results from our laboratory information system in a 7-day period. Six patients had low HbA1c (4.5–4.9%) levels. We then investigated their clinical information through the electronic medical record system of our hospital to get the possible reasons for their low HbA1c levels (Table 1). We found three patients with diabetes mellitus, chronic kidney disease (CKD) stage 3–4 and anemia, one patient with end-stage renal disease under regular hemodialysis and anemia, one individual with human immunodeficiency virus and lymphoma, and one individual with no underlying disease.

HbA1c is useful in monitoring the glycemic control in diabetics without CKD. HbA1c level is intimately correlated with mean plasma glucose level and with microangiopathic complications of diabetes mellitus.[2] HbA1c is formed by glycation (nonenzymatic glycosylation); glucose covalently binds hemoglobin molecules in red blood cells (RBCs) in circulating blood during its life span which is about 120 days in a normal situation. HbA1c level depends on mean plasma level of glucose, its rate-limiting step of glycation. In addition, HbA1c level also depends on the life span of RBCs; old RBCs carry more HbA1c than young ones. Several pathologic conditions, such as hemolysis, dialysis, or severe CKD (Stage 4 or 5; estimated glomerular filtration rate <30 mL/min/1.73 m^2) shorten RBC life span, and destroy more old RBCs than young, leading to falsely low HbA1c levels.[3] Therefore the correlation between levels of HbA1c and mean plasma glucose is different in diabetics with severe CKD from without.[3] Enhanced erythropoiesis, such as under medication of erythropoietin (EPO) or iron supplement, can produce more young RBCs, which also falsely lowers HbA1c levels.

Medications, such as dapsone, can induce hemolysis, which shortens the life span of RBCs and results in a falsely low level of HbA1c. In our observation, four of six patients with low HbA1c had CKD, anemia, and one under regular hemodialysis. The cause of low HbA1c levels is probably a shortened RBC life span in CKD with or without hemodialysis. One patient was under EPO therapy, which stimulates erythropoiesis, produces more young RBCs, and then decreases HbA1c level further.

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Table 1 Clinical information of the six patients with low HbA1c levels.

No.	Age (y)	Gender	HbA1c (%)	Glucose (mg/dL) AC/PC	Clinical information	Possible reason for low HbA1c
1	37	Male	4.7	86	HIV infection Lymphoma Hb: 14.4 g/dL	Within normal limits
2	63	Male	4.9	88	DM EPO usage, Hb: 10.1 g/dL ESRD, eGFR: 9.6 mL/min/1.73 m^2	CKD EPO usage
3	83	Female	4.9	71/203	DM CKD stage 3, eGFR: 41.6 mL/min/1.73 m^2 Anemia, Hb: 8.6 g/dL	CKD
4	96	Male	4.5	139	DM CKD stage 4, eGFR: 25.6 mL/min/1.73 m^2 Anemia, Hb: 9.9 g/dL	CKD
5	37	Female	4.8	107	ESRD/HD, eGFR: 6.1 mL/min/1.73 m^2 Anemia, Hb: 7.6 g/dL	CKD, dialysis
6	46	Male	4.9	85/85	Routine health examination	Within normal limits

AC/PC = *antecibum* (fasting)/*postcibum* (2 hours after meal); CKD = chronic kidney disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; EPO = erythropoietin; ESRD = end-stage renal disease; HD = hemodialysis; HIV = human immunodeficiency virus.

Carbamylated hemoglobin, which results from urea reacting with the hemoglobin molecule on the same site as does glucose, may be an analytic issue for HbA1c measurement by ion-exchange high-pressure liquid chromatography method in patients with uremia. HbA1c values measured by this method are falsely high in uremic patients because the isoelectric point of carbamylated hemoglobin is similar to that of HbA1c.[4] In our laboratory, we perform HbA1c by a different method, affinity chromatography, which has less interference from carbamylated hemoglobin.[4]

In summary, the interpretation of HbA1c should be cautious on conditions altering RBC life span, such as hemolysis, CKD, or EPO usage, which falsely decreases HbA1c levels. Tests that are not altered by RBC life span, such as fructosamine, glycated albumin, continuous glucose monitoring, or self-monitoring blood glucose tests, may be suitable in these patients for glycemic control.

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