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Research Article

Newly Onset Diabetes With Normal Glycohemoglobin? An Interesting Case Report And Review of Literature In A Cirrhotic Patient

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ABSTRACT

Introduction: Diabetes is a major global health issue, affecting more than half a billion people worldwide with a current global prevalence rate of 10.51 Underscoring the importance of early diagnosis and monitoring to prevent acute complications and reduce the risk of long-term complications.

Case presentation: A 57-year-old female with a history of decompensated cirrhosis secondary to Metabolic dysfunction-associated steatotic liver disease (MASLD) and Heart Failure with Reduced Ejection Fraction (HFrEF) presented with worsening symptoms and sugar levels since her last hospital discharge for hepatic encephalopathy.

The patient was treated accordingly for her new onset diabetes diagnosed as shown by her consistently elevated postprandial blood sugars despite a normal HbA1c at 5.2%. Hence, alternative markers like fructosamine, was used to make the diagnosis, which was elevated.

The patient was subsequently discharged on medications and continuous glucose monitor was arranged at outpatient two weeks later.

Discussion: HbA1c, approved for diagnosing and monitoring diabetes mellitus, has limitations in accuracy, in conditions like cirrhosis and chronic kidney disease (CKD). Alternatives like fructosamine and glycated albumin offer shorter-term glucose control insights and are less affected by these conditions.

Conclusion: Emerging evidence suggests that additional biomarkers like fructosamine and GA are gaining importance as surrogate for HbA1c, particularly in patien with anemia, hemorrhage, pregnancy and cirrhosis.

Keywords: HbA1c; Fructosamine; Cirrhosis; Glycemic marker; Diabetes mellitus; Liver failure

Introduction

Diabetes is a major global health issue, affecting more than half a billion people worldwide with a current global prevalence rate of 10.5%[1]. This number is expected to more than double to 1.3 billion people in the next 30 years, with every country seeing an increase and making diabetes one of the top 10 leading

causes of death and disability[2]. Due to its high prevalence and associated complications, such as retinopathy, nephropathy, neuropathy and cardiovascular disease, diabetes represents a serious and growing global health burden.

The latest American Diabetes Association (ADA) Standards of Medical Care in Diabetes stress the importance of early diagnosis and monitoring to prevent acute complications and reduce the risk of long-term complications. Diagnostic criteria for diabetes include glycohemoglobin (HbA1c) ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an OGTT or random plasma glucose ≥200 mg/dL. Prediabetes is indicated by HbA1c between 5.7-6.4%, fasting plasma glucose between 100-126 mg/dL or 2-hour plasma glucose between 140-199 mg/dL during OGTT.

We present a noteworthy case of a 57-year-old female who presented with new onset diabetes as indicated by random glucose levels more than 400 mg/dl yet exhibited normal HbA1c levels upon initial and subsequent testing. Given the discrepancy between clinical presentation and HbA1c values, further work-up was pursued. Fructosamine, an alternative marker for assessing glycemic control, was utilized for both diagnosis and management of her glucose levels in this unique clinical scenario.

Case Presentation

A 57-year-old female with a past medical history of decompensated cirrhosis secondary to Metabolic dysfunction- associated steatotic liver disease (MASLD), heart failure with reduced ejection fraction (HFrEF) presented to PCP office with increasing fatigue, thirst and urination since several days. Testing revealed blood glucose of 454 mg/dl four hours post meal, sodium 123 (normal range: 136-144 mmol/L) and potassium 5.4(normal range:3.3-5.0 mmol/dL) that prompted referral to ED and hospitalization. She reported weight gain in the past year of about 50lbs with a current BMI of 40. She denied any fever, chills, other urinary symptoms, changes in bowel habits, vision changes, confusion, chest pain, abdominal pain, nausea, vomiting and paresthesias. The patient reported taking quetiapine 100 mg twice a day as a new medication for a month for insomnia and anxiety and three vaginal yeast infections in past one and half months.

The patient's vitals were stable. Physical examination revealed an ill appearance, no acute distress, scleral icterus, jaundiced skin and spider angiomas on chest. Laboratory results showed elevated blood glucose 377 mg/dL (normal range: 64-128 mg/dL), AG 8 (normal range: 8-14 mmol/L), HCO3 21 mmol/L (normal range: 20-26 mmol/L) , creatinine 0.82 mg/dL (normal range: 0.57- 1.11mg/dL), hemoglobin of 11 g/dL, platelet count of 76 mcL, potassium of 5.4 (normal range: 3.3-5.0 mmol/L), AST 80 U/L(normal range: 16-40 U/L), ALT 49 U/L (normal range: 5-60 U/L), ALP 199 U/L (normal range: 38-126 U/L) and bilirubin 11.7 mg/dL(normal range: 0.2-1.4mg/dL). Urinalysis indicated significant glucose of 500 and trace blood. Abdominal ultrasound was unremarkable for pancreatic pathology.

The patient was treated with intravenous isotonic fluids and subcutaneous insulin for new onset diabetes diagnosed with consistently elevated postprandial blood sugars more than 200 mg/dl. HbA1c came out to be normal at 5.2 with a value of 4.9% a month prior. We confirmed diagnosis of new onset diabetes with alternative marker fructosamine which was elevated to 565 µmol/L (normal range: 205-285 µmol/L), which corresponds to equivalent HbA1c levels of >10%. (3). On further review patient's fasting blood sugars were elevated a month prior as well with range 128-149 mg/dl (diabetic range) with likely falsely low HbA1c at that time as well. 24-hour urine cortisol of 13.3 mg/d (normal range: <45) and creatinine were normal.

The patient was discharged 2 days later on sitagliptin100 mg daily and insulin glargine and continuous glucose monitor was arranged at outpatient visit two weeks later.

Discussion

Hemoglobin is formed in red blood cells (RBCs) which enter the circulation with minimal glucose attached. As RBCs are freely permeable to glucose, when there is transient increase in blood glucose concentration, aldimines (glucose bound to available amino groups, so-called Schiff bases, on internal lysine's and N-terminal valines) are formed through non-enzymatic reaction in RBCs, which are proportional to the serum glucose concentration. This reaction is reversible if the concentration goes back to normal. However, the subsequent formation of ketoimines from aldimines is irreversible and glucose remains permanently attached to the protein over the course of its lifespan. When hemoglobin is glycated, the degree of glycation, specifically, the percentage of hemoglobin with glucose attached (HbA1c), reflects the average glucose exposure integrated over the half-life of hemoglobin in the red blood cell.

Most commercially available assays of HbA1c only measure the stable ketoimine and do not measure the labile (aldimine) fraction. Although the HbA1C reflects mean blood glucose over the entire approximate 120-day lifespan of the red blood cell, it correlates best with mean blood glucose over the previous 8 to 12 weeks. It is relatively unaffected by recent acute fluctuations in glucose levels[3].

HbA1c was approved for diagnosis of diabetes mellitus in 1997 and is currently the most widely used test to estimate average blood sugar and therefore diagnose and monitor diabetes[4]. It is the measurement used in many diabetes outcome trials and is the endpoint required by FDA to assess efficacy of new diabetes drugs. The sensitivities of HbA1c, FPG and HbA1c together with FPG were 0.51, 0.49 and 0.64 while the specificities were 0.96, 0.98 and 0.95 respectively with OGTT as the reference diagnostic test (Duong). Other studies have reported sensitivity of HbA1c as high as 0.85. In situations where HbA1c is inconclusive, other tests that can be used to make the diagnosis of diabetes include Fasting Plasma Glucose (FPG), 2-hour post prandial blood glucose (PPG) oral Glucose tolerance test, Fructosamine and glycated albumin. **(Table 1)** details the features of alternative markers and highlights their advantages and disadvantages.

Table 1: Characteristics of routine and non-standard tests for hyperglycemia.

	Overview	Glycemic period	Advantages	Disadvantages
Routine tests Hyperglycemia				

Fasting Blood glucose	Direct measure of circulating blood glucose level	immediate	1)inexpensive 2)Direct measure	1) Requires fasting[5]
Glycohemoglobin (HbA1c)	Percentage of glycated hemoglobin	2-3 months	Reflects 2-3 months control	1) Falsely high HbA1c values in low red cell turnover such as in vitamin B12 or folate deficiency anemia (2) falsely low HbA1c values in high turnover like in chronic hemolysis and Iron/B12/folate/erythropoietin replacement therapy. (2)
Non-standard tests for hyperglycemia				
	Overview	**Glycemic Period**	**Advantages**	**Disadvantages**
Fructosamine	Total glycation of serum proteins	2-3 weeks	1) inexpensive and easy to measure in the laboratory 2) reliable 3) can be measured in serum or plasma 4)doesn't not require fasting	1) falsely low values with rapid serum protein turnover, as occurs in patients with protein-losing enteropathy such as Crohn's disease, celiac disease, Kaposi's sarcoma or gastrointestinal sarcoidosis or the nephrotic syndrome. 2) falsely elevated when albumin turnover is decreased, which can be seen in hypothyroidism or cirrhosis

It is important to be aware of the limited accuracy of HbA1c in multiple conditions such as red blood cell disorders like anemia, cirrhosis and CKD. For instance, Dr Brook et al. proposed that concentration of HbA1c in one erythrocyte will increase linearly with the cell's age[6] so low red cell turnover leads to falsely high HbA1c values like in vitamin B12 or folate deficiency anemia and high turnover leads to falsely low HbA1c like in chronic hemolysis and iron, B12, folate, erythropoietin replacement therapy[2]. Normal hemoglobin or mild anemia levels associated with higher sensitivity and specificity 0.96 and 0.82 respectively. Whereas the sensitivity and specificity drop to 0.72 and 0.86 respectively, in cases of moderate to severe anemia[3].

In our patient Hb of 11 mg/dl, fails to qualify for anemia and therefore as the cause of lower test sensitivity of HbA1c in our case. Additionally, the absence of any replacement therapy excludes this from being a potential cause behind falsely low HbA1c.

Overall, cirrhosis increases the quantity of glycated end products, accounting for an increased prevalence of diabetes related illnesses in these patients, ranging from mildly impaired glucose tolerance to presence of overt diabetes in 30% patients. Comparable patterns in sensitivity and specificity of HbA1c for diagnosis of diabetes have been noted in cirrhotic patients as well with drop in sensitivity and specificity to 0.77 and 0.90 respectively[7]. As a result, HbA1c is considered neither accurate nor reliable in patients with cirrhosis due to the various kinds of anemia common in liver disease such as anemia secondary to b12 and folate deficiency, due to hemorrhage especially in gastrointestinal tract, defective coagulation factors leading to increased bleeding tendency and hypersplenism due to portal hypertension.

Hence the use of other parameters like fructosamine seems more useful in these patients. One of the studies showed how the levels of HbA1c were low in non-diabetic patient in cirrhotic compared to normal control despite equal levels of glucose intolerance or FPG and only slightly elevated in cirrhotic with diabetes. Conversely, serum fructosamine was concluded to be more reliable alternate as higher levels were documented in non-diabetic cirrhotic and even higher in diabetic cirrhotics[4]. This was also seen in our patient who had a low HbA1c level and a proportionately high fructosamine level accurately reflective of her diabetes.

Additionally, HbA1c is also not considered reliable in patients with advanced CKD due to the linear relationship between average glucose and HbA1c getting weaker with (eGFR) <30 mL/min/1.73 m2. Inaccuracy is mostly due to altered red cell turnover, with contribution from higher bleeding risk and erythropoiesis-stimulating agents (ESAs) leading to rapid red cell turnover and falsely low A1C values[8].

Like HbA1c, Fructosamine and glycated albumin measure average glucose control through the non-enzymatic reaction of glucose with serum proteins. Fructosamine, which reflects glucose control over the past two to three weeks due to albumin's 20-day half-life, is a stable marker of glycemic control, correlating with HbA1c levels. It measures total irreversibly glycated proteins, with albumin being the primary protein involved. A fructosamine level of 255–290 µmol/L closely correlates to a HbA1c level of 6.5%, which is diagnostic for diabetes[9].

Average fructosamine levels were found to be higher than normal in the people with cirrhosis who had either insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) compared to individuals with normal glycemic control[3]. A similar trend was noted in HbA1c levels, which were higher in patients with diabetes than in those with glycemic control. The differences in HbA1c levels among the groups of patients were statistically significant[3].

Fructosamine is considered unreliable if serum albumin level is below 3.0 g/dl. This is seen in illnesses like nephrotic syndrome, cirrhosis and protein losing enteropathies where albumin loss is witnessed. Alternatively, conditions with elevated protein counts, like multiple myeloma, can affect Fructosamine levels as well. There is debate over whether fructosamine should be adjusted for abnormal albumin levels; a practical method involves multiplying the measured fructosamine by the ratio of normal albumin (4g/L) to the measured albumin level in g/L. as without adjustment, hypoalbuminemia can lead to lower fructosamine values even at the same blood glucose levels.

Moreover, glycated albumin, reported as a percentage of glycated to total albumin, offers a clearer picture of glucose control without needing adjustment for albumin levels, although it can be challenging in cases of altered albumin turnover. This value can increase in diabetes and can go up to five times the upper limit. Of the glycemic alternatives, glycated albumin has the strongest correlation with A1C and fasting blood glucose. Estimates state that an A1C of 6.5% corresponds to a glycated albumin of 16.0 to 18.5%[3]. Using glycated proteins alongside or instead of HbA1c offers several benefits as listed in table 1.

Furthermore, 1,5-anhydroglucitol (1,5-AG) is another

non-traditional marker of hyperglycemia which provides information on glycosuria[10]. The kidneys filter and totally reabsorb 1,5-AG during euglycemia, maintaining steady blood levels. However, increased blood glucose competitively slows its reabsorption, which results in a reduction in 1,5-AG levels within 24 hours of high blood glucose, indicating short-term glycemic management[11]. Nevertheless, because of its limited benefits and unpredictable interference from SGLT2 inhibitors and dietary modifications, 1,5-AG is not commonly used in conjunction with HbA1c.

Moreover, some other factors were considered to better understand the late new onset of hyperglycemia in our patient. One such factor could be quetiapine, which has been reported to be associated with hyperglycemia. The retrospective descriptive case series done in Tokyo described the characteristics of patient who developed diabetes after the initiation of quetiapine. Almost all patients who developed quetiapine-associated diabetes had dyslipidemia and increased BMI. Out of 1688 patients, eighteen (1.1%) were considered to have new-onset diabetes associated with quetiapine. (12) All of the patients discontinued quetiapine within 3 months after the diagnosis of diabetes and 4 patients achieved HbA1c of less than 6.4% without hypoglycemic drugs[12].

It is proposed that reduced insulin action and secretion can occur due to antagonistic interactions of central and peripheral muscarinic 3 receptors, histamine, serotonergic and adrenergic receptors. The primary cause of antipsychotic-induced hyperglycemia is histaminergic and serotonergic antagonistic interactions and quetiapine has a significant affinity for both the H1- and 5-HT2C receptors. Since our patient started quetiapine for anxiety a month before she presented with hyperglycemia, there might be some contribution to hyperglycemia from quetiapine.

Our patient's BMI of 40 likely contributed to new onset diabetes as well. It is estimated that obesity accounts for around 90% of type 2 diabetes[5]. Insulin resistance and insulin deficiency are the main causes of the pathophysiology linking obesity and diabetes.

Conclusion

Early detection of diabetes and strict glucose control are vital in preventing or delaying serious, potentially life-threatening complications of the disease. While HbA1c remains the gold standard for diagnosing diabetes and monitoring glycemic levels, emerging evidence suggests that additional biomarkers like fructosamine and GA can be of particular importance as surrogate for HbA1c in certain patient groups where HbA1c measurement may be inaccurate. This includes patients with red blood cell disorders, cirrhosis and CKD. Fructosamine and GA offers advantages over HbA1c, such as lower cost and the availability of commercially accessible reagents for conventional laboratory equipment. Though further research is necessary to determine if these markers could supplement or even replace traditional measures like HbA1c, it's evident that these markers are already enhancing the clinical care of diabetic patients for whom HbA1c readings are unreliable. They are especially helpful as an indicator of glycemic control in hematologic diseases, including anemia, hemorrhage, renal anemia, pregnancy and liver cirrhosis, as they remain unaffected by abnormal RBC lifespan or variant hemoglobin.

Author Contributions

Data collection, literature search, manuscript writing P.K, Manuscript writing, figures I.M and idea development and manuscript editing M.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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