(REVIEW ARTICLE)

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Discordance between fasting plasma glucose and A1c in the diagnosis and management of diabetes

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Abstract

There are pros and cons of using fasting plasma glucose (FPG) and A1c for the diagnosis and management of diabetes. Still, discordance between FPG and A1c is a common problem in clinical practice, and there are no definite international guidelines for dealing with it. This article explains the causes of these anomalies and the factors that affect the results of tests, and it also recommends some appropriate techniques for investigation and management of cases of discordance between FPG and A1c.

Keywords: Fasting plasma glucose (FPG); A1c; Discordance; Diagnosis; Management

1. Introduction

Globally, 1 in 11 adults (20-79 years) have diabetes, and on average, half of all cases are undiagnosed; furthermore, 1 in 13 adults have impaired glucose tolerance [1]. Diabetes is a leading cause of micro- and macrovascular complications that affect both a population's health status and its economy, with diabetes accounting for 10% of global health expenditure [1]. Early diagnosis and appropriate management are essential to reduce complications, mortality, and cost of treatment. Both FPG and A1c are beneficial in diagnosing diabetes [2,3] and in monitoring glycemic control [4], and A1c levels can often indicate chronic complications from diabetes [5,6,7,8,9,10,11,12,13]; however, there are often problems with discordance between FPG and A1c.

2. Measurement of fasting blood glucose (FBG) and A1c

2.1. Fasting blood glucose (FBG)

Most blood glucose tests use enzymatic methods (such as glucose oxidase, hexokinase, and glucose dehydrogenase) because they have more specificity than other techniques [14]. In blood collection, if whole blood is collected with fluoride to inhibit glucose's cellular metabolism, there may be a 10 percent reduction in glucose at room temperature if left for many hours, and there could be an even more rapid decrease in cases of high ambient temperature [15,16,16,17]; therefore, inspectors should centrifuge the serum if it is not immediately tested. Glucose values from whole blood are 10-15 percent lower than those of plasma, while arterial blood glucose is about 7 percent higher than that of venous blood.

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While following each treatment, a single glucose test may be insufficient to assess whether glucose control is reasonable or not, especially in type 1 diabetes, where there are changes in glucose levels at different times of the day. Moreover, single glucose levels do not correlate with long-term diabetes control [18,19].

2.2. A1c

Normal adult hemoglobin consists primarily of hemoglobin A (90-95%), A2 (2-3%), F (0.5%), A1a (1.6%), A1b (0.8%), and A1c (3-6%). HbA1a1, fructose, is bound to N terminal valine, while HbA1a2, glucose-6 phosphate, is bound to N terminal valine, and A1c, glucose, is bound to N terminal valine. A1c is a non-enzymatic glycosylated product of hemoglobin, and its levels reflect the mean glucose concentration in the blood for approximately the preceding three months. A1c levels can be expressed as eAG for most patients with type 1 and type 2 diabetes [20]. Published consensus guidelines have endorsed reporting A1c values along with the calculated eAG level, assuming that the results of the ADAG are acceptable [21].A1c is reliable and accepted in assessing chronic glycemia conditions [22,23,24]. Table 1 shows the history of A1c information.

Table 1 The historical of A1c information [25]

Year	Information
1966	Holmquist and Schroeder identify five subtypes of hemoglobin A, including A1c
1968	Rahbar recognizes that A1c is elevated in people with diabetes. [26]
1975	Koenig and Cerami suggest that A1c is related to metabolic control. [27]
1993	DCCT establishes A1c as a valuable clinical marker in people with type 1 DM. [29]
1998	UKPDS establishesA1c as a valuable clinical marker in people with type 2 DM.
2010	ADA recommends using the A1c test to diagnose diabetes and prediabetes.[28]

Several methods are used for A1c testing, and there are two basic approaches to measuring it. One technique is to separate A1c from other hemoglobin fractions, which includes methods such as chromatography and electrophoresis. The other approach targets A1c as an antigen using methods such as immunochemistry [29,30]. The four methods most used are ion-exchange high-performance liquid chromatography (HPLC), affinity HPLC, immunoassays, and enzymatic assays. High-pressure liquid chromatography (HPLC) is currently considered the best method since it is the most accurate, although immunoassay is rated as equally effective. Electrophoresis is a method of electrical separation, while affinity chromatography is currently less popular due to its non-automatic procedure. Column chromatograph is easily disturbed by measurement results. Colorimetry involves machine measurement of color while spectrophotometers facilitate consistently accurate preparation of medicine; however, examination with this latter is quite complicated and time-consuming, so it is generally not recommended. There are 2 standardA1c detection methods. First, that of the National Glycohemoglobin Standardization Program (NGSP), which was created in 1996 to standardize A1c results with those of the UKPDS and DCCT trials which established the relationship between A1c and vascular complications. When measured in NGSP-certified laboratories, a change in A1c of at least 0.5 % is considered both statistically and clinically significant [31]. The second standard system of measurement is that of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) established by a working group convention in 1995. While NGSP-derived A1c levels are reported as percentages, IFCC results employ the International System of Units (SI) as millimole of A1c per mole of HbA [32].

Individual hospitals should choose the standard method of examination, which is most suitable for their institute. The factors affecting A1c examination [33] are hemoglobinopathies, erythrocyte abnormalities, and acute blood loss, which increases the number of reticulocytes. Iron deficiency may cause the A1C to rise due to increased erythrocyte survival. Table 2 shows the factors that cause false positives and negatives of A1c.

Table 2 Diseases or conditions associated with false elevation and false lowering of A1c levels [34]

False elevated A1c	False lowered A1c	False elevated or lowered A1c
Anemia associated with decreased red cell turnover e.g., iron deficiency [35,36,37], vitamin B-12 folate deficiency, anemia [38,39]	Anemia from acute or chronic blood loss [40] (Includes hemolytic anemia)	Red blood cell transfusion (Typically reported to elevate A1c falsely, but may also result in a false decrease because of the dilution effect)
Asplenia (Increased erythrocyte lifespan)	Splenomegaly (Decreased erythrocyte lifespan)	Hemoglobin variants (depends on method and assay used [41,42,43,44]
Severe hypertriglyceridemia [45], (When level >19.8 mmol/L or >1,750 mg/dL)	Vitamin E ingestion [46]	Vitamin C ingestion (may increase A1c when measured by electrophoresis or decrease levels when measured by chromatography) [47]
Severe hyperbilirubinemia [48] (When level >342 umol/L or >20 mg/dL)	Reduced glycation [49,50]	Uremia (May increase from carbamyl-hemoglobin and decrease from chronic anemia with decreased red cell survival)
Chronic alcohol consumption (Formation of an acetaldehyde-HbA1 compound) [51,52]	Ribavirin and interferon-alpha [50,49]	Pregnancy [53,54,55,56]* *Expect falsely low A1c values through the 2nd trimester, but these may arise during the 3rd trimester
Chronic salicylate ingestion (Mechanism uncertain, may interfere with assay)		
Chronic opioid ingestion [57] (Mechanism uncertain)		
Lead poisoning (Mechanism uncertain)		

2.3. FPG and A1c in the diagnosis of diabetes

Table 3 ADA criteria for normal and abnormal glucose tests

	FPG mmol/L	2 hr 75 g OGTT mmol/L	A1c g/L (%)
Normal	<5.6	<7.8	< 57 (5.7)
Increased risk of DM Impaired FPG IGT	5.6-6.9	7.8-11.0	57-64 (5.7-6.4)
DM	≥7.0	≥11.1	≥ 65 (6.5)

FDA criteria for diagnosis claim approval A1c test systems must comply with the FDA Special Controls (Class II):

- Annual standardization verification by a certifying glucohemoglobin standardization organization deemed acceptable by FDA (e.g., NGSP)
- Performance Data
- Precision (CV <2%)
- Bias vs. standardized method
- Total error less than or equal to 6%
- Little to no interference from common Hb variants including HbAS, HbAC, HbAE, HbAD & HbA2

The coefficients of variation of A1C, FPG, and 2-h PG are 3.6, 5.7, and 16.6%, respectively [58], and the biological variability of A1C is several times lower than that of FPG (1 vs. 4%) [59]. The diagnostic cutoff for A1c or FPG in diabetes should depend on the optimal accuracy of diabetes retinopathy [60]. The A1c and FPG thresholds for diagnosing diabetes in an Iranian population were found to be lower than the current diagnostic criteria, and the use of A1c measurement to diagnose diabetes remains somewhat controversial [61]. According to the Iranian investigation, the prevalence of retinopathy increased when the A1c and FPG cutoff values were 62 g/L (6.2%) and 6.5 mmol/L (117 mg/dL) [62].

A1c has several diagnostic benefits over FPG, such as its independence from fasting, lower day-to-day variation and pre-analytical instability, and reduced biologic variability. The disadvantages of A1c include the possibility of errors caused by factors other than glucose, e.g., ethnicity or change in erythrocyte life span. Some conditions have impacts on the suitability of measurement techniques, e.g., their selected hemoglobinopathies, their lack of availability in some laboratories, and also their cost. Table 4 shows the advantages and disadvantages of FPG and A1c.

Table 4 Advantage and disadvantage of FPG and A1c for the diagnosis of diabetes

	Glucose	A1c
Advantages	-Glucose assay easily automated -Widely available -Inexpensive	-No fasting needed -Minimal biological variability Sample stable -Reflects long-term blood glucose concentration -Assay standardized across instruments, more accurate -Useful in predicting complications -Useful in guiding treatment -May be used in acute illness or stress [63,65]
Disadvantages	-Patients must fast ≥8 hours -Large biological variability -Diurnal variation -Sample not stable -Glucose concentrations altered by numerous factors, e.g., stress, acute illness -No harmonization of glucose testing -The concentration varies with the source of the sample -Reflects glucose homeostasis only at a single point in time	-May be altered by factors other than glucose, e.g., change in erythrocyte life span, ethnicity -Some conditions interfere with the measurement, e.g., selected hemoglobinopathies -May not be available in some laboratories -Cost

The benefits of using FPG in diagnosing diabetes include its simplicity, widespread availability and low cost; however, its limitations include the need for two tests to confirm the diagnosis, its low reproducibility, and the fact that values change depending on food eaten and daily activities. Other factors that adversely affect FPG's effectiveness are prolonged fasting, intercurrent illness, and medication.

OGTT is time-consuming and expensive, and it is influenced by numerous medications. It is also unpalatable, and it requires extensive subject preparation, including ingestion of at least 150 g of dietary carbohydrate per day for three days before the test, a 10- to 16-h fast, and commencement of the test between 7:00 AM and 9:00 AM; furthermore, a high degree of intraindividual variability in OGTT has been reported, with a CV of 16.7%, considerably more than that of FPG [58].

The advantages of using A1c in the diagnosis of diabetes include its lower association with chronic complications, its lack of necessity for fasting, and the fact that it entails no acute perturbations (e.g., stress, diet, exercise); furthermore, it can be cheaper because it can be assessed at any time. The drawbacks of A1c in the diagnosis of diabetes are its reduced sensitivity and the fact that it can change the epidemiology of diabetes; furthermore, standardization of A1C assays is very poor, and the standardization of glucose assays is simpler [64].

Table 5 Prevalence of diabetes mellitus using criteria of FPG, A1c, and OGTT

Native	Prevalence of diabetes mellitus by criteria of		
	FPG (%)	A1c (%)	OGTT (%)
US [65] NHANES 2005–2010 (n=5,395)	4.7	2.8	9.1
Filipino (in San Diego) [66] (n=382)	6.5	12.6	22.0
Filipino (in Hawaii) [66] (n=171)	4.1	8.8	11.7
Japanese (in Hawaii) [66] (n=170)	6.5	4.2	11.8
Native Hawaiian [66] (n=210)	8.6	5.2	10.0

A1c has been found to have low sensitivity and high specificity in identifying diabetes and prediabetes, varying with age and race in the US [65]. It is essential to bear in mind that A1c values below 65 g/L (6.5%) do not reliably exclude the presence of diabetes. Overall, the data argue for greater use of oral glucose tolerance tests (OGTTs) and both FPG and 2-hr glucose values. If the current cutoff of A1c for diabetes were lowered by 20 g/L (65 g/L to 63 g/L or 6.5% to 6.3%) among non-Hispanic whites and Mexican Americans, the prevalence rates of diabetes would be similar to those found using FPG criteria, with optimal sensitivity and specificity as indicated by the J value [65]. In some studies, 2 h PG had the highest sensitivity (97%) for diabetes diagnosis, followed closely by A1c (94%), while FPG had the lowest (84%), similar to the findings of earlier studies [67]. For example, in some races, such as Filipinos and some Asians, A1c has been found to have higher sensitivity than FPG in diabetes diagnosis [66].

2.4. Discordance of FPG and A1c in monitoring and management

Because diabetes mellitus causes acute complications, high glucose conditions such as DKA, HHS, hypoglycemia, and chronic issues such as cardiovascular complications, kidney disease, diabetic retinopathy, neuropathy, and foot ulcers, which require high medical expenses, it is essential to improve care by monitoring both diabetes patients and the hospitals that provide care. The goal of monitoring diabetes treatment is to minimize complications by controlling glucose levels and various other risk factors. Monitoring, assessing, and dealing with complications are essential parts of treating diabetic patients. There are four main steps: evaluation of glycemic control; assessment and treatment of co-morbid risk factors of cardiovascular disease; evaluation and treatment of diabetes complications; and finally, evaluation and empowerment of self-care management.

2.5. Quintet of targets of glycemic control

The quintet of targets of glycemic control is A1c, FPG, PPG, glucose variability, and elimination or minimization of hypoglycemia. The goals of treatment should be shared between the patients and their doctors. A university hospital

outpatients department in Zambia conducted a study of the relationship of A1c test results with previous and current fasting plasma glucose and found a deep and medium relationship, respectively (r = 0.282 and r = 0.385) [68]. In developing countries, such as Cameroon and Guinea, most patients still have poor control of glucose levels, and one of the main reasons for this is the restriction of access to A1c testing [69].

2.6. Discordance of FPG and A1c

Some factors which may cause discordance between FPG and A1c are shown in Table 6.

Table 6 The factors which trigger discordance between FPG and A1c

High A1c and normal FPG interpretation	
1.1 Good glycemic control	
Causes	**Suggestion**
A1c measurement error (false high of A1c) such as -iron, B12, folate deficiency -splenectomy -Hypertriglyceridemia -hyperbilirubinemia	-Record the history of symptoms and signs of hypo- and hyperglycemia -PE: Bodyweight measurement Lab: CBC, check method and standardization of A1c measurement -SMBG
1.2 Poor glycemic control	
Causes	**Suggestion**
-Tight control for only a short period before meeting the doctor -Postprandial hyperglycemia -Glucose high during other times of the day, not fasting, especially with insulin therapy	-Record history of diet, exercise, and medication -check 1-2 postprandial glucose -SMBG
High FPG and normal A1c interpretation	
2.1 Good glycemic control	
Causes	**Suggestion**
Temporarily high FPG -Diet (late-night meal, large dinner, party, etc.) -Medication (lack of adherence to medication, exogenous steroids) -Acute illness (fever, stress) -Glucokinase-maturity-onset diabetes of the young (GCK-MODY) [70]	-Keep a history of diet -Record a history of medication -Note history of acute illness -SMBG -Family history and lab test
2.2 Poor glycemic control	
Causes	**Suggestion**
Errors in A1c measurement (false low A1c) such as abnormal Hb -Hemolytic anemia -Hypersplenism -Drugs (vitamin E, ribavirin, interferon-alpha) -Unstandardized A1c	-Check the history of thalassemia, liver disease, medication -PE: hypersplenism Lab: CBC, check method and standardization of A1c measurement -SMBG

3. The causes and management of discordance between FPG and A1c

3.1. Normal FPG but elevated A1c

3.1.1. Case 1

A 45-year-old woman with type 2 diabetes, with no diabetes complications, taking metformin 2,000 mg/day. FPG 6.7 mmol/L (120 mg / dl), A1c 80 g/L (8.0%)

Question 1 Does this patient have well-controlled blood glucose?

Based on the high A1c value, her glucose is poorly controlled even if the FPG is under control (except in cases of A1c error, such as thalassemia). The cause of poor management may be:

- Poor diet control
- Poor adherence to medical treatment
- Elevated blood glucose after eating (postprandial hyperglycemia)

The relative contribution of postprandial plasma glucose has been found to be high (70%) in patients with relatively reasonable control of diabetes (A1c < 73 g/L or 7.3%) and to decrease progressively (30%) with worsening diabetes (A1c > 102 g/L or 10.2%). The level of post-meal glycemia has been found to be a better predictor of good or satisfactory control of diabetes (A1c < 70 g/L or 7%) than fasting glucose [71].

In Asian patients with type 2 diabetes, PPG 24 and 4 h after meals was a predominant contributor to excess hyperglycemia in well-controlled patients, and they were equally as crucial as FPG or pre-prandial glucose in moderately to poorly controlled patients with mean A1c of up to 10 g/L.

- Elevated glucose between meals, such as before lunch or dinner, especially in patients who inject insulin.
- Error in A1c. The causes of false high A1c such as iron, B12, or folate deficiency, asplenism, hypertriglyceridemia, and hyperbilirubinemia are shown in Table 6.

Question 2 What should be the next step in management?

The doctor should advise the patient to eat a healthy, balanced diet regularly and check postprandial glucose if possible.

More information: post-meal blood glucose was 12.21 mmol/L (220 mg/dl), indicating postprandial hyperglycemia, which contributed to long-term complications.

Question 3 How should postprandial hyperglycemia be treated?

Postprandial hyperglycemia is associated with a two-fold risk of death from heart disease. Epidemiological studies have shown that postprandial glucose is associated with a chance of vascular disease.

3.2. Treatment of postprandial hyperglycemia [72]

3.2.1. Non-pharmacologic intervention

Lifestyle modification by dieting, exercising, and losing weight can help patients with IGT return to normal glucose levels to reduce the risk of developing diabetes.

Consumption of a diet with a low glycemic index [73] and load [73] can reduce postprandial glucose.

3.2.2. Pharmacologic intervention

- Insulin secretagogue affects fasting hyperglycemia. In the case of high fasting plasma glucose and postprandial hyperglycemia, when fasting plasma glucose is reduced, postprandial glucose will also decrease. This drug should not be chosen for patients with postprandial hyperglycemia with average fasting glucose because it will increase hypoglycemia.

- Glinide; Glinides (repaglinide and nateglinide) have a much shorter action (of only a few hours) than sulfonylureas because of their pharmacokinetic properties. When given at mealtimes at the beginning of the meal, postprandial glucose was found to be lowered effectively [74]; however, glinide should not be used in combination with sulfonylurea.
- Metformin reduces glucose production during the fasting state, while Thiazolidinedione improves glucose use, which may not be the main postprandial factor; however, studies have shown that using Metformin and Glyburide reduces glucose levels after meals.
- α-Glucosidase inhibitors reduce digestion and absorption of carbohydrates, lowering glucose levels after meals by 0.5%, but patients may have gastrointestinal side effects [75,76,77,80].
- Amylin analog decreases postprandial blood glucose by glucagon suppression and delays gastric emptying time [78].
- Short-acting insulin [79] and rapid-acting insulin analog or premix insulin [80,81].
- GLP-1 is a hormone secreted by intestinal L cells after eating, which increases the level of glucose-dependent insulin secretion through cyclic adenosine monophosphate-dependent protein kinase stimulation in the pancreas [82,83,84].
- DPP4 inhibitors impede DPP4 enzymes, causing an increase in GLP-1 levels [85].
- SGLT2 inhibitors reduce glucose reabsorption and increase urinary glucose excretion. In animal models and humans with type 2 diabetes, this effect has been found to reduce fasting and postprandial blood glucose levels, as well as A1c[86].

3.3. Target A1c but elevated FPG

3.3.1. Case 2

A 50-year-old woman with type 2 diabetes, with no diabetes complications, taking metformin 2,000 mg/day with glipizide 20 mg/day. FPG 12.21 mmol/L (220 mg /dl), A1c 65 g/L (6.5%)

Question: Does this patient have well-controlled blood glucose?

Based on FPG, this patient's blood glucose appears to be poorly controlled; however, A1c indicates that this patient has appropriately controlled diabetes, and this is one of the errors found in interpreting diabetes control results. Because A1c stays in the bloodstream longer than FPG, itis generally more reliable in the interpretation of glycemic control and should therefore be used in preference to FPG.

When evaluating A1c levels, the average values and the method of the examination must be considered. The ADA criteria for A1c at < 70 g/L (7%) have normal A1c at 40-60 g/L (4-6%), which is different from the standard set by The National Glycohemoglobin Standardization program. We suggest recording diet and exercise history and medical compliance, checking complete blood count to rule out thalassemia, and measuring glucose after meals.

In what cases could A1c be incorrect?

- The patient has SMBG, but results do not correlate with A1c levels.
- A1c does not correspond to the patient's symptoms.
- The patient has very high A1c values, such as values above 15% [87].
- The A1c value has changed a lot, despite no change in treatment.
- A1c and FPG values may not be relevant in the examination. Many patients have discordance between FPG and A1c on certain days.

This patient should be tested using the A1c method to verify that no condition is causing the A1c value to be higher or lower than reality. If A1c is correct, this could be caused by several factors:

- Overeating on the day before check-up, such as eating out or consuming late-night meals.
- Failure to take medicine before the examination.
- Development of hyperglycemia before the tests a result of infection or steroid therapy.
- High and low blood glucose, keeping the average A1c level in the well-controlled range.
- MODY 2: MODY 2 is caused by several mutations in the GCK gene on chromosome 7 for glucokinase present with a chronic, mild increase in blood sugar, usually asymptomatic [70].

Monitoring patient history is advised to see whether there are any of the causes, as mentioned above, which should be corrected.

4. Conclusion

Discordance between FPG and A1c is common in diabetes management. It is essential to have knowledge of testing pros and cons, ensure proper interpretation of results, find the causes for discordance, and manage them appropriately to achieve the targeted glycemic control.

Compliance with ethical standards

Disclosure of conflict of interest

All authors have no conflict of interest.

Statement of informed consent

This is a review article, so we waived the consent form.

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