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PRACTICE

RATIONAL TESTING

Monitoring glycaemic control in patients with diabetes mellitus

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What you need to know

- Be aware of the factors that give rise to a lower, or higher than expected haemoglobin A1c (HbA1c)
- Discordant HbA1c and glucose results may identify underlying pathology such as a haemoglobinopathy, or occur as a result of anaemia or chronic kidney disease; discuss appropriate investigations with a clinical biochemist or diabetologist
- Alternatives to HbA1c for monitoring glycaemia in a patient include glucose profiling using quality assured glucose meters, fructosamine, glycated albumin, or total glycated haemoglobin
- Discuss with the patient ways to monitor treatment for diabetes, so that they are fully empowered to manage their condition

A 73 year old man with obesity and type 2 diabetes mellitus was referred to the diabetes clinic for advice. He had chronic kidney disease stage 3 and chronic anaemia from angiodysplasia of the small intestine. He was on insulin glargine 35 units every night and soluble human insulin 30 units three times daily before main meals. He was referred because of the discrepancy between his high fasting plasma glucose concentrations (16-21 mmol/L) and lower than expected haemoglobin A1c (HbA1c) concentration (49 mmol/mol) (expected with this fasting plasma glucose concentration ~108-140 mmol/mol or 12-15%). Table 1 gives glucose and HbA1c reference intervals. Other selected blood tests were: haemoglobin 106 g/L (reference interval: 125-180), ferritin 315 µg/L (reference interval: 24-250), creatinine 107 µmol/L (reference interval: 59-104), and albumin 32 g/L (reference interval: 35-50).

What is the next investigation?

Monitoring diabetes mellitus

The diagnosis of diabetes mellitus is well described[1-4]; however, the monitoring of diabetes with HbA1c (which is common practice) has introduced some uncertainty. Glycaemic control is integral to effective treatment of diabetes.[1 2] HbA1c concentration is used as the biomarker for long term glycaemic control as it correlates well with average blood glucose levels over a period of 90-120 days before measurement.[3 4] It is recommended that all patients with diabetes on insulin therapy, and select patients on non-insulin therapies, are monitored by their glucose concentration (fig 1) for planning appropriate individualised therapeutic strategies with active patient involvement.[5] Guidelines from the American Diabetes Association and the European Association for the Study of Diabetes[5] recommend combining this with periodic (twice a year on those meeting targets; quarterly in those whose treatment has been changed or who are not meeting targets) HbA1c testing for effective management and risk stratification of patients with complications of diabetes. However, there are circumstances when HbA1c alongside glucose testing becomes unreliable for monitoring patients with diabetes. It is not clear how prevalent this situation is, but is likely to be present in geographical regions such as South East Asia and some parts of Africa where haemoglobinopathies are common.

What affects the accuracy of HbA1c and glucose measurements?

When plasma proteins, including haemoglobin, are exposed to glucose they are glycated.[6] The degree of glycation usually depends on the plasma glucose concentration. Red blood cells have an average lifespan of 120 days, therefore measuring HbA1c gives an estimate of blood glucose concentration over that period.

Glucose is measured by methods that use enzymes in reactions involving either generation of an electric current or formation of a coloured product in a proportional manner.[7] The advantages and disadvantages of monitoring blood glucose are listed in

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table 2. By contrast, clinical laboratories use methods such as ion exchange chromatography, capillary electrophoresis, immunoassays, enzymatic assays, and mass spectroscopy to measure HbA1c.[8] There are advantages to using HbA1c (table 2), but where the patient has haemoglobinopathies, haemoglobin variants, and factors that increase or decrease HbA1c concentration (box 1), these can cause variations in the results. The UK's National Institute for Health and Care Excellence (NICE) guideline NG28 recommends that clinicians liaise with clinical biochemists or diabetes specialists if they detect unexplained discrepancies or discordant HbA1c and blood glucose measurements.[9]

Box 1: Disadvantages of HbA1c for monitoring diabetes[4 6 8]

Factors that decrease HbA1c

- Decreased average red blood cell age: haemolytic anaemia (because of congenital conditions, immunological causes, drug related, liver disease, splenomegaly); reticulocytosis (because of haemolytic anaemia, erythropoietin therapy, or haemorrhage)
- Chronic kidney disease owing to shortened life span of red blood cells (partly owing to renal anaemia and/or erythropoietin deficiency)
- Blood transfusion and pregnancy (resulting from haemodilution)
- HIV infection as a direct effect of using nucleoside reverse transcriptase inhibitors, possibly as a result of red blood cell destruction
- Decreased glycation: high dose vitamins C and E, alcohol, some antiviral drugs (eg, ribavirin), or antibiotics (eg, trimethoprim-cotrixamole)

Factors that increase HbA1c

- Increased mean age of red blood cells (eg, from splenectomy); decreased percentage of reticulocytes (eg, in aplastic anaemia); and increased glycation rates (eg, from iron deficiency)

What is the next investigation when a discordant HbA1c and glucose result is observed?

There is some linear relationship between HbA1c and estimated average glucose over the lifespan of red blood cells (120 days), however, recent (ie, 3-4 weeks earlier) plasma glucose levels contribute relatively more to the final plasma HbA1c concentration.[10] Therefore, in situations where there are abrupt changes in glycaemia or rapid turnover of red blood cells, such as in chronic kidney disease and anaemia, using HbA1c to monitor patients may give unexpected results. When there is an apparent discordance between glucose and HbA1c, re-testing can exclude a random test error.[11] Occasionally these discordant results might reveal the presence of an analytical interference, presence of haemoglobin variant, or haemoglobinopathy.[12] If there is evidence of microcytic anaemia, clinical evidence of haemoglobinopathy or family history of the same, haemoglobin electrophoresis, and/or genetic studies are suggested (fig 1).[13] Clinical laboratories that measure HbA1c will have procedures in place to deal with haemoglobin variants or haemoglobinopathy detected during analyses. As different methods and analysers are affected differently by haemoglobin variants, if a variant is suspected it might be necessary to use an alternative method not prone to interferences. It has been suggested that, in geographical areas where there is a large prevalence of a specific variant(s), methods that are less affected by those variants should be used, but such decisions have economic implications.[14]

How to monitor patients with diabetes when HbA1c is unsuitable?

In situations where HbA1c is not suitable to monitor patients with diabetes, as in the presented case or in situations listed in box 1, alternatives to consider include glucose profiling using quality assured devices, total glycated haemoglobin, fructosamine, or glycated albumin (table 3).[15] NICE guideline NG28 recommends total glycated haemoglobin, fructosamine, and glucose profiling for monitoring when HbA1c is unreliable (fig1).[9] Currently, costs, inadequate assay standardisation, and lack of consensus about specific treatment targets are hampering the widespread use of these alternative tests.

Outcome

The patient was re-tested with a fructosamine assay, which gave a concentration of 564 µmol/L (reference interval 215-310). HbA1c concentration was 54 mmol/mol and haemoglobin concentration 105 g/L. HbA1c of 48 mmol/mol or 6.5% approximately equates to fructosamine of 270.2 µmol/L.[15] The relatively low HbA1c was related to low haemoglobin and rapid turnover of red blood cells owing to gastrointestinal blood loss and consequently accelerated erythropoiesis. The patient agreed to undertake glucose self monitoring and fructosamine measurements every four months. He was advised to increase insulin doses gradually, attempting to keep pre-meal glucose concentrations at an individualised target level of 7-9 mmol/L.[9] When reviewed at the diabetes clinic four months later, his blood glucose concentration was in the range 8-12 mmol/L, and fructosamine was 384 µmol/L (reference interval 215–310) without hypoglycaemic episodes while he was on insulin glargine 50 units per night and soluble human insulin 40 units before main meals—a diabetes control acceptable for his age and associated comorbidities.

Education into practice

How might your approach to monitoring patients with diabetes and haemoglobinopathies, anaemia, or chronic kidney disease change as a result of reading this article?

How often have your patients with diabetes had HbA1c results that were unexpected or appeared discordant with the measured glucose concentration?

When and how might you contact specialists such as clinical biochemists or diabetes specialists for assistance with interpreting HbA1c results or seek advice on further investigations?

How patients were involved in the creation of this article

The idea for this manuscript came from discussions with general practitioners and their patients regarding either discordant or unexpected HbA1c and blood glucose results. We took the case discussed here as an example. We discussed the plan of future monitoring and management with the patient and gave him knowledge about his specific situation of rapid red blood cell turnover that resulted in unreliable HbA1c concentration. We discussed the importance of glucose monitoring and fructosamine testing for his diabetes self-management. He was happy about using his case scenario to educate other patients and healthcare professionals. Although the contents of the article were discussed with him, he did not make comments to modify the paper

Additional educational resources

Information for laboratory professionals

The National Glycohemoglobin Standardization Program, NGSP (http://www.ngsp.org): website providing information regarding the HbA1c standardisation programme; lists interferences in various commercial HbA1c assays and methods, and provides an online calculator to convert between Diabetes Control and Complications Trial (HbA1c %), International Federation of Clinical Chemistry (mmol/mol Hb), and estimated average glucose (mg/dL)

Information for healthcare professionals

The A1C Test & Diabetes (https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis/a1c-test): website providing information on diabetes and other conditions. Also provides hyperlinks to other relevant sites including the NGSP

Information for patients

Lab Tests Online (http://labtestsonline.org.uk): useful, simplified information regarding various laboratory tests

How this article was made

We searched PubMed for original meta-analyses and review articles using the keywords "monitoring diabetes mellitus," or "monitoring complications of diabetes mellitus," or "discordant glucose and HbA1c," or "discordant glucose and haemoglobin A1c," or "diabetes management," or "haemoglobinopathy" or "hemoglobinopathy," or "hemoglobin variants." We also searched the National Institute for Health and Care Excellence (NICE) and Cochrane Database for guidelines and evidence regarding managing diabetes mellitus. This article mainly draws from the latest guidelines (at the time of writing) regarding the management of diabetes mellitus as specified by NICE guideline NG28 and the Joint American Diabetes Association and European Association for the Study of Diabetes. For alternative tests (table 2), the suggestions are based on NICE NG28, but meta-analyses are required to provide further definite evidence.

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Contributions: RS conceptualised the review following conversations with general practitioners, researched the subject matter, wrote the first draft, and is the guarantor. KM contacted the laboratory to inquire about the management of patients with haemoglobinopathies and revised drafts of the paper. SD and JMP advised on clinical management and revised drafts of the paper. JMP was involved in the management of the patient described here.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent: Patient consent not required (patient anonymised).

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Tables

Table 1| Reference interval for fasting glucose and HbA1c

	Reference interval (non-diabetic)	Diagnostic threshold for diabetes	Target*
Fasting plasma glucose concentration (mmol/L)*	4.1-5.6	≥7.0	4.0-7.0
HbA1c mmol/mol	42	48	<53
HbA1c %	<6.0	6.5	<7.0

* Target for adults on a drug associated with hypoglycaemia (NICE guideline NG28).

Table 2| Key tests: using blood glucose or HbA1c concentrations for monitoring diabetes mellitus[3 4 6]

Measure	Advantages	Disadvantages
Blood glucose	Low cost	May require fasting
	Widely available	Instability in blood collection bottles
	Amenable to point-of-care testing	Only reflects hyperglycaemia at the time of sampling
		Large biological variability
		Increased in acute illness
		Lack of global standardisation of plasma glucose
		Develops late in type 2 diabetes, potentially delaying diagnosis and treatment
HbA1c	Fasting not required	See box 1
	Low biological variability	
	Marker of long term glycaemia over average lifespan of red blood cells (~120 days)	
	Stable during acute illnesses	
	Good sample stability in blood collection bottles reduces concerns with delay in analysis	
	Assays are now standardised, allowing comparisons between laboratories	
	Blood levels correlate with complications related to diabetes, such as cardiovascular disease	

Table 3| Alternative tests for monitoring glycaemic control in patients with diabetes[12 13 15]

Test	Description	Advantages	Disadvantages	Reference interval (RI)
Quality assured blood glucose profile	Measurement of blood glucose using quality assured glucose meters. It may be undertaken by the patient at home	Empowers patient to self-manage condition. Results available in real time. Allows for immediate corrective actions.	Glucose meters have to be maintained and quality controlled. May give erroneous results if instructions for use not followed	4.1-5.6 mmol/L
Fructosamine	Measures all glycated proteins including albumin in plasma	Useful in conditions where HbA1c is not suitable. Age, gender, and race-based reference intervals now available	As albumin has a shorter half life of 20 days, the past profile of glycaemia obtained is shorter than with HbA1c. Assays are not standardised, so results cannot be directly compared. Falsely low results are seen with decreased serum total protein and/or albumin. Iron deficiency anaemia will give falsely higher results as a result of enhanced glycation	Assay, age, gender, and race dependent. Overall RI: 194.8-258.0 µmol/L[15]
Glycated albumin	Specifically measures glycated albumin expressed as a percentage of total serum albumin	As for fructosamine	As for fructosamine. Assays not yet widely available	Assay, age, gender, and race dependent. Overall RI: 10.7-15.1%.[15]
Total glycated haemoglobin	Measures HbA1c based on the separation of proteins resulting from structural differences. The method uses boronate, which reacts specifically with glucose bound to haemoglobin (boronate-affinity chromatography)	Shows the least analytical interference from the presence of haemoglobin variants. Has good assay precision. Available on point-of-care devices	May be affected by abnormal glycation of proteins. Measures all total glycated haemoglobins, which includes HbA1c. Therefore, the user is unable to discern the presence of haemoglobin variants, if present	20-42 mmol/mol (International Federation of Clinical Chemistry, IFCC) or 4-6% (National Glycohemoglobin Standardization program, NGSP)

Figure

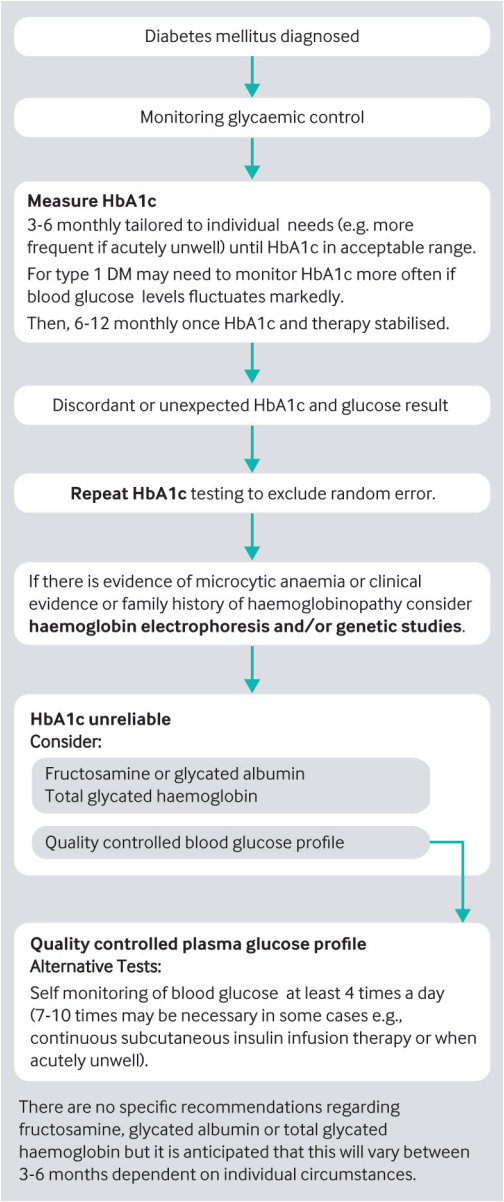

Fig 1 Monitoring glycaemic control in patients with diabetes mellitus. Monitoring frequency is based on the UK National Institute for Health and Care Excellence guideline NG28 (2015).[9] DM: diabetes mellitus; HbA1c: haemoglobin A1c