When is HbA1c useful and what do the numbers mean – do they help or hinder?

SUSAN E MANLEY,1,2,3 SAMIUL MOSTAFA,1,2,4 JONATHAN WEBBER,1,4 KAVITHA D GANAPATHY,5 ROY TAYLOR,6 RANDIE R LITTLE,7 RAJEEV P RAGHAVAN,8 CRAIG WEBSTER,9 ALISON BARRATT,10 RACHEL A ROUND,1,5 IRENE M STRATTON,1,11,12 ANDREAS KARWATH,1,13,14,15 JOHN A WILLIAMS,1,14,15,16,17 GEORGIOS V GKOUTOS,1,13,14,15,18,19,20,21* GRAHAM A ROBERTS,1,22,23,24* SANDIP GHOSH,1,25* on behalf of the Diabetes Translational Research Group (DTRG), Queen Elizabeth Hospital Birmingham and Birmingham University

Abstract

Background: Glycated haemoglobin (HbA1c) measurement is used for diagnosis, management and remission of type 2 diabetes (T2DM), with measurements comparable worldwide and the World Health Organization listing medical conditions that affect its accuracy. Admission glucose is in the ‘diabetes’ range in 5% of emergency hospital admissions without prior diagnosis, with literature searches indicating inconsistent practice on using HbA1c to confirm diagnosis. As oral glucose tolerance tests (OGTT) were not possible during the COVID-19 pandemic, guidance was issued by the Royal College of Obstetrics and Gynaecology on using HbA1c for gestational diabetes mellitus.

Aims: This study explores use of HbA1c at Queen Elizabeth Hospital Birmingham, a large university hospital serving a multi-ethnic adult population.

Methods: Information is presented on comparability, clinical audits, research studies and current practice, and is illustrated by case reports.

Results: Data from the National Glycohemoglobin Standardization Program show comparability of laboratory HbA1c and point-of-care testing methods from 1993 to 2023. Although HbA1c was used to diagnose gestational diabetes during the COVID-19 pandemic, hospitals have reverted to OGTT post pandemic. In contrast, HbA1c is now being used to assess T2DM remission. Case reports illustrate these scenarios and highlight the complexity of decision-making when the accuracy of the HbA1c reading is affected by multiple co-morbidities.

Conclusions: This wider use of HbA1c includes remission of T2DM but the diagnosis of gestational diabetes has reverted to OGTT post pandemic. A pictorial representation of HbA1c range is presented to aid understanding of this test. It is suitable for diagnosis of diabetes in most people except those with some variant haemoglobins or abnormal red blood cell turnover.

Key words: HbA1c, inpatient diagnosis, gestational diabetes, remission, red blood cells

*Joint last authors

1 Diabetes Translational Research Group, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
2 College of Medical and Dental Sciences, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK
3 Green Templeton College, University of Oxford, Oxford, UK
4 Diabetes Centre, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
5 City Hospitals, Birmingham, UK
6 Magnetic Resonance Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
7 Department of Pathology and Anatomical Sciences, University of Missouri, Columbia, Missouri, USA
8 Diabetes Endocrine Services, Diabetes Endocrine Centre, Location C28, New Cross Hospital, Royal Wolverhampton Trust, Wednesfield Road, Wolverhampton, WV10 0QP, UK
9 Clinical Laboratory Services, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
10 https://aisionbarratt.com/
11 University of Oxford, Oxford UK
12 University of Southampton, Southampton, UK
13 MRC Health Data Research UK (HDR UK) Midlands, Birmingham, UK
14 College of Medical and Dental Sciences, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK
15 Institute of Translational Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
16 Mammalian Genetics Unit, Medical Research Council Harwell Institute, Harwell, UK
17 Eisai Inc, Cambridge, MA, USA
18 NIHR Experimental Cancer Medicine Centre, Birmingham, UK
19 NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK
20 NIHR Biomedical Research Centre, Birmingham, UK
21 BHP Centre for Health Data Research, University of Birmingham, Birmingham, B15 2TT, UK
22 Diabetes Research Unit (Cymru), Grove Building, Swansea University, Swansea, UK
23 HRB-Clinical Research Facility – University College Cork, Cork, Ireland
24 Department of Endocrinology and Diabetes, University Hospital Waterford, Waterford, Ireland
25 Department of Endocrinology, Zulekha Hospital Sharjah, UAE

Address for correspondence: Dr Susan Manley
26 Hayward Road, Oxford, OX2 8LW
E-mail: se.manley@btinternet.com

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Introduction

Measurement of glycated haemoglobin (HbA1c), a surrogate marker of average blood glucose reflects its non-enzymatic binding to haemoglobin over the previous two to three months, the lifespan of red blood cells. HbA1c is widely used now for the diagnosis, management, and definition of remission of type 2 diabetes (T2DM). It was included in the Diabetes Control and Complications Trial (DCCT), and the UK Prospective Diabetes Study (UKPDS). In the 1990s, these randomised controlled clinical trials reported that lower HbA1c was associated with fewer of the complications caused by type 1 diabetes (T1DM) and T2DM, respectively. Findings from the UKPDS, first presented by Professor Robert Turner in Barcelona, included what is now an iconic graph illustrating the relationship between updated HbA1c and complications of T2DM (Figure 1). This graph has been cited more than 12,100 times and highlighted the need for international standardisation. In 2002, the DCCT defined the relationship between 24-hour snapshot glucose profiles and HbA1c for T1DM.

Laboratory methods for HbA1c testing are certified now by the National Glycohemoglobin Standardization Program (NGSP), that also confirmed UKPDS Bio-Rad HPLC methods as equivalent to the DCCT when the UKPDS results were reported. Comparability of routine HbA1c measurement has much improved since then due to upgrades in laboratory methods and equipment (Figure 2 [note DCCT units %]). After production of a suitable reference standard for HbA1c, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method was introduced at the manufacturer level for standardisation of all routine methods in 2011. IFCC units (mmol/mol) were adopted for reporting HbA1c results in the UK and some other countries but DCCT units were retained in the US. Some point-of-care testing (POCT) devices, advantageous from a wider perspective, are NGSP certified. However, the American Diabetes Association does not recommend using them for diagnosis of T2DM at sites where the required education, training and oversight of performance are not in place. Similarly, constraints apply for this purpose in the UK, with confirmation of a possible POCT diabetes diagnosis required from the laboratory using a venous sample. With laboratory tests, a second HbA1c test should be requested if the patient is asymptomatic.

Figure 1. Incidence rates and 95% CI for myocardial infarction and microvascular complications by updated mean HbA1c in UKPDS

Figure 2. Comparison of HbA1c results in DCCT units from different methods by National Glycohemoglobin Standardization Program from 1993 to 2023 - from chaos to order
Table 1. Important issues to consider when requesting HbA1c testing

<table>
<thead>
<tr>
<th>Issues affecting HbA1c accuracy</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>1, 3, 4</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4, 5</td>
</tr>
<tr>
<td>Diabetic status</td>
<td>1, 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td>COVID-19</td>
<td>4, 5</td>
</tr>
<tr>
<td>Physical and clinical symptoms</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td>Post blood transfusion/loss</td>
<td>see ref 28</td>
</tr>
<tr>
<td>Presence of certain abnormal haemoglobins, including fetal haemoglobin</td>
<td>3</td>
</tr>
<tr>
<td>Anaemia e.g. polycythaemia rubra vera, sickle cell disease, haemolytic anaemia, post-transplant anaemia, iron deficiency anaemia* and thalassaemias*</td>
<td>3</td>
</tr>
<tr>
<td>Drugs causing severe anaemia or affecting red cell turnover, e.g. erythropoietin, some antiviral drugs</td>
<td>2</td>
</tr>
<tr>
<td>Macrocytosis (fewer, larger red blood cells) associated with drugs e.g. dapsone, ribavirin or excess alcohol intake</td>
<td>see refs 21 &amp; 51</td>
</tr>
<tr>
<td>Liver disease including pre-transplant*</td>
<td>2, see ref 21</td>
</tr>
<tr>
<td>Renal disease</td>
<td>2</td>
</tr>
</tbody>
</table>

*Can in some cases cause increased HbA1c relative to glucose

HbA1c for diagnosis of T2DM
In 2011, the World Health Organisation (WHO) adopted the recommendation from an expert committee to use HbA1c for diagnosis of T2DM in the community. The HbA1c workload at Queen Elizabeth Hospital Birmingham (QEHB) laboratory increased markedly, with a consequent reduction in glucose requests. OGTTs are rarely requested now, mainly in circumstances when HbA1c measurement is precluded or questionable, and when fasting glucose is impaired. Some variant haemoglobins negate actual HbA1c measurement and other conditions alter red blood cell turnover, affecting its accuracy (Table 1).

Data on OGTT and HbA1c from the QEHB diabetes clinic have shown >97.5% agreement in sensitivity and specificity between diagnoses on OGTT and HbA1c when HbA1c >57 mmol/mol. Therefore, some people can be diagnosed with T2DM by HbA1c but not OGTT and vice versa, as the tests do not represent the same short- or longer-term glycaemic profiles. Clinicians are advised to accept the diagnosis from either test unless conditions are present that compromise the accuracy of HbA1c or its suitability, and to use glucose instead (Table 1). More recently, HbA1c has been suggested for diagnosis of diabetes in hospital patients with blood glucose concentrations in ‘at risk’ or ‘diabetes’ ranges on admission, but this strategy has not yet been adopted systematically in the UK.

High HbA1c results
Laboratory alerts for very high (>150 mmol/mol) HbA1c identified South Asian males in their 20s who had not accessed medical services previously in relation to the disease being diagnosed with diabetes on admission to QEHB. This resulted in a laboratory survey showing approximately one in 200 HbA1c results were >120 mmol/mol, with 20% possibly new diagnoses of diabetes. In addition to young male South Asians, patients with diabetic ketoacidosis or pancreatitis, and patients on steroids or antipsychotic drugs were identified. One of the highest HbA1c results reported before the pandemic was 203 mmol/mol, equivalent to 30.3 mmol/L when expressed as estimated average glucose (eAG). A result of 234 mmol/mol, or 34.8 mmol/L eAG, has been reported elsewhere in Birmingham.

As very high HbA1c reflects poor glucose control over the previous few months, it can also be associated with physical symptoms as well as metabolic conditions. Recently, a patient who presented to QEHB with ballistic movements was found to have extremely high HbA1c, Case 1.

Case 1
A 68-year-old Afro-Caribbean with T2DM on metformin before admission, presented with new-onset, jerky ballistic movements of high amplitude in the right arm, 10-15 movements every 5 minutes. Admission glucose was >33 mmol/L, ketones 1.8 mmol/L (normal range <0.6 mmol/L) and HbA1c >217 mmol/mol. Hemichorea-hemiballism, a hyperglycaemia-related movement, was diagnosed, and insulin was commenced. Glucose decreased to 8-20 mmol/L, reaching 5-15 mmol/L by the time of discharge. Ballistic movements resolved when glycaemic control improved; with HbA1c 169 mmol/mol 25 days after discharge.

In general, HbA1c is measured at 3-monthly intervals but in certain circumstances it can be measured more often after consideration of the half-life of red blood cells. For assessment of changes in glycaemia over time periods shorter than three months, glucose or fructosamine measurement is recommended. Higher than normal HbA1c relative to glucose has also been reported for a patient with alpha-1-antitrypsin disorder, and in patients with certain, but not all, thalassaemias; this inaccuracy may be caused by longer red blood cell half-life.

HbA1c testing on admission to hospital
Admission glucose was in the ‘diabetes’ range in 5% of White European and 8% South Asian emergency admissions without a prior diagnosis of diabetes; Figure 3) but literature searches show inconsistent practice on the use of HbA1c for this purpose. Additional testing with HbA1c in hospital patients can confirm pre-existing T2DM but their medical background should be considered. Multiple medical conditions may be present with various drug regimens involved in the patient’s care, Case 2. Inadequate understanding of HbA1c can lead to acute presentations of dysglycaemia: clinical assessment and triangulation are key to the management of patients in these circumstances.
Accuracy of HbA1c

Which tests should be requested to assess glycaemia when a patient is admitted to the hospital, and which factors need to be considered? For most cases of people identified at QEHB with HbA1c below the reference range (<20 mmol/mol), there was a medical or scientific explanation. They were either on ribavirin,21,24 or dapsone,25,26 they had macrocytic red blood cells or haematological disorders, or in a few people malnourishment or end-of-life scenarios. In addition, HbA1c was depressed by 28 mmol/mol across the range of glucose in an audit of 27 outpatients with cirrhosis pre-transplant but elevated relative to glucose in one outpatient whose cirrhosis was caused by alpha-1-antitrypsin disorder.21 This depression was associated with the presence of macrocytic red blood cells, fewer cells and higher mean cell volume, but not in the patient with alpha-1-antitrypsin related liver disease whose HbA1c was elevated relative to glucose.

Hypoglycaemia causes acute situations requiring medical attention but there is little relationship between HbA1c and severe hypoglycaemia in modern practice. However, in the presence of some thalassaemias and other red cell disorders, HbA1c may be higher than normal relative to glucose, causing severe hypoglycaemia when inaccurate HbA1c results are used for management of blood glucose.27 This issue was illustrated in a case presented at the Diabetes UK professional conference in 2023, when an additional hypoglycaemic agent was added but the HbA1c was artificially high due to β-thalassaemia undetected by the HbA1c high performance liquid chromatography method.28 Glucose testing is required to assess these situations. Case 3 from another hospital in the West Midlands also illustrates this problem and highlights the need for electronic systems for flagging, taking background information into account and consistent communication between those providing medical care.

Case 3

A 58-year-old Afro-Caribbean female with a background of diet-treated diabetes, hypertension, previous GDM, sickle cell trait and a strong family history of diabetes was reviewed by her GP due to elevated HbA1c (reported as 109 mmol/mol by the laboratory but flagged as variant haemoglobin AS) and high random glucose (16 mmol/L). After dietary and lifestyle advice, she was started on gliclazide but experienced frequent hypoglycaemia. Gliclazide was stopped, HbA1c repeated and fructosamine requested along with referral to the diabetes clinic. Her subsequent HbA1c was reported as 106 mmol/mol and fructosamine as 421 µmol/L (reference range 211 to 328 µmol/L), equivalent to an estimated HbA1c of 72 mmol/mol. Her glucometer readings had ranged from 6 to 14 mmol/L in the eight weeks prior to this hospital presentation. Since her BMI was elevated at 28 kg/m² and she did not tolerate metformin, alogliptin was commenced. She was referred to a dietician and given further advice on lifestyle measures. The GP was notified and asked to rely on glucose data for therapy decisions and on fructosamine to monitor glycaemic control over the shorter term i.e. 2 to 3 weeks, as the clinicians questioned the accuracy of HbA1c due to the hypoglycaemic incidents.

No difference was found between the relationship of HbA1c and fructosamine in a small study of heterozygous patients with AD or AS haemoglobins but there is wide scatter around the linear regression lines.29 Any drugs, including anti-retrovirals, which reduce erythrocyte lifespan can potentially lower HbA1c by increasing the proportion of younger cells in the blood, and these have less exposure of haemoglobin to glucose than normal red blood cells. Laboratory glucose estimation is the only option for the diagnosis of T2DM in these circumstances,30 as fructosamine representing glycated plasma proteins is not validated for this purpose.

Ethnicity can also influence how HbA1c relates to glucose. In Birmingham, HbA1c levels were 10% higher relative to admission glucose levels in South Asians and Afro-Caribbeans than in White Europeans.31 This may reflect haematological differences affecting red blood cell lifespan. Questions have been raised as...
to whether HbA1c cut-offs for diagnostic purposes should be determined by ethnicity.\textsuperscript{32,33}

**HbA1c during the COVID-19 pandemic**

Hyperglycaemia causes excess morbidity and mortality in hospital patients with COVID-19.\textsuperscript{14} Unusual manifestations of ketoacidosis with very high HbA1c have been reported for people admitted with COVID-19.\textsuperscript{28,35} The virus particularly affects people with additional medical problems, and those who present for inpatient treatment of the viral illness may not be representative of all the people with diabetes who become infected. There is insufficient evidence/research to establish whether the virus directly affects the glycation of haemoglobin.

**HbA1c in pregnancy and gestational diabetes**

Before the emergence of COVID-19, routine HbA1c testing was not advised during pregnancy for diagnostic purposes or glucose control,\textsuperscript{28} as HbA1c falls to a modest extent in normal pregnancy due to decreased fasting blood glucose and reduced erythrocyte lifespan.\textsuperscript{37} HbA1c will most likely only be raised in the first half of pregnancy in those with pre-existing diabetes because in gestational diabetes mellitus (GDM) glucose levels start to rise in the second half of pregnancy, Case 4.

**Case 4**

A 36-year-old South Asian female had an HbA1c of 55 mmol/mol and random plasma glucose 9.5 mmol/L at her clinic booking visit at 10 weeks’ gestation, suggesting undiagnosed T2DM. She was initially managed with dietary advice and home blood glucose monitoring; metformin was added when self-monitored glucose was above pregnancy targets (fasting and pre-meal <5.3 mmol/L or 1-hour post meal <7.8 mmol/L) but insulin was required later in the pregnancy. The metformin and insulin were stopped after delivery at 38 weeks. Her HbA1c was 50 mmol/mol three months postpartum, supporting the earlier diagnosis of T2DM.

Adjustment of glycaemic regimens has relied primarily on home blood glucose monitoring although longer-term measurement of HbA1c is valuable for some individuals.\textsuperscript{38,39} Recently, continuous blood glucose monitoring has been introduced as data relating pregnancy outcome to measures such as time in range become available for various glycaemic situations.\textsuperscript{40,41}

GDM, defined as glucose intolerance identified for the first time during a pregnancy, is associated with adverse outcomes such as shoulder dystocia, birth injury, increased caesarean section rate and neonatal hypoglycaemia, with a much-increased risk of subsequent T2DM. Pre-COVID NICE guidelines for screening specify a 75g OGTT at 24 to 28 weeks’ gestation for high-risk women (BMI ≥30 kg/m\textsuperscript{2} at booking, ethnicity with high prevalence or first-degree relative with T2DM), with cut-offs for fasting glucose ≥5.6 mmol/L and 2-hour glucose ≥7.8 mmol/L.\textsuperscript{46} However, as this strategy entails large numbers of OGTTs, it was not feasible to perform them in many areas of England during the pandemic.

Temporary guidance on the diagnosis of GDM unsupported by research or guidelines was issued in 2020 by the Royal College of Obstetrics and Gynaecology (RCOG) for logistic reasons and was widely adopted.\textsuperscript{42} The guidance advised screening at the booking visit for pre-existing T2DM with HbA1c, i.e. when HbA1c ≥48 mmol/mol or random plasma glucose ≥11.1 mmol/L, with the provision of appropriate treatment. An HbA1c result between 41 and 47 mmol/mol or random plasma glucose 9 to 11 mmol/L indicated possible GDM. Repeat tests were required at 24 to 28 weeks’ gestation in high-risk women whose earlier results were normal. If the resulting HbA1c was ≥39 mmol/mol, fasting plasma glucose ≥5.6 mmol/L or random plasma glucose ≥9 mmol/L, they should be also treated for GDM, Case 5.

**Case 5**

A 32-year-old White Caucasian female was screened for GDM on booking at 11 weeks as her BMI was 38 kg/m\textsuperscript{2}. An HbA1c of 44 mmol/mol and random plasma glucose 6.9 mmol/L confirmed GDM. It was managed by dietary/lifestyle changes, with glucose and pregnancy targets achieved until 28 weeks when metformin was added. She had a normal delivery at 40 weeks but her HbA1c was 40 mmol/mol three months post-partum, triggering advice on long-term dietary/lifestyle changes and annual HbA1c checks.

It was not known whether these temporary RCOG guidelines would alter the prevalence of GDM or change the outcomes. A recent paper based on screening for GDM in one Dublin hospital for three months in 2019 and the same period in 2020 reported a decreased prevalence and concluded that OGTT should be maintained as the gold-standard test where possible.\textsuperscript{43} It has been debated whether the population identified would differ from those identified using OGTT but no significant differences in clinical outcomes were observed in this small study. There was increased use of medication (metformin and insulin) for those diagnosed with GDM using HbA1c, the assumption being that they had higher glucose levels than those identified by OGTT.

Although HbA1c measurement was useful during the pandemic, clinicians have reverted to OGTT for GDM screening due to a significant fall in diagnoses using HbA1c ≥39 mmol/mol.\textsuperscript{44} But HbA1c testing was advantageous at booking to diagnose T2DM earlier. There is a strong case for screening with HbA1c on booking for high-risk women given the increasing prevalence of T2DM in the background population in Birmingham and elsewhere in the UK. At present, many of these women would only have been identified as having diabetes when presenting with highly abnormal OGTT results at 24 to 28 weeks’ gestation.

**HbA1c in remission of T2DM**

Remission of T2DM can occur if people achieve substantial weight loss when placed on a very low-calorie diet, and oral
anti-diabetic medication such as metformin and gliclazide can be withdrawn safely.\textsuperscript{45} HbA\textsubscript{1c} measurement is included in protocols introduced for this purpose in the UK in 2016,\textsuperscript{46} and in a 2019 UK consensus report.\textsuperscript{47,48} They define remission as lowering HbA\textsubscript{1c} to below the diagnostic level for diabetes (<48 mmol/mol) and off all hypoglycaemic drugs for a minimum of six months. An international consensus confirmed this practice in 2021.\textsuperscript{1} Case 6.

**Case 6**

A 68-year-old man who had had T2DM for four years was treated with gliclazide 80 mg twice daily plus lisinopril and a statin. On recruitment to the Counterpoint study,\textsuperscript{49} he weighed 78.6 kg, being 1.70 m tall with a BMI of 27.2 kg/m\textsuperscript{2}. He was commenced on an 800 kcal/day weight loss diet and gliclazide was discontinued. His HbA\textsubscript{1c} was 63 mmol/mol and after dieting for one week it dropped to 59 mmol/mol. After four weeks, his HbA\textsubscript{1c} was 50 mmol/mol and at eight weeks it was 43 mmol/mol (below the diabetes range).

The average weight loss over eight weeks in the Counterpoint study (n=11) was 15.3(1.2) kg, mean (SE), with 15% of initial body weight lost overall.\textsuperscript{40} This amounted to 3.9(0.2) kg over the first week, 5.7(0.6) kg for weeks 1 to 4 and 5.7(0.7) kg for weeks 4 to 8. Fasting plasma glucose decreased in the first week from 9.2(0.4) mmol/L to 5.9(0.4) mmol/L, p=0.003, (not different from the control group without diabetes, 5.3(0.1) mmol/L, p=0.18) and remained stable for the next eight weeks at 5.7(0.5) mmol/L. Correspondingly, HbA\textsubscript{1c} dropped from 57±3 mmol/mol to 55±3 mmol/mol, p=<0.001, after the first week, was 47±3 mmol/mol, p=<0.001, by week 4 and 42±2 mmol/mol, p=<0.001, by week 8. HbA\textsubscript{1c} data are also available for patients in the DiRECT study at 12 months but not at 6 months.\textsuperscript{50} Weight loss of 15 kg or more was reported for 24% of participants in the intervention group, remission was achieved in 46% and HbA\textsubscript{1c} was <48 mmol/mol in 49% of participants.

Remission of T2DM is more likely in people diagnosed for less than six years, although remission remains possible but less likely for many years following diagnosis of T2DM. In any situation, the degree of weight loss is the absolute determinant.\textsuperscript{50}

**Conclusions**

Appropriate interpretation of results for HbA\textsubscript{1c} is essential as a diagnosis of diabetes is life-changing and given that results are used to adjust potentially life-threatening medication and make other clinical decisions. The clinical cases presented here highlight the complexity of decision-making, with additional clinical information and laboratory data required for patients with multiple co-morbidities or on certain drugs or with variant haemoglobins that affect red blood cell turnover.\textsuperscript{51} A paper from 2020 involving randomly selected adults from the National Health and Nutrition Examination Survey (NHANES) has also highlighted the lack of concordance of HbA\textsubscript{1c} and OGTT glucose for diagnosis of T2DM when HbA\textsubscript{1c} <57 mmol/mol,\textsuperscript{52} as demonstrated in Birmingham.\textsuperscript{14} Figure 4. Range of HbA\textsubscript{1c} results reported mmol/mol in Birmingham, England.

Although laboratory HbA\textsubscript{1c} results are available on primary and secondary care information systems, no prompts to exercise caution when interpreting them or requesting tests are available when details of medical conditions/drugs that affect their accuracy are recorded there. Systems management with timely decision prompts could link pertinent clinical and laboratory information so that patients can be managed safely in non-diabetes specialist areas of healthcare. Previous haematology reports of abnormal haemoglobin or red blood cell count and morphology could be flagged on electronic patient records to alert requesters when HbA\textsubscript{1c} is not accurate.

There is an urgent need for more effective, personalised health care given the risks associated with hyperglycaemia/hypoglycaemia and undiagnosed T2DM, poorer outcomes with COVID-19 in people with diabetes or metabolic syndrome, and advantages of remission. Recent initiatives in digital medicine support these objectives and when introduced will overcome the various hurdles now apparent.\textsuperscript{53-55}

Currently, HbA\textsubscript{1c} is used routinely for diagnosis of diabetes in the community in the UK and is advised for hospital admissions with hyperglycaemia but not widely implemented.\textsuperscript{6,56,57} HbA\textsubscript{1c} measurement was introduced in pregnancy for diagnosis of GDM during the COVID-19 pandemic. This usage has reverted to OGTT post-pandemic, but HbA\textsubscript{1c} screening of high-risk patients in the first trimester should be considered. International guidelines published in 2021 specify that HbA\textsubscript{1c} testing is required to confirm remission of T2DM.\textsuperscript{3}

There is increasing public awareness in recent years regarding HbA\textsubscript{1c} use in diagnosis of T2DM and pre-diabetes, and availability of POCT A1c testing, given routine screening in the over-40 age group and the introduction of the National Guidelines on Prediabetes and Type 2 Diabetes (NHPCG) in 2019.\textsuperscript{58}
Diabetes Prevention Program. Information on the definition of HbA1c as an indication of blood glucose over the previous 2 to 3 months and its overall range is presented in a pictorial format in Figure 4. Careful evaluation of HbA1c results is even more necessary now that the test features in so many on-going diabetes prevention programmes and strategies for facilitating the remission of T2DM. In routine clinical practice at tertiary centres such as QEH, clinicians come across a wide variety of conditions that underline the unsuitability of HbA1c on its own as a surrogate glycaemic marker. Whilst no laboratory test is ideal for everyone, HbA1c is only inappropriate in a very small proportion of the population and it is widely applicable. We hope this review will help to update decision-makers on the wider use of HbA1c as a surrogate marker of blood glucose, and its pitfalls.

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References
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29. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (NICE Guideline [NG3]). Published: 25 February 2015


34. Diabetes in pregnancy: management from preconception to the postnatal period (NICE Guideline [NG3]). Published: 25 February 2015 Last updated: 16 December 2020


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