When is HbA_{1c} 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,[1,9] 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 (HbA_{1c}) 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 HbA_{1c} 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 HbA_{1c} for gestational diabetes mellitus.

Aims: This study explores use of HbA_{1c} 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 HbA_{1c} and point-of-care testing methods from 1993 to 2023. Although HbA_{1c} was used to diagnose gestational diabetes during the COVID-19 pandemic, hospitals have reverted to OGTT post pandemic. In contrast, HbA_{1c} 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 HbA_{1c} reading is affected by multiple co-morbidities.

Conclusions: This wider use of HbA_{1c} includes remission of T2DM but the diagnosis of gestational diabetes has reverted to OGTT post pandemic. A pictorial representation of HbA_{1c} 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.

Br J Diabetes 2023;23:105-113
https://doi.org/10.15277/bjd.2023.417

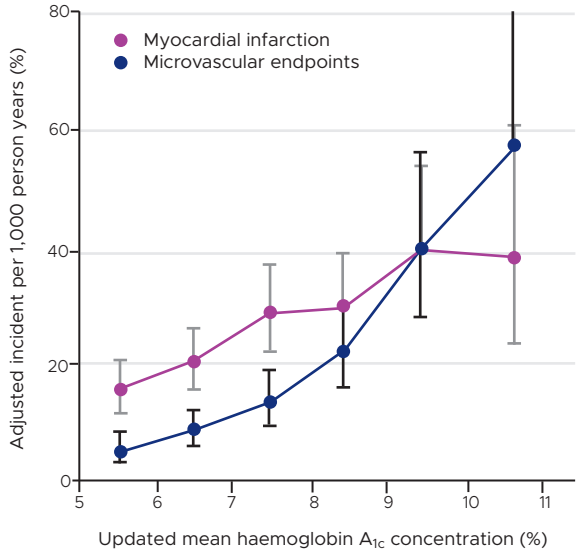
Key words: HbA_{1c}, inpatient diagnosis, gestational diabetes, remission, red blood cells

*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://alisonbarratt.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

Figure 1. Incidence rates and 95% CI for myocardial infarction and microvascular complications by updated mean HbA_{1c} in UKPDS



Introduction

Measurement of glycated haemoglobin (HbA_{1c}), 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. HbA_{1c} is widely used now for the diagnosis,[1] management,[2] and definition of remission of type 2 diabetes (T2DM).[3] It was included in the Diabetes Control and Complications Trial (DCCT),[4] and the UK Prospective Diabetes Study (UKPDS).[5] In the 1990s, these randomised controlled clinical trials reported that lower HbA_{1c} 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 HbA_{1c} and complications of T2DM (Figure 1). This graph has been cited more than 12,100 times,[6] and highlighted the need for international standardisation. In 2002, the DCCT defined the relationship between 24-hour snapshot glucose profiles and HbA_{1c} for T1DM.[7]

Laboratory methods for HbA_{1c} testing are certified now by the National Glycohemoglobin Standardization Program (NGSP),[8] that also confirmed UKPDS Bio-Rad HPLC methods as equivalent to the DCCT when the UKPDS results were reported. Comparability of routine HbA_{1c} 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 HbA_{1c}, 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 HbA_{1c} results in the UK and some other countries but DCCT units were retained in the US.[9] 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.[1] 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 HbA_{1c} test should be requested if the patient is asymptomatic.[10]

Figure 2. Comparison of HbA_{1c} results in DCCT units from different methods by National Glycohemoglobin Standardization Program from 1993 to 2023 - from chaos to order

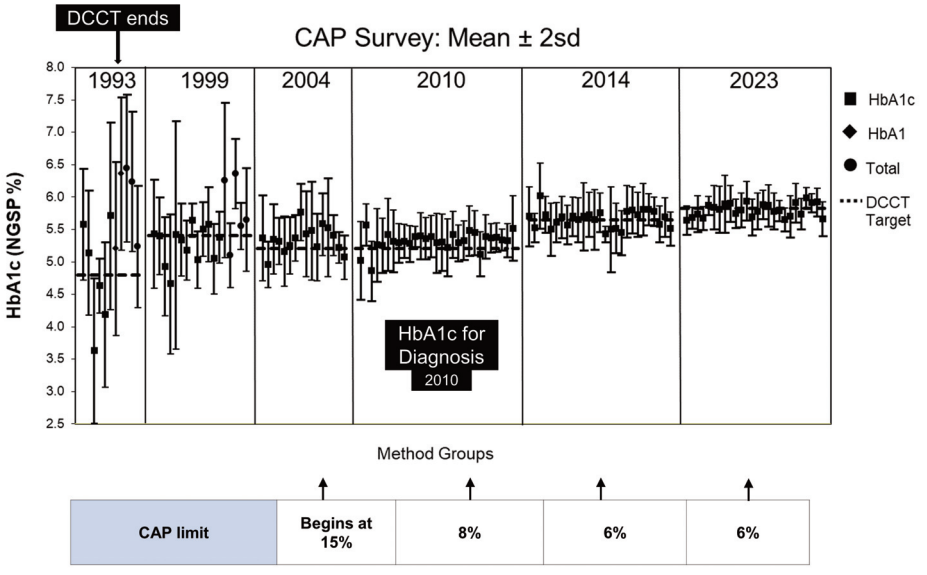


Table 1. Important issues to consider when requesting HbA_{1c} testing

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

* Can in some cases cause increased HbA_{1c} relative to glucose

HbA_{1c} for diagnosis of T2DM

In 2011, the World Health Organisation (WHO) adopted the recommendation from an expert committee to use HbA_{1c} for diagnosis of T2DM in the community.[11] The HbA_{1c} workload at Queen Elizabeth Hospital Birmingham (QEHB) laboratory increased markedly, with a consequent reduction in glucose requests.[12] OGTTs are rarely requested now, mainly in circumstances when HbA_{1c} measurement is precluded or questionable, and when fasting glucose is impaired. Some variant haemoglobins negate actual HbA_{1c} measurement and other conditions alter red blood cell turnover, affecting its accuracy (Table 1).[13]

Data on OGTT and HbA_{1c} from the QEHB diabetes clinic have shown >97.5% agreement in sensitivity and specificity between diagnoses on OGTT and HbA_{1c} when HbA_{1c} >57 mmol/mol.[14] Therefore, some people can be diagnosed with T2DM by HbA_{1c} 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 HbA_{1c} or its suitability, and to use glucose instead (Table 1). More recently, HbA_{1c} has been suggested for diagnosis of diabetes in hospital patients with blood glucose concentrations in 'at risk' or 'diabetes' ranges on admission,[1,15] but this strategy has not yet been adopted systematically in the UK.[16]

High HbA_{1c} results

Laboratory alerts for very high (>150 mmol/mol) HbA_{1c} 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 HbA_{1c} 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.[17,18] One of the highest HbA_{1c} 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 HbA_{1c} reflects poor glucose control over the previous few months, it can also be associated with physical symptoms as well as metabolic conditions.[19] Recently, a patient who presented to QEHB with ballistic movements was found to have extremely high HbA_{1c}, Case 1.[20]

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 HbA_{1c} >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 HbA_{1c} 169 mmol/mol 25 days after discharge.

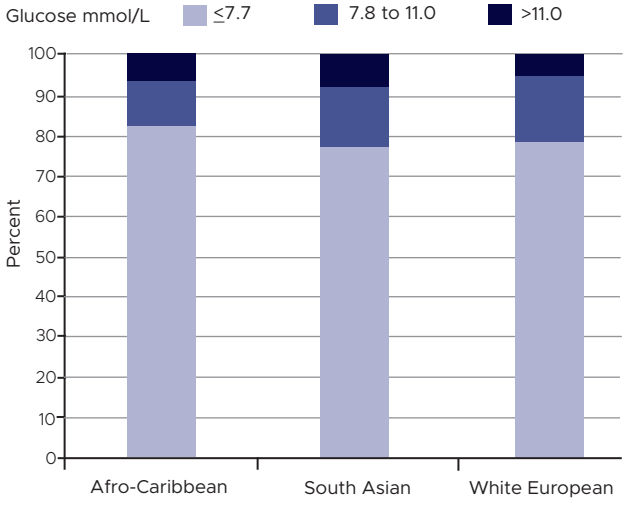
In general, HbA_{1c} is measured at 3-monthly intervals but in certain circumstances it can be measured more often after consideration of the half-life of red blood cells. For assessment of changes in glycaemia over time periods shorter than three months, glucose or fructosamine measurement is recommended.

Higher than normal HbA_{1c} relative to glucose has also been reported for a patient with alpha-1-antitrypsin disorder,[21] and in patients with certain, but not all, thalassaemias; this inaccuracy may be caused by longer red blood cell half-life.[22]

HbA_{1c} 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,[23] (Figure 3) but literature searches show inconsistent practice on the use of HbA_{1c} for this purpose.[16] Additional testing with HbA_{1c} 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 HbA_{1c} can lead to acute presentations of dysglycaemia: clinical assessment and triangulation are key to the management of patients in these circumstances.

Figure 3. Admission glucose ranges by ethnicity for people admitted as an emergency to Queen Elizabeth Hospital Birmingham without a prior diabetes diagnosis



Case 2

A 48-year-old woman diagnosed with HIV and hepatitis B and with normal HbA_{1c} on haemodialysis was admitted for fistuloplasty with a fever diagnosed as Klebsiella pneumonia. Persistently raised capillary glucose (>12 mmol/L) triggered referral to endocrine services. HbA_{1c} was inappropriate as ritonavir had been prescribed, which is an anti-retroviral affecting red blood cell turnover. Glucose testing was required to confirm T2DM diagnosis six weeks after discharge since stress hyperglycaemia also raises glucose.

Accuracy of HbA_{1c}

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 HbA_{1c} 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, HbA_{1c} 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 HbA_{1c} was elevated relative to glucose.

Hypoglycaemia causes acute situations requiring medical attention but there is little relationship between HbA_{1c} and severe hypoglycaemia in modern practice. However, in the presence of some thalassaemias and other red cell disorders, HbA_{1c} may be higher than normal relative to glucose, causing severe hypoglycaemia when inaccurate HbA_{1c} 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 HbA_{1c} was artificially high due to β-thalassaemia undetected by the HbA_{1c} 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 HbA_{1c} (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, HbA_{1c} repeated and fructosamine requested along with referral to the diabetes clinic. Her subsequent HbA_{1c} was reported as 106 mmol/mol and fructosamine as 421 µmol/L (reference range 211 to 328 µmol/L), equivalent to an estimated HbA_{1c} 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/m^2 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 HbA_{1c} due to the hypoglycaemic incidents.

No difference was found between the relationship of HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} relates to glucose. In Birmingham, HbA_{1c} 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 HbA_{1c} cut-offs for diagnostic purposes should be determined by ethnicity.[32,33]

HbA_{1c} during the COVID-19 pandemic

Hyperglycaemia causes excess morbidity and mortality in hospital patients with COVID-19.[34] Unusual manifestations of ketoacidosis with very high HbA_{1c} have been reported for people admitted with COVID-19.[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.

HbA_{1c} in pregnancy and gestational diabetes

Before the emergence of COVID-19, routine HbA_{1c} testing was not advised during pregnancy for diagnostic purposes or glucose control,[36] as HbA_{1c} falls to a modest extent in normal pregnancy due to decreased fasting blood glucose and reduced erythrocyte lifespan.[37] HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} is valuable for some individuals.[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.[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^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.[36] 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.[42] The guidance advised screening at the booking visit for pre-existing T2DM with HbA_{1c}, i.e. when HbA_{1c} ≥48 mmol/mol or random plasma glucose ≥11.1 mmol/L, with the provision of appropriate treatment. An HbA_{1c} 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 HbA_{1c} 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 38kg/m^2. An HbA_{1c} 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 HbA_{1c} was 40 mmol/mol three months post-partum, triggering advice on long-term dietary/lifestyle changes and annual HbA_{1c} 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.[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 HbA_{1c}, the assumption being that they had higher glucose levels than those identified by OGTT.

Although HbA_{1c} measurement was useful during the pandemic, clinicians have reverted to OGTT for GDM screening due to a significant fall in diagnoses using HbA_{1c} ≥39 mmol/mol.[44] But HbA_{1c} testing was advantageous at booking to diagnose T2DM earlier. There is a strong case for screening with HbA_{1c} 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.

HbA_{1c} 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.[45] HbA_{1c} measurement is included in protocols introduced for this purpose in the UK in 2016,[46] and in a 2019 UK consensus report.[47,48] They define remission as lowering HbA_{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,[3] 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,[49] he weighed 78.6 kg, being 1.70 m tall with a BMI of 27.2 kg/m^2. He was commenced on an 800 kcal/day weight loss diet and gliclazide was discontinued. His HbA_{1c} was 63 mmol/mol and after dieting for one week it dropped to 59 mmol/mol. After four weeks, his HbA_{1c} was 50 mmol/mol and at eight weeks it was 43 mmol/mol (below the diabetes range).

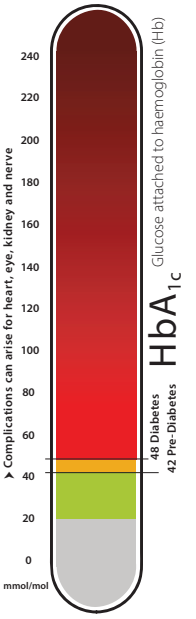
The average weight loss over eight weeks in the Counterpoint study (n=11) was 15.3(1.2) kg, mean (SE), with 15% of initial body weight lost overall.[49] This amounted to 3.9(0.2) kg over the first week, 5.7(0.6) kg for weeks 1 to 4 and 5.7(0.7) kg for weeks 4 to 8. Fasting plasma glucose decreased in 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_{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_{1c} data are also available for patients in the DiRECT study at 12 months but not at 6 months.[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_{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.[50]

Conclusions

Appropriate interpretation of results for HbA_{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.[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_{1c} and OGTT glucose for diagnosis of T2DM when HbA_{1c} <57 mmol/mol,[52] as demonstrated in Birmingham.[14]

Figure 4. Range of HbA_{1c} results reported mmol/mol in Birmingham, England



Although laboratory HbA_{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_{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.[53-55]

Currently, HbA_{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.[16,56,57] HbA_{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_{1c} screening of high-risk patients in the first trimester should be considered. International guidelines published in 2021 specify that HbA_{1c} testing is required to confirm remission of T2DM.[3]

There is increasing public awareness in recent years regarding HbA_{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

Key messages

- HbA_{1c} is now used to diagnose T2DM in the community, to manage the disease and to confirm remission
- HbA_{1c} results from laboratories across the world are comparable and can range from 20 to over 200 mmol/mol, with 42 to 47 mmol/mol indicating pre-diabetes and ≥48 mmol/mol diabetes
- Complexities can arise in decision-making if red blood cell turnover is abnormal e.g. HbA_{1c} can be depressed by >20 mmol/mol when macrocytes are present
- As concordance with OGTT and glucose data is limited when HbA_{1c} is <57 mmol/mol, clinical judgement should be exercised
- During the COVID-19 pandemic HbA_{1c} was used to diagnose GDM, but post pandemic clinicians have reverted to OGTT given the evidence base
- Relevant cases are reported from hospital settings, pregnancy outpatient clinics and recent studies on remission of T2DM

Diabetes Prevention Program.[58] Information on the definition of HbA_{1c} 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 HbA_{1c} 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 QEHB, clinicians come across a wide variety of conditions that underline the unsuitability of HbA_{1c} on its own as a surrogate glycaemic marker. Whilst no laboratory test is ideal for everyone, HbA_{1c} 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 HbA_{1c} as a surrogate marker of blood glucose, and its pitfalls.

Conflict of interest SEM, SM, JW, KDG, RRL, CW, AB, RAR, IMS, AK, GVG, GAR and SG have no conflicts of interest to declare in relation to this paper. RT has received lecture fees from Lilly, Janssen and Novartis and is author of the book 'Life Without Diabetes'. RPR has received consultation and/or lecture fees or unrestricted travel grants from Novo Nordisk, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Takeda, NAPP and Abbott Diabetes. JAW is an employee of Eisai Inc. Eisai Inc had no role in study design or funding.

Funding The DTRG acknowledges support from the GA Roberts Research Fund and University Hospitals Birmingham Charity. AK acknowledges support from the UK Medical Research Council (MRC grant MR/S003991/1; GVG acknowledges support from the NIHR Birmingham ECMC, NIHR Birmingham SRMRC, Nanocommons H2020-EU (731032), MAESTRIA (Grant agreement ID 965286), HYPERMARKER (Grant agreement ID 101095480), PARC (Grant Agreement No 101057014) and the MRC Heath Data Research UK (HDRUK/CFC/01), an initiative funded by UK Research and Innovation, Department of Health and Social Care (England) and the devolved administrations, and leading medical research charities. The funding organisations had no role in the design of this study, data collection, analysis or interpretation, or preparation of the manuscript, and did not approve or disapprove of, or delay, publication of the work.

Acknowledgements Drs Susan Manley and Andreas Karwath attended the Clinical Advisory Committee Meeting of the National Glycohemoglobin Standardization Program in New Orleans in 2023, as did Dr Sandip Ghosh in 2018.

Dr Susan Manley is a member of the Joint British Diabetes Societies Inpatient Committee and the National Advisory Panel for Care Home Diabetes.

Dr Jonathan Webber is a Consultant Diabetologist based in Birmingham.

Dr Kavitha Ganapathy is a specialty registrar in Diabetes and Endocrine, West Midlands.

Professor Roy Taylor is Emeritus Professor of Medicine and Metabolism, previous Honorary Consultant Physician to Newcastle Hospitals NHS Foundation Trust, with special interest in adult diabetes and pregnancy diabetes. He was a member of the International Consensus Group on Remission of Type 2 Diabetes.

Dr Randie Little is a Research Professor at the University of Missouri School of Medicine and is the network coordinator for the National Glycated Hemoglobin Standardization Program (NGSP).

Craig Webster is a consultant clinical scientist at University Hospitals Birmingham NHS Foundation Trust.

Alison Barratt is a freelance graphic designer, illustrator and lecturer.

Irene Stratton is a member of the Diabetes UK Acute Care Study Group.

Professor Georgios Gkoutos is the director of the Health Data Science Centre, associate Director of Health Data Research UK Midlands and member of the Diabetes UK Acute Care Study Group.

Dr Sandip Ghosh is a consultant endocrinologist in the UAE, founder member of DTRG, University Hospitals Birmingham and has attended Joint British Diabetes Societies inpatient meetings.

The authors are grateful for support and encouragement from Janet Smith, previously head of Clinical Biochemistry, University Hospitals Birmingham NHS Foundation Trust, and the laboratory for the Birmingham UKPDS centre.

References

1. ElSayed NA, Aleppo G, Aroda VR, *et al*; on behalf of the American Diabetes Association; 2. Classification and diagnosis of diabetes: standards of care in diabetes—2023. *Diabetes Care* 2023;**46**(Suppl 1):S19–S40. https://doi.org/10.2337/dc23-S002
2. Sacks DB, Arnold M, Bakris GL, *et al*. Executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2023;**69**(8):777-84. https://doi.org/10.1093/clinchem/hvad079
3. Riddle MC, Cefalu WT, Evans PH, *et al*. Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetes Care* 2021;**44**(10):2438-44. https://doi.org/10.2337/dci21-0034
4. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**(14):977-86. https://doi.org/10.1056/NEJM199309303291401
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**(9131):837-53. https://doi.org/10.1016/S0140-6736(98)07019-6
6. Stratton IM, Adler AI, Neil HAW, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**:405-12. https://doi.org/10.1136/bmj.321.7258.405
7. Rohlfing CL, Wiedmeyer H-M, Little RR, *et al*. Defining the relationship between plasma glucose and HbA_{1c}: analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial.

Diabetes Care 2002;**25**(2):275–8. https://doi.org/10.2337/diacare.25.2.275
8. National Glycohemoglobin Standardization Program. Certified methods and laboratories. Updated 11/23. https://ngsp.org/certified.asp
9. Manley S, John WG, Marshall S. Introduction of IFCC reference method for calibration of HbA_{1c}: implications for clinical care. *Diabet Med* 2004;**21**(7):673-6. https://doi.org/10.1111/j.1464-5491. 2004.01311.x
10. https://www.diabetes.org.uk/professionals/position-statements-reports/diagnosis-ongoing-management-monitoring/new_diagnostic_criteria_for_diabetes
11. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;**32**(7):1327–34. https://doi.org/10.2337/dc09-9033
12. Dowd RP, Manning PW, Ahmed N, *et al*. Post introduction of HbA_{1c} as a diagnostic test: consequences for requesting and reporting. *Diabet Med* 2015;**32**(Suppl 1):163(P440)
13. Gough S, Manley S, Stratton I (eds). HbA_{1c} in diabetes: case studies using IFCC units Wiley Blackwell 2010. ISBN: 9781444334449
14. Manley S, Nightingale P, Stratton I, *et al*. Diagnosis of diabetes: HbA_{1c} versus WHO criteria. *Diabetes Primary Care* 2010;**12**(2):87–96
15. James J, Kong M-F, Berrington R, Dhatariya K. Diabetes at the front door. A guideline from the Joint British Diabetes Society (JBDS) for Inpatient Care Group. JBDS 16. https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group
16. Manley SE, Karwath A, Williams JA, *et al.* on behalf of the Diabetes Translational Research Group (DTRG), Queen Elizabeth Hospital Birmingham and Birmingham University. The use of HbA_{1c} for new diagnosis of diabetes in those with hyperglycaemia on admission to or attendance at hospital urgently requires research. *Br J Diabetes* 2022;**22**(2):95-104. https://doi.org/10.15277/bjd.2022.386
17. Dowd RP, Round RA, Mason CL, *et al*. Review of HbA_{1c} results >120 mmol/mol as patients may require urgent assessment if request for diagnosis of type 2 diabetes. *Diabet Med* 2014;**31**(Suppl 1):P466
18. Dowd RP, Round RA Mason CL, *et al*. Hyperglycaemia and diabetic ketoacidosis in patients presenting to hospital with HbA1c >13.1%/120 mmol/mol but no previous diagnosis of diabetes. *Diabetes* 2014;**63**(Suppl 1):A634 (2501-PO)
19. Sperling M, Bhowansingh R. Chorea hyperglycemia basal ganglia syndrome in a 63-year-old male. *Case Reports in Medicine* 2018, Article ID 9101207. https://doi.org/10.1155/2018/9101207
20. Ganapathy K, Palani R, Manley S, *et al*. Rare presentation of hyperglycaemia related ballistic movement. *Dubai Diabetes Endocrinol J* 2021;**27**:104. https://doi.org/10.1159/000518884
21. Bhattacharjee D, Vracar S, Round RA, *et al*. Utility of HbA_{1c} assessment in people with diabetes awaiting liver transplantation. *Diabet Med* 2019;**36**(11):1444-52. https://doi.org/10.1111/dme.13870
22. Flamini M (2022). A holistic overview of hemoglobinopathies interactions with glycated hemoglobin. https://www.mlo-online.com/disease/diabetes/article/21276454/a-holistic-overview-of-hemoglobinopathies-interactions-with-glycated-hemoglobin, accessed March 12, 2023
23. Ghosh S, Manley SE, Nightingale PG, *et al*. Prevalence of admission plasma glucose in 'diabetes' or 'at risk' ranges in hospital emergencies with no prior diagnosis of diabetes by gender, age and ethnicity. *Endocrinol Diab Metab* 2020;**3**(3):e00140. https://doi.org/10.1002/edm2.140
24. Piso RJ, Walter P, Rudofsky G. False low HbA_{1c} levels under treatment with ribavirin. *J Clin Microbiol Lab Med* 2018:JCMLM-101. https://doi.org/10.29011/JCMLM-101. 100001
25. Carr J, Nightingale P, Round R, *et al*. Dapsone effects the accuracy of HbA1c measurements and can have implications for monitoring glycaemic control or diagnosis of diabetes. *Br J Dermatol* 2016; **175**(Suppl S1):75(P111). https://doi.org/10.1111/bjd.14524
26. Shah AD, Fox RK, Rushakoff RJ. Falsely decreased HbA_{1c} in a type 2 diabetic patient treated with dapsone. *Endocr Pract* 2014; **20**(11):229-32. https://doi.org/10.4158/EP14291.CR
27. Kadri F, Stuart K, Cramb R, *et al*. HbA_{1c} interpretation and its caveats: a case of targeting apparently good glycaemic control causing severe hypoglycaemia. Abstract: 0550-P. International Diabetes Federation (IDF) meeting Vancouver, December 2015
28. Mostafa S, Webber J, Ganapathy K, *et al*. Complex presentations in people with diabetes: does HbA_{1c} help or hinder. *Diabet Med* 2023;**40**(Suppl 1):P153. https://doi.org/10.1111/dme.15048
29. Morgan LJ, Syed AA, Carr-Smith J, *et al*. The relationship between HbA_{1c} and fructosamine in patients with diabetes and sickle cell or haemoglobin D trait. Poster presented at the National Meeting of the Association for Clinical Biochemistry, Birmingham, 2008. Personal communication.
30. Use of glycated haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation © World Health Organization 2011. PMID: 26158184
31. Manley SE, Susarla R, Round RA, *et al*. 1312-P: Admission plasma glucose and HbA_{1c} in emergency hospital admissions by ethnicity. *Diabetes* 2019;**68**(Suppl 1):1312-P. https://doi.org/10.2337/db19-1312-P
32. Razi F, Khashayar P, Ghodssi-Ghassemabadi R, *et al*. Optimal glycated hemoglobin cutoff point for diagnosis of type 2 diabetes in Iranian adults. *Can J Diabetes* 2018;**42**(6):582-7. https://doi.org/10.1016/j.jcjd.2018.03.005
33. Williams JA, Karwath A, Round RA, *et al*. 133-LB: Relationship of HbA_{1c} and glucose by ethnicity in UK Biobank. Diabetes 2022; **71**(Suppl 1):133-LB. https://doi.org/10.2337/db22-133-LB
34. Costa FF, Rosário WR, Ribeiro Farias AC, *et al*. Metabolic syndrome and COVID-19: an update on the associated comorbidities and proposed therapies. *Diabetes Metab Syndr* 2020;**14**(5):809-14. https://doi.org/10.1016/j.dsx.2020.06.016
35. Reddy PK, Kuchay MS, Mehta Y, Mishra SK. Diabetic ketoacidosis precipitated by COVID-19: a report of two cases and review of literature. *Diabetes Metab Syndr* 2020;**14**(5):1459-62. https://doi.org/10.1016/j.dsx.2020.07.050
36. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period (NICE Guideline [NG3]). Published: 25 February 2015
37. Nielsen LR, Ekbom P, Damm P, *et al*. HbA_{1c} levels are significantly lower in early and late pregnancy. *Diabetes Care* 2004;**27**(5):1200-1. https://doi.org/10.2337/diacare.27.5.1200
38. Taylor R, Lee C, Kyne-Grzebalski D *et al.* Clinical outcomes of pregnancy in women with type 1 diabetes. *Obstet Gynecol* 2002;**99**(4):537-41. https://doi.org/10.1016/s0029-7844(01)01790-2
39. Carron Brown S, Kyne-Grzebalski D, Mwangi B, Taylor R. Effect of management policy upon 120 type 1 diabetic pregnancies: policy decisions in practice. *Diabet Med* 1999;**16**(7):573-8. https://doi.org/10.1046/j.1464-5491.1999.00124.x
40. Battelino T, Danne T, Bergenstal RM, *et al*. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019;**42**(8):1593 603. https://doi.org/10.2337/dci19-0028
41. Diabetes in pregnancy: management from preconception to the postnatal period (NICE Guideline [NG3]). Published: 25 February 2015 Last updated: 16 December 2020
42. Royal College of Obstetricians and Gynaecologists. Guidance for maternal medicine in the evolving coronavirus (COVID-19) pandemic. Information for healthcare professionals. Version 1: Published Monday 30 March 2020. London: RCOG, 2020
43. Keating N, Carpenter K, McCarthy K, *et al*. Clinical outcomes following a change in gestational diabetes mellitus diagnostic criteria due to the COVID-19 pandemic: a case-control study. *Int J Environ Res Public Health* 2022;**19**(3):1884. https://doi.org/10.3390/ijerph19031884
44. Curtis AM, Farmer AJ, Roberts NW, Armitage LC. Performance of guidelines for the screening and diagnosis of gestational diabetes mellitus during the COVID-19 pandemic: a scoping review of the guidelines and diagnostic studies evaluating the recommended testing strategies. *Diabet Epidemiol Manag* 2021;**3**:100023.

https://doi.org/10.1016/j.deman.2021.100023
45. Steven S, Hollingsworth KG, Al-Mrabeh A, *et al*. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiologic changes in responders and nonresponders. *Diabetes Care* 2016;**39**(5):808-15. https://doi.org/10.2337/dc15-1942
46. Leslie WS, Ford I, Sattar N, *et al*. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. *BMC Fam Pract* 2016;**17**:20. https://doi.org/10.1186/s12875-016-0406-2
47. Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). *Br J Diabetes* 2019;**19**(1):73-6. https://doi.org/10.15277/bjd.2019.221
48. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. *J Intern Med* 2021;**289**(6):754–70. http://dx.doi.org/10.1111/joim.13214
49. Lim EL, Hollingsworth KG, Aribisala BS, *et al*. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; **54**(10):2506-14. https://doi.org/10.1007/s00125-011-2204-7
50. Lean MEJ, Leslie WS, Barnes AC, *et al*. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018;**391**(10120):541-51. https://doi.org/10.1016/S0140-6736(17)33102-1
51. Karwath A, Williams JA, Round RA, *et al*. 973-P: By how much does red blood cell status affect the accuracy of HbA_{1c}? *Diabetes* 2022;**71**(Suppl 1):973-P. https://doi.org/10.2337/db22-973-P
52. Tucker LA. Limited agreement between classifications of diabetes and prediabetes resulting from the OGTT, hemoglobin A1c, and fasting glucose tests in 7412 US adults. *J Clin Med* 2020;**9**(7):2207. https://doi.org/10.3390/jcm9072207
53. Chung WK, Erion K, Florez JC, *et al*. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020;**63**:1671-93. https://doi.org/10.1007/s00125-020-05181-w and *Diabetes Care* 2020;**43**:1617-35. https://doi.org/10.2337/dci20-0022
54. Manley SE, Stratton IM, Nightingale PG, *et al*. Increasing knowledge about HbA_{1c} to improve patient outcomes using clinical audit as a research tool. Research symposium advancing precision diabetes medicine. Madrid, Spain 8-9 October 2019. Publication 2
55. Nolan JJ, Kahkoska AR, Semnani-Azad Z, *et al*. ADA/EASD Precision medicine in diabetes initiative: an international perspective and future vision for precision medicine in diabetes. *Diabetes Care* 2022;**45**(2):261-6. https://doi.org/10.2337/dc21-2216
56. Thornton-Swan TD, Armitage LC, Curtis AM, Farmer AJ. Assessment of glycaemic status in adult hospital patients for the detection of undiagnosed diabetes mellitus: a systematic review. *Diabet Med* 2022;**39**(4):e14777. https://doi.org/10.1111/dme.14777
57. Farmer AJ, Shine B, Armitage LC, *et al*. The potential for utilising in-hospital glucose measurements to detect individuals at high risk of previously undiagnosed diabetes: retrospective cohort study. *Diabet Med* 2022;**39**(10):e14918. https://doi.org/10.1111/dme.14918
58. Diabetes Prevention Programme 2018-19, Short Report. NHS Digital, Part of National Diabetes Audit. Publication Date: 13 Dec 2019.