The use of HbA_{1c} for new diagnosis of diabetes in those with hyperglycaemia on admission to or attendance at hospital urgently requires research

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Abstract

The prevalence of diabetes in Birmingham is 11% but it is 22% in hospital inpatients. Queen Elizabeth Hospital in Birmingham (QEHB) serves a multi-ethnic population with 6% Afro-Caribbean, 19% South Asian and 70% White European.

A clinical audit of 18,965 emergency admissions to QEHB showed that 5% were undiagnosed but had admission glucose in the 'diabetes' range and 16% were in the 'at risk' range. The proportion of Afro-Caribbeans (7%) and South Asians (8%) in the 'diabetes' range was higher than White Europeans (5%). Given the magnitude of the problem, this paper explores the issues concerning the use of reflex HbA_{1c} testing in the UK for diagnosis of diabetes in hospital admissions. HbA_{1c} testing is suitable for most patients but conditions affecting red blood cell turnover invalidate the results in a small number of people.

However, there are pertinent questions relating to the introduction of such testing in the NHS on a routine basis. Literature searches on a topical question '*Is hyperglycaemia identified during emergency admission/attendance acted upon?*', were performed from 2016 to 2021 and 2016 to 2022.

They identified 21 different, relevant, research papers - 5 from Australia, 9 from Europe including 4 from the UK, 5 from America and 1 each from Canada and Africa. These papers revealed an absence of established procedures for the management and follow-up of routinely detected hyperglycaemia using HbA_{1c} when no previous diabetes diagnosis was recorded.

Further work is required to determine the role of reflex HbA_{1c} testing for diagnosis of diabetes in admissions with hyperglycaemia, and the cost-effectiveness and role of point-of-care HbA_{1c} testing.

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Introduction

The in-hospital prevalence of known diabetes in Birmingham is 22%, with the local population prevalence 11%.[1] Over and above this, acute illnesses can cause stress- induced hyperglycaemia, which is associated with increased mortality in medical and surgical

patients.[2] Although stress induced hyperglycaemia does usually resolve, up to 60% of patients with stress hyperglycaemia may have a diagnosis of diabetes based on stepwise testing as per American Diabetes Association (ADA) criteria.[3]

Inpatient mortality is nine times greater in the short term for patients with newly diagnosed hyperglycaemia than normoglycaemia, and five times more than for diabetes. Mortality for those with de novo hyperglycaemia is 16% compared to 3% if diabetes is already diagnosed and 2% in those with normoglycaemia.[4]

An audit was undertaken locally in Queen Elizabeth Hospital Birmingham (QEHB), a large university hospital and major trauma centre in the West Midlands serving a multi-ethnic population. It recorded >30,000 admission plasma glucose results with glucose measured on capillary blood using point-of-care glucose meters (75%), blood gas machines on arterial/venous whole blood (18%) and in the laboratory on blood collected into fluoride oxalate vacutainers (7%) with all the glucose results reported as plasma. High blood glucose on admission to hospital in those without diabetes was common. Routine random blood glucose measurement on admission identified glucose in the 'diabetes' range (>11.0 mmol/L) in 5% of 18,965 emergency hospital admissions between 2014 and 2015,[5] and 16% in the 'at risk' range (7.8 to 11.0 mmol/L) in those without a prior diabetes diagnosis. More South Asians and Afro-Caribbeans were in the 'diabetes' range at 8% compared with 5% for White Europeans. The South Asian and Afro-Caribbean admissions were younger than White Europeans.

Ensuring that undiagnosed diabetes is identified in patients admitted to hospital is important, especially as hyperglycaemia observed in emergency admissions to hospital in those not previously diagnosed with diabetes may not be subject to further investigation,[6] or followed up, as indicated in a recent literature review.[7]

The UK National Service Framework for Diabetes: Standards 2001 aims '*to ensure that people with diabetes are identified as early as possible*' and states that '*the NHS will develop, implement, and monitor strategies to identify people who do not know they have diabetes*'.[8]

A report on the prospective measurement of HbA_{1c} in the acute setting published in 2016 provided evidence on the use of HbA_{1c} testing in hospital to identify those with undiagnosed diabetes.[9]

The ADA (2021) and Joint British Diabetes Societies (JBDS) (2020) have suggested HbA_{1c} testing to confirm diabetes in hospital admissions when random plasma glucose ≥7.8 mmol/L.[10,11]

However, in-hospital studies[5,7,12] illustrate the complexity of decision making when the diagnosis of diabetes is based on a surrogate glycaemic marker and such testing is still not employed universally[7,12] nor adopted systematically in the UK.

Literature searches were performed in January 2021 and October 2022. Their aim was to locate papers on established procedures to identify people with no known history of diabetes who attended or were admitted to hospital via the emergency department and were found to have hyperglycaemia, and on their follow-up in the community.

Methods

Scoping literature searches of papers published from 2016 up to January 2021 and 24th October 2022 were performed. They were set up to identify articles if the keywords or phrases appeared in either the title or abstract. The Healthcare Databases Advanced Search (HDAS) interface was used for the first search and the second was performed using the OVID interface as the HDAS resource was no longer available. PubMed, MEDLINE and Embase databases, Table 1, were used to answer the question – '*Is hyperglycaemia identified during emergency admission/attendance acted upon?*'. Date limits were set for the MEDLINE and Embase searches, with those listed by PubMed as published prior to 2016 excluded. The research assistant screened the resulting papers for eligibility from the title and abstract. The search terms used are outlined in Table 1; they did not distinguish between attendance at the emergency

Table 1 Literature searches from 2016 to 2021 & 2016 to 2022

Database	PubMed[a]	MEDLINE 1[b]	MEDLINE 2[c]	MEDLINE[d]	Embase[d]
Native interface	HDAS	HDAS	HDAS	OVID	OVID
Timescale	NA	2016-Jan 2021	2016-Jan 2021	2016-24 Oct 2022	2016-24 Oct 2022
Papers	328	105	55	23	59
Relevant papers	8	5	3	9	13
In total*		**12**		**9**	

[a, b, c, d] See below for details of search terms; *after exclusion of duplicates, letters and conference abstracts

2016-2021

a "Emergency Department" OR "Emergency Room" OR "Accident and Emergency Department" OR "Emergency medicine" AND "hyperglycaemia"

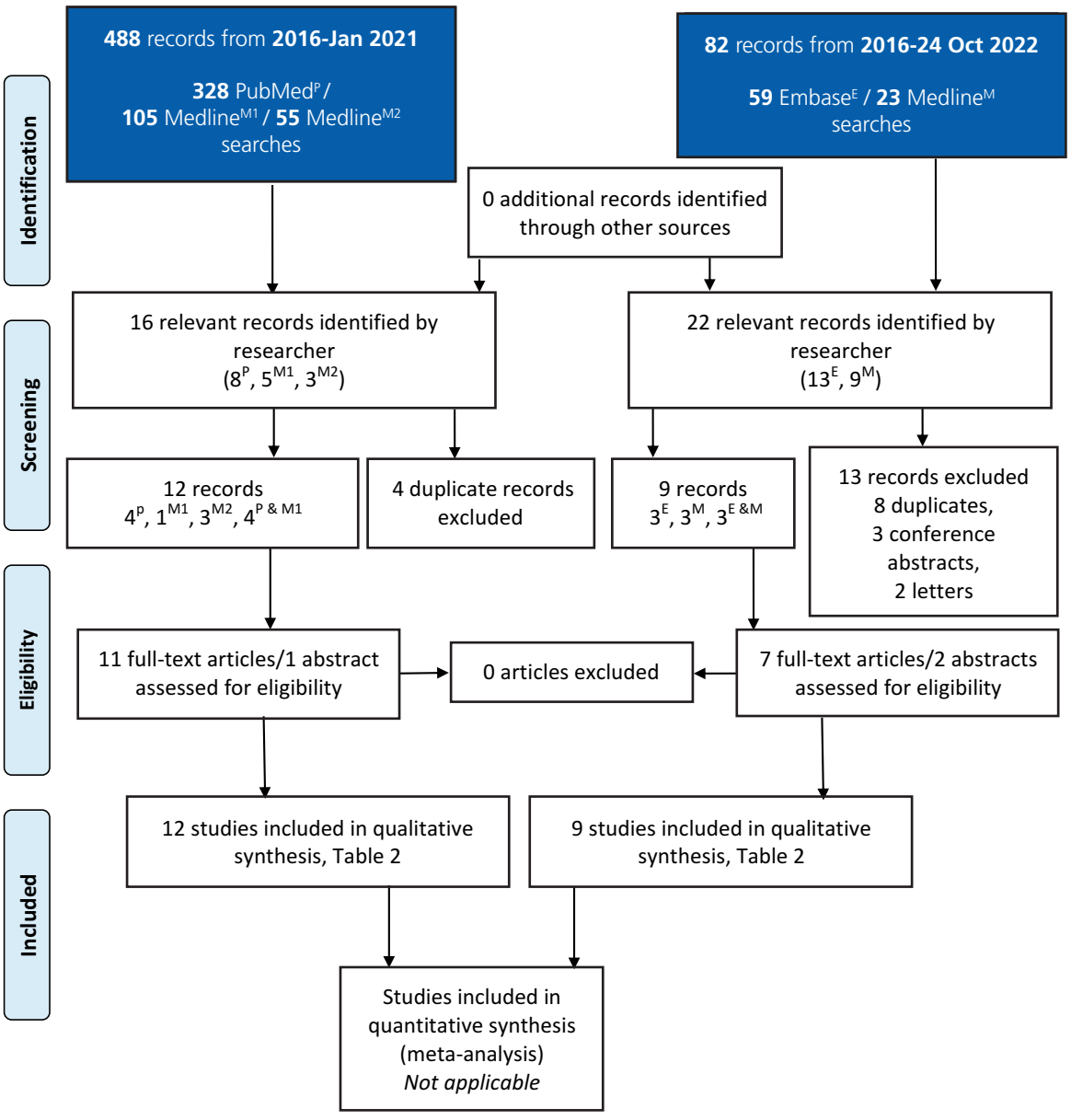
b "Emergency Department" OR "Emergency Room" OR "Accident and Emergency Department" OR "Emergency medicine" OR "hospitalisation" OR "hospital admission" AND "hyperglycaemia" OR "glycated haemoglobin" OR "glycated haemoglobin A" OR "unrecognised diabetes"

c "Blood glucose" OR "glycated haemoglobin A" AND "undiagnosed diabetes"

2016-2022

d "Emergency Department" OR "Emergency Room" OR "Accident and Emergency Department" OR "Emergency Medicine" OR "hospitalisation" OR "hospitalisation" OR "hospital admission" OR "hospital attendance" AND "hyperglycaemia" OR "hyperglycemia" OR "glycated haemoglobin" OR "glycated haemoglobin" OR "glycated haemoglobin A" OR "glycated hemoglobin A" OR "HbA_{1c}" OR "haemoglobin A1c" OR "hemoglobin A1c" AND "undiagnosed diabetes" OR "unrecognised diabetes"

Figure 1. PRISMA 2009 flow diagram for systematic review on '*Is hyperglycaemia identified during emergency admission/ attendance acted upon?*'



department alone versus admission to hospital. The numbers of papers identified in the searches are outlined in Figure 1, prepared according to PRISMA 2009 guidance.[13,14]

Results of literature searches

PubMed identified 328 papers, MEDLINE 105, 55 and 23 papers, and Embase 59 papers overall for the searches (Table 1 and Figure 1). From these 570 papers, 21 relevant records were followed up after duplicate papers, conference abstracts and letters were excluded.[5-7,9,15-30] Full text was available for 18 papers with abstracts for three entries. The relevant, research papers were from Europe (9, including 4 from the UK), Australia (5), America (5), Canada (1) and East Africa (1). The paper referred to in the introduction published by this translational research group in 2016 was listed in the second search,[9] as was the systematic review from the UK published in December 2021 by Thornton-Swan *et al*.[7] Of the twelve relevant papers identified in their systematic review performed using PubMed and Embase, seven papers were published before 2016 when the searches reported here were started. Of the remaining five papers in the systematic review, three were identified in these searches (Table 2).

Ten papers reported on studies with fewer than 1,000 participants, four between 1,000 and 6,000 participants, four between 10,000 and 20,000 participants and two with more

Table 2 Papers identified in literature searches on 'Is hyperglycaemia identified during emergency admission/attendance acted upon?' from 2016 to 2022 (* 2016-2021; † 2016-2022; ‡ also in systematic review[7])

Papers	Author, journal, doi and country	Aims	Patient group	Key results	Conclusions	Study weaknesses
1†	15. Farmer AJ *et al*. *Diabet Med* 2022; **39**(10):e14918. https://doi.org/10.1111/dme.14918 UK	To assess the potential of using in-hospital glucose measurements to identify those with undiagnosed diabetes.	Adults. Participants had to be registered with a GP that used the trust laboratory and had some tests requested by GP since 2008.	764,241 glucose measurements for 81,763 individuals. 70.7% White Caucasian, 3.1% Asian, 1.1% Black background, 23.1% unstated. 27.4% no previous HbA_{1c}. 2.5% had a diabetes-range HbA_{1c}. Estimated 2.2% may have undiagnosed diabetes.	The number of people to be tested to identify one individual who may have diabetes decreases as the maximum in-hospital glucose concentration threshold increases. There was a lack of follow-up for those with hyperglycaemia and no previous HbA_{1c} in the diabetes range.	Study was conducted at a single centre. Interval between the random glucose and HbA_{1c} measurement varied. May be systematic bias in the population receiving an HbA_{1c}. HbA_{1c} has limitations as a diagnostic test.
2†	7. Thornton-Swan *et al*. *Diabet Med* 2022; **39**(1):e14777. https://doi.org/10.1111/dme.14777 Systematic Review UK	To ascertain the extent to which random plasma glucose in acute and inpatient hospital settings predicts undiagnosed diabetes.	Patients >18 years (yrs). No pre-existing diagnosis of diabetes. Initial admission to a surgical/medical ward or attendance at emergency department (ED). Admission not due to diabetes, acute coronary syndrome or stroke. Patient not in intensive care. Patient not pregnant.	PubMed and Embase search from database inception to 11.01.2021. Search returned 3,326 citations, 3,245 after duplicates were removed. 62 studies were selected for full text review. 12 met the inclusion criteria.	All studies identified some participants with hyperglycaemia who had a diabetes-range HbA_{1c}, indicating that in-hospital blood glucose screening can facilitate diabetes diagnosis.	Some studies included which did not fully meet the inclusion criteria. Studies using a diagnostic test for diabetes other that HbA_{1c} were excluded.
3†	16. Lapic *et al*. *Biochem Med* 2022; **32**(1):010903. https://doi.org/10.11613/BM.2022.010903 Croatia	To perform HbA_{1c} based screening to estimate the prevalence of prediabetes and undiagnosed diabetes according to ADA criteria.	n=5,527. A multi-centre, cross-sectional study performed in 6 hospitals from January to July 2021. Patients aged 40 to 70 yrs admitted to ED or undergoing a primary care check-up.	435 patients with known diabetes were excluded. 882 (17.3%) patients had HbA_{1c} values in the prediabetes range. 214 (4.2%) patients had HbA_{1c} values in the diabetes range.	Impairment of glucose metabolism was identified in approximately one in five adults. A significant number of patients already had overt diabetes. These results indicate further steps should be taken to promote preventive measures for diabetes.	Diagnosis of prediabetes or diabetes was based on a single HbA_{1c} result. The period of enrolment may have influenced the spectrum of emergencies and therefore possibly enhanced patient selection bias.
4†	17. Mendez CE *et al*. *Endocr Pract* 2021; **27**(8):807-12. https://doi.org/10.1016/j.eprac.2021.04.003 USA	To assess the value of a validated diabetes risk test (the Cambridge Risk Score (CRS)) to identify patients admitted to hospital without diabetes at risk of new hyperglycaemia.	Adults admitted to hospital over a 4-year period. Patients had no diabetes diagnosis and were not on antidiabetics. n=19,830.	The CRS and HbA_{1c} levels were significantly associated with the risk of developing new hyperglycaemia in inpatient adults without diabetes.	The CRS could be useful for early identification and management of hyperglycaemia, leading to better outcomes.	Unable to assess – abstract only available.
5†	12. Rkieh L *et al*. *Can J Diabetes* 2021; **45**(7):629-33. https://doi.org/10.1016/j.jcjd.2021.01.002 Canada	To determine the prevalence of probable undiagnosed diabetes in hospitalized medicine patients. Also to identify the prevalence of undiagnosed prediabetes and subsequent management of these cases.	Adults admitted to internal medicine over a 3 month period were screened for diabetes using an A1c test. n=53.	The prevalence of undiagnosed diabetes was 7.5% (n=4). The prevalence of undiagnosed dysglycaemia was 30.2% (n=16). Implementation of diabetes management strategies/documentation of the finding occurred in 4 of 16 patients.	A broader screening approach may capture more cases of undiagnosed diabetes that do not belong to the traditionally at-risk populations. Future studies should focus on identifying risk factors including ethnicity and barriers to access so that appropriate screening programs can be developed.	Unable to assess – abstract only available.
6†	5. Ghosh *et al*. *Endocrinol Diabetes Metab* 2020; **3**(3):e00140. https://doi.org/10.1002/edm2.140 UK	To establish the prevalence of admission plasma glucose in 'diabetes' and 'at risk' ranges in emergency hospital admissions.	Adult hospital admissions over a one-year period. Data presented for 18,965 people with no prior diabetes diagnosis and glucose available on first attendance.	75% White Europeans, 12% South Asians, 9% Unknown/Other, 4% Afro-Caribbean. Overall 5% had glucose in the 'diabetes' range with 16% in the 'at risk' range. Glucose increased with age and was more often in the 'diabetes range' for South Asians.	Hyperglycaemia was evident in 21% of adults admitted as an emergency. South Asian men were particularly affected. Aspects relating to follow-up and ethnicity should be considered when addressing undiagnosed diabetes in hospital admissions.	Audit is limited by the length of time the various ethnic groups have resided in the area.
7*	6. Levi OU *et al*. *Int J Environ Res Public Health* 2020;**17**(3):980. https://doi.org/10.3390/ijerph17030980	To determine proportion of patients >60 yrs admitted with a diabetes diagnosis or diagnosed during admission.	>60 yrs, n=875 Males n=449.	Low diabetes diagnosis rate in ED suggests many patients with diabetes remain undiagnosed by current practice. Clinically important HbA_{1c}	Missed opportunity. Potential medico-legal liability of diagnosing without ensuring follow-up.	Study relied on accurate clinical coding.

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Papers	Author, journal, doi and country	Aims	Patient group	Key results	Conclusions	Study weaknesses
	Australia	Follow-up requests on discharge regarding diabetes management.		results were rarely communicated to GPs.		
8*‡	18. Seneviratne Epa D *et al*. I*ntern Med J* 2020; **50**(11):1397-1403. https://doi.org/10.1111/imj.14720 Australia	To determine prevalence of unrecognised diabetes in all patients screened in ED. Extent of HbA_{1c} testing, monitoring, treatment and documented follow-up.	>18 yrs. n=200 (randomly selected) hyperglycaemic patients. No pre-existing diabetes.	High prevalence of hyperglycaemia in ED patients with no diabetes diagnosis. Low rates of further investigation and follow-up.	Hyperglycaemia without a diabetes diagnosis is commonly seen and justifies ED screening. Management of these patients requires improvement.	Relatively small sample number. Retrospective nature of study may lead to unintended bias.
9†	19. Anderson ES *et al*. *Am J Public Health* 2019; **109**(2):270-2. https://doi.org/10.2105/AJPH.2018.304799 USA	To improve the detection of previously undiagnosed diabetes.	Adults aged ≥ 18 yrs presenting at ED who underwent blood testing were eligible for A_{1c} screening. The system automatically cancelled the A_{1c} request if a result was available within the past 75 days.	924 patients were screened over a 3- month period. 28.8% screened positive for undiagnosed diabetes or prediabetes. Of the newly identified patients 54.9% attended follow-up.	Widespread implementation of non-targeted ED diabetes screening in this population using this electronic health record algorithm would identify many people with diabetes or prediabetes. This significant opportunity for screening should not be overlooked. 75-day cut off for repeat A_{1c} testing may be overly inclusive leading to capacity issues.	The A_{1c} test has limitations in patients with certain comorbidities. Not all eligible patients were screened.
10†‡	20. Karakonstantis S *et al*. *Rom J Intern Med* 2019; **57**(4):315-21. https://doi.org/10.2478/rjim-2019-0015 Greece	To evaluate a screening protocol based on HbA_{1c} to identify inpatients with undiagnosed diabetes in an internal medicine department.	All admissions to the internal medicine department of a 412-bed community hospital during a 6 month period. n=463. Patients with conditions that may interfere with HbA_{1c} measurement or interpretation were excluded.	After applying strict inclusion/exclusion criteria 55 patients were screened. 7 (12.7%) had undiagnosed diabetes. 37 (67.3%) had prediabetes.	In this study most patients were elderly and many ineligible for screening. In situations such as this untargeted screening with HbA_{1c} is unlikely to be cost-effective.	The number of patients screened was small. This was a single centre study. Patients were not followed up after discharge. The study was stopped early as interim analysis indicated systematic screening of patients in this department was unlikely to be cost-effective.
11*†	21. Cheung NW *et al*. *Med J Aust* 2019; **211**(10):454-9. https://doi.org/10.5694/mja2.50394 Australia	To determine whether routine blood glucose assessment of patients admitted from ED results in higher rate of new diagnosis of diabetes and documentation of follow-up plans.	>18 yrs admitted from ED (if sufficient blood available). n=784. Intervention – Blood glucose ≥14 mmol/L – HbA_{1c} automatically requested. Control – Blood glucose measured but HbA_{1c} not automatically requested.	Routine blood glucose testing of patients admitted from ED resulted in 31% with newly detected hyperglycaemia being diagnosed with diabetes. Adding HbA_{1c} automatically did not lead to more diagnoses or significantly affect patient outcomes.	Blood glucose and HbA_{1c} screening alone does not improve diabetes detection or care for patients admitted from ED. Adequate resourcing and effective management pathways are also needed. Poor communication between hospital and GPs contributes to lack of follow-up.	No data on baseline diabetes detection rates for comparison. Unable to obtain paper records of 18% of patients with hyperglycaemia and therefore unable to ascertain diabetes status.
12*	22. Hertz JT *et al*. *Ethn Dis* 2019; **29**(4):559-66. https://doi.org/10.18865/ed.29.4.559 Tanzania	To determine the prevalence of uncontrolled hypertension and diabetes among ED patients.	Adults. All patients presenting at ED n=3,961. Patients with diabetes n=518 (male n=236). Patients with uncontrolled diabetes n=253.	Prevalence of diabetes among ED patients was high. 45% of patients did not have random blood glucose recorded and it was therefore assumed to be normal.	Diabetes was prevalent among adult patients in an ED in northern Tanzania, and complications of poorly controlled diabetes were a common reason for inpatient admission. ED may be an opportune location for screening and linkage-to-care interventions to improve identification and control of this disease.	True proportion of patients with diabetes likely underestimated. Evaluation of the accuracy of the diagnosis not possible.
13*	23. Meyerowitz-Katz G *et al*. *Diabetes Res Clin Pract* 2019;**151**:247-51. https://doi.org/10.1016/j.diabres.2019.04.019 Australia	To examine rates of pre-diabetes and diabetes using HbA_{1c} in ED and General Practice (GP).	≥18 yrs. Study of HbA_{1c} measurements in Individuals receiving a blood test in ED or at GP. ED n=55,568. GP n=5,911.	Diabetes prevalence 17.3% in ED n=9,704. Diabetes prevalence 17.4% for GP n=1,027. Pre-diabetes prevalence 30.2% in ED n=16,854. Pre-diabetes prevalence 26.6% for GP n=1,576.	Opportunistic testing in EDs and GP is feasible for identifying patients with diabetes. High rates of diabetes exist in tested patients at ED and in GP. This has implications for diabetes policy and testing practice guidelines.	Unable to assess - Abstract only available.

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14*	24. Crilly CJ *et al*. *Am J Emerg Med* 2018; **36**(11):1975-79. https://doi.org/10.1016/j.ajem.2018.02.027 USA	Can hyperglycaemia be successfully managed in ED Observation Unit as determined by inpatient admission.	≥18 yrs. Blood glucose ≥ 300 mg/dL. Admitted from ED to ED Observation Unit. n=124.	119/124 (96%) had HbA_{1c} test. 112/119 (94%) had HbA_{1c} ≥ 9.0%.	Nearly all patients managed in the ED Observation Unit for hyperglycaemia had an HbA_{1c} ≥9.0%, suggesting unrecognized or poorly controlled chronic diabetes as the basis for hyperglycaemia.	Retrospective chart review. ED Observation Unit in only one centre.
15*	25. Sop J *et al*. *Cureus* 2018; **10**(10):e3390. https://doi.org/10.7759/cureus.3390 USA	To determine whether the patient population admitted to a Clinical Decision Unit (CDU) from ED is at risk for undiagnosed diabetes by analysing fasting blood glucose levels the morning following admission.	>18 yrs. No previous diagnosis of diabetes. n=259 (113 males).	27.8% (72/259) of patients in CDU had a fasting plasma glucose >126 mg/dL and were at risk of diabetes. 21.2% (55/259) were at risk for pre-diabetes.	Obtaining a fasting plasma glucose and HbA_{1c} in patients admitted to CDU from ED who do not have a diagnosis of diabetes would allow for early detection of those with undiagnosed diabetes.	Patients nil by mouth for fasting plasma glucose - not possible to confirm patient adherence. Only 24.7% of patients admitted to CDU had bloods collected on the morning following admission.
16†	9. Manley *et al*. *Diabetes Res Clin Pract* 2016;**115**:106-14. https://doi.org/10.1016/j.diabres.2016.01.023 UK & Ireland	To study hyperglycaemia in acute medical admissions.	White Caucasians aged >18 yrs admitted to a regional hospital over a 2-year period. n=14,432. Comparable data obtained for a group of primary care patients.	The study provides evidence on the use of HbA_{1c} testing to identify those with undiagnosed diabetes.	It highlights the need for local, national and international guidance on additional testing with HbA_{1c} to ensure appropriate treatment plans and follow-up.	Various conditions compromise the accuracy of HbA_{1c}. Only one HbA_{1c} result was available for this study. The ADA has now suggested diagnosis should not be based on a single HbA_{1c} result.
17*‡	26. Hng T-M *et al*. *BMJ Open Diabetes Res Care* 2016;**4**(1):e000191. https://doi.org/10.1136/bmjdrc-2015-000191 Australia	To assess the efficacy of routine HbA_{1c} testing to detect undiagnosed diabetes and pre-diabetes in an ED located in an area of high diabetes prevalence.	Non-pregnant individuals ≥16 yrs who had blood collected in ED. HbA_{1c} automatically measured if random blood glucose ≥5.5 mmol/L (n=1,646). HbA_{1c} available n=1,267.	487/1,267 identified with diabetes. 157/487 were newly diagnosed with diabetes. 347/1,267 identified with pre-diabetes.	HbA_{1c} measurement in ED is an effective and feasible means of finding cases of diabetes and pre-diabetes particularly in an area known to have a high prevalence of diabetes. Approximately one third of patients tested were unaware that they had diabetes. Earlier detection of pre-diabetes provides an opportunity to introduce measures that may prevent progression to diabetes and improve care.	Possibility of coding inaccuracies. Only included patients who had bloods collected. HbA_{1c} not always available.
18*	27. Gomez-Peralta F *et al*. *Int J Emerg Med* 2016; **9**(1):7. https://doi.org/10.1186/s12245-016-0107-6 Spain	To examine whether determination of capillary HbA_{1c} is a reliable method for detecting unknown diabetes and poor glycaemic control in the ED.	>18 yrs. Asked via questionnaire if they have diabetes diagnosis. Excluded if used corticosteroids in previous 2 months. n=187 (males n=101).	32/187 (17.1%) had a known diagnosis of diabetes. 10/187 (5.4%) – prior undiagnosed were revealed using the 2015 ADA criteria for diagnosis of diabetes. Capillary HbA_{1c} detected 11/187 (5.9%) additional cases of unknown diabetes.	Determination of capillary HbA_{1c} in ED is a reliable, fast, and simple system for the screening of unknown or uncontrolled diabetes.	Study only carried out at one institution. Possibility of selection bias.
19*	28. Bar-Dayan Y *et al*. *Int J Clin Pract* 2016; **70**(9):771-4. https://doi.org/10.1111/ijcp.12867 Israel	To measure prevalence of hyperglycaemia in adults with no known history of diabetes presenting at ED and to evaluate how often follow-up of this as an outpatient was recommended.	Patients with random blood glucose ≥140mg/dL and no known history of diabetes. Discharge letter examined for presence of instructions to conduct follow-up.	16,784 patients presented at ED. 402 patients without known diabetes had hyperglycaemia. Only 35/402 patient files contained instructions for follow-up.	Instructions for investigation and follow-up were rare among patients with hyperglycaemia. Medical staff do not perceive random hyperglycaemia as a marker for further evaluation. ED staff should be educated on the importance of hyperglycaemia to ensure follow-up.	Study was conducted at a single site. Random blood glucose has limitations.
20*	29. Pieralli F *et al*. *Intern Emerg Med* 2016; **11**(5):649-56.	To determine the prevalence, in-hospital mortality, and length of	n=1,447.	28.6% (415/1,447) had hyperglycaemia. Hyperglycaemic patients:	HbA_{1c} and clinical history are useful tools to identify subgroups of hyper-	HbA_{1c} is inappropriate in certain conditions.

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Papers	Author, journal, doi and country	Aims	Patient group	Key results	Conclusions	Study weaknesses
	https://doi.org/10.1007/s11739-015-1358-6 Italy	stay in a cohort of hyperglycaemic patients according to 3 classifications (known diabetes, newly discovered diabetes, stress hyperglycaemia) in three Internal Medicine units of a large community hospital.		71.6% had diabetes, 21.2% had stress hyperglycaemia, 7.2% had undiagnosed diabetes.	glycaemia. Identifying previously unknown diabetes has relevant therapeutic implications and represents a great opportunity for prevention of diabetes-related acute and chronic complications.	Lack of follow-up after discharge.
21*†	30. Jones D *et al*. *J Am Osteopath Assoc* 2016;**116**(6):350-7. https://doi.org/10.7556/jaoa.2016.075 USA	To explore the use of HbA_{1c} testing in patients treated for hyperglycaemia in a rural community hospital inpatient setting. The study specifically examined the use of HbA_{1c} tests for patients with hyperglycaemia and no known history of diabetes and whether these patients were more likely than those who did not get the HbA_{1c} test to receive a diagnosis of diabetes on discharge.	All patients >18 yrs with hyperglycaemia at admission over a period of 1 year – excluding pregnancy etc. n=348.	298/348 (85%) had previous diagnosis of diabetes. 50/348 (15%) had no known history of diabetes. 31/50 (62%) of those with no known history of diabetes had HbA_{1c} measured. 17/31 (55%) of those with no known history of diabetes had a discharge diagnosis that included diabetes.	Hospitalized patients with no known history of diabetes and hyperglycaemia are more likely to receive an appropriate diagnosis if HbA_{1c} is measured. Failing to fully use HbA_{1c} tests in the inpatient setting constitutes a missed opportunity to distinguish transient hyperglycaemia from chronic disease. The HbA_{1c} level can elucidate the course of dysglycaemia and trigger mechanisms for timely intervention. The implementation of a hospital protocol whereby hyperglycaemia is recognized and automatically triggers a reflex HbA_{1c} test should become part of normal routines.	Data collected retrospectively. Study conducted at a single site.

than 50,000 participants with the other being the systematic review. The length of the studies and size of the institutions also varied. The weaknesses of the various studies included retrospective design, location at only one hospital site, systematic bias in the population screened, limitations of random blood glucose testing, availability of HbA_{1c} testing, inability to evaluate the accuracy of diagnosis using HbA_{1c}, and coding inaccuracies.

All the papers noted that hyperglycaemia was common in people in emergency departments, but none reported on well established procedures to confirm a diabetes diagnosis or protocols for follow-up. It might be expected that admissions with hyperglycaemia would be more likely to receive an appropriate diabetes diagnosis but there was no consistency in this aspect of patient care. In one paper, it was noted that 'clinically important HbA_{1c} results were rarely communicated to GPs'.[6]

Discussion

At present WHO have only adopted the recommendation to use HbA_{1c} ≥48 mmol/mol (6.5%) for diagnosis of T2DM in the community.[31] For this reason, requests from GPs for an oral glucose tolerance test (OGTT), which are more expensive, are now rare in the UK and only performed for patients in whom HbA_{1c} testing would be inappropriate. More recently, the Diabetes Remission Clinical Trial (DiRECT) has recommended use of HbA_{1c} to define remission of T2DM at least three months after cessation of glucose-lowering pharmacotherapy,[32] with delivery of the study protocol possible now in primary care with appropriate support and training.[33] Thus, whilst HbA_{1c} is now widely used for diagnosis in the UK primary care setting, it is not used consistently in hospital inpatients.

Stress hyperglycaemia may reverse without intervention when the underlying medical cause is resolved. In contrast, hyperglycaemia associated with undiagnosed diabetes is likely to have been present for long enough to affect HbA_{1c}.[9]

Theoretically, HbA_{1c} can thus be used to distinguish between stress hyperglycaemia and chronic disease. Jones *et al* in 2016 conclude that 'the implementation of a hospital protocol whereby hyperglycaemia is recognized and automatically triggers a reflex HbA_{1c} test should become part of normal routines.'[30]

There is a paucity of evidence on how many hospital admissions with glucose in the 'diabetes' range would benefit from additional HbA_{1c} testing to diagnose diabetes. Previous studies have illustrated the issues associated with other measures of glycaemia, such as fasting glucose or OGTT, with the constraints involved in terms of preparation of patients and the time and staffing involved.[7] They highlight the need for appropriate additional testing, the influence of stress hyperglycaemia and the challenges of appropriate follow-up.[6,12]

As the literature searches reveal, HbA_{1c} is used more in American and Australian hospitals for diagnosis but there are major issues with consistency in the definition of hyperglycaemia in clinical practice.[7] Screening for diabetes and pre-diabetes using HbA_{1c} in admissions is recommended when glucose is ≥7.8 mmol/L by ADA standards for medical care,[10] and in JBDS guidance.[11]

The published systematic review[7] concurred with the searches presented here, concluding that more research is required to identify the optimal glucose value for addition of HbA_{1c} to diagnose diabetes in hospital admissions and that standardised protocols are required for routine practice.

There is potential for medico-legal liability if a diagnosis is not made or is made without robust follow-up.[6] As far as measurement is concerned, although the correlation between point-of-care testing (POCT) and laboratory HbA_{1c} testing is high,[34] the ADA does not recommend using POCT devices for diagnosis of diabetes at sites where the required education, training and oversight of performance are not in place.[35]

It is also important to be mindful of drug regimens, ethnicity and comorbidities when requesting HbA_{1c} in hospitalised patients who are more likely to present with multiple comorbidities.

Any medical condition or drug that alters erythrocyte lifespan can potentially affect HbA_{1c}. If the proportion of younger red blood cells is increased, with less exposure of haemoglobin to glucose than normal, HbA_{1c} values are depressed;[36] and similarly (although less often observed) increased if red cell life span is lengthened e.g. in alpha-1-antitrypsin disorder,[36] and some thalassaemias and anaemias.[37,38]

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 White Europeans.[39] 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.[40]

A few hospitals already cancel HbA_{1c} requests electronically when abnormal haemoglobin is present. It should be possible to flag on the patient's record when HbA_{1c} may not be accurate if conditions such as ethnicity,[41] use of certain drugs such as dapsone and ribavirin, and other illnesses that affect red blood cell turnover are present.[42]

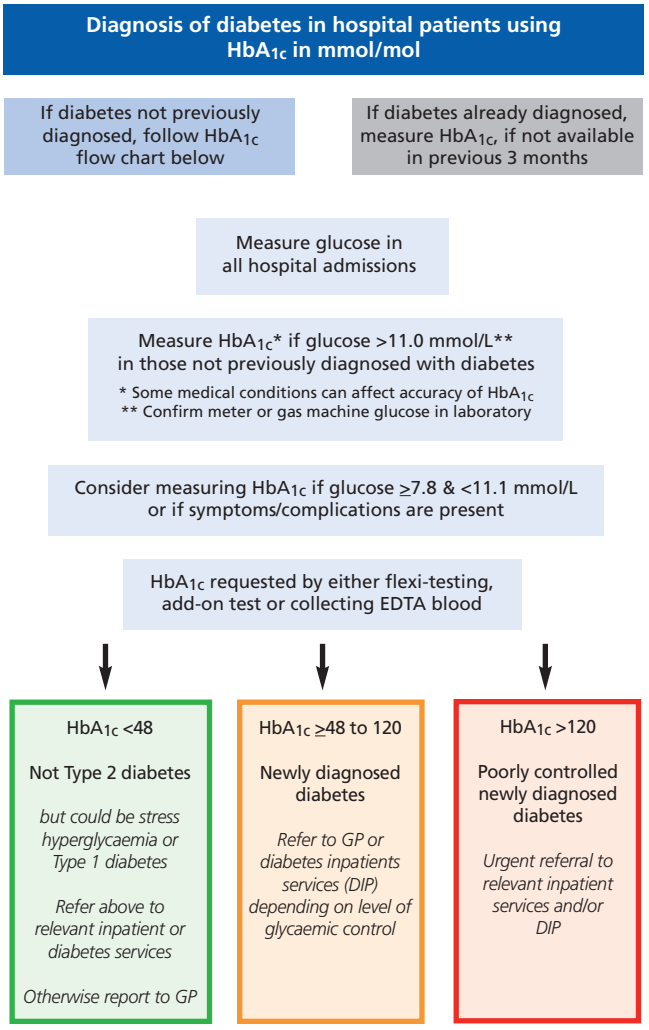
The team of authors (clinicians, clinical and laboratory scientists, statisticians and data visualists) have compiled a list of important questions to be addressed about additional HbA_{1c} testing for diagnostic purposes in a hospital setting (Table 3) and a possible flowchart (Figure 2) based on their experience and expertise.

A possible approach using flexi-testing

A digital approach, involving flexi-testing appropriate inpatients with HbA_{1c} to diagnose diabetes and preliminary algorithms for use in primary and secondary care to detect any inaccuracy, would permit practice of translational and precision medicine (Figure 2). HbA_{1c} can be added automatically when an EDTA sample is available from a full blood count request or an EDTA sample requested for the test.

Flexi-testing requires liaison between the hospital laboratory and electronic patient record system to identify people with admission glucose in the 'diabetes' range who have not previously been diagnosed with diabetes. If this electronic facility is not available, the test can be requested by clinical staff when hyperglycaemia is flagged on the electronic patient record.

Figure 2. Possible pathway for diagnosis of diabetes in hospital patients using HbA_{1c}



Consideration of additional HbA_{1c} testing for those in the 'at risk' range will depend on the prevalence and cost, and negotiation with relevant national clinical bodies. In terms of costing, the consumables for HbA_{1c}, a routine test, are higher than for glucose but the actual cost to the NHS involves the percentage of admissions requiring the test, whether they would be eligible in other diabetes protocols and the actual costing process in hospital for the laboratory and clinical staff input.

It may be possible to consider omitting patients who would be routinely tested elsewhere currently from the calculations on costing e.g. those over 40 years-old who are eligible for HbA_{1c} testing by their GP and those with symptoms or complications of diabetes on admission to hospital. There may be differences to the workload generated in hospitals across the UK as the prevalence of glucose in the 'diabetes' range on admission to hospital is higher in South Asians and Afro-Caribbeans.[5] None of this has been established accurately yet due to lack of prospective data.

Table 3. Issues to consider before the introduction of HbA_{1c} for diagnosis of diabetes in hospital admissions on a routine basis

Issues	Questions
Healthcare delivery	• How many people have capillary/venous glucose measured on admission to hospital and subsequently additional HbA_{1c} testing if glucose in 'diabetes' or 'at risk' ranges? • Could near-patient testing in medical assessment units be advantageous given its shorter turnaround time? • Can HbA_{1c} testing strategies be integrated for people over 40 years-old with diabetes prevention, remission and regular secondary care screening programs?
Epidemiology	• Do more hospital admissions with glucose and HbA_{1c} in the 'diabetes' range present at a younger age or with complications of diabetes, for example retinopathy, than in the community? • When, and by how much, is HbA_{1c} compromised relative to venous/plasma glucose if patients have multiple comorbidities or are treated with certain drugs that affect red blood cell turnover? • Does using HbA_{1c} routinely identify the same group of hospital admissions with diabetes as repeat glucose testing or OGTT? • How many missed diabetes diagnoses would additional HbA_{1c} testing identify?
Health economics	• Could a digital approach be introduced involving flexi-testing with HbA_{1c} in the laboratory and highlighting conditions that may compromise HbA_{1c}? • What are the short and longerterm clinical and economic implications of this HbA_{1c} testing strategy for patient care in hospital and on discharge? • How much would this strategy cost the health service and economy?

In conclusion

The overall message is of a missed opportunity for diabetes diagnosis in hospitals given the high population prevalence,[1] the burden of diabetes related to hospital admissions and consequences resulting from a delayed diagnosis.[43] There is potential for identifying diabetes by additional testing with HbA_{1c} during an acute hospital admission for those with hyperglycaemia but no previous diabetes diagnosis.

Although currently ADA and JBDS advise the addition of HbA_{1c} when glucose ≥7.8 mmol/L, perhaps a more nuanced approach should be offered now as this cut-off is not being followed up systematically in UK hospitals or elsewhere for various reasons. However, there are caveats to widespread HbA_{1c} testing in the UK, and clarity is needed around the exact approach to be adopted.

In future, a digital approach to confirming a diagnosis of diabetes in hospital patients is required with evidence-based standard algorithms and protocols which include flexi-testing with HbA_{1c} derived by research methodology. The overall cost/benefit of this should be obtained from such studies. An expert task force could design a UK-wide, prospective study to arrive at an evidence-based approach to a program for such a digital pathway.

Key messages

- Admission glucose in the 'diabetes' range was present in 5% of emergency admissions to a Birmingham hospital without a prior diabetes diagnosis (7% Afro-Caribbeans, 8% South Asians and 5% White Europeans)
- Literature searches demonstrate a lack of established procedures in hospitals for the management/follow-up of routinely detected inpatient hyperglycaemia
- Additional testing with HbA_{1c} and careful interpretation of results should be considered for diagnostic purposes in this setting
- Guidance should be developed on which patients to target and the methodology for HbA_{1c} analysis e.g. flexi-testing or point-of-care and its interpretation
- Criteria for targeted screening require epidemiological and health economic data for more detailed national and international guidelines

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