Detecting undiagnosed diabetes using glycated haemoglobin: an automated screening test in hospitalised patients

Nyoli A Valentine, Tariq M Alhawassi, Greg W Roberts, Parind P Vora, Stephen N Stranks and Matthew P Doogue

ABSTRACT

Objective: To assess the utility of glycated haemoglobin (HbA_{1c}) level as an automated screening test for undiagnosed diabetes among hospitalised patients and to estimate the prevalence of undiagnosed diabetes among hospitalised patients.

Design, participants and setting: A 3-month prospective study of all adult patients admitted to a tertiary hospital. An HbA_{1c} test was automatically undertaken on admission for all patients with a random plasma glucose (RPG) level ⩾ 5.5 mmol/L. Demographic, admission and biochemical data were obtained from hospital databases. A subset of patients was recruited for an oral glucose tolerance test (OGTT) after discharge.

Main outcome measures: Prevalence of undiagnosed diabetes (defined as HbA_{1c} ⩾ 6.5% in accordance with International Expert Committee and American Diabetes Association recommendations) and utility of automated HbA_{1c} testing.

Results: The prevalence of undiagnosed diabetes was 11% (95% CI, 9.8%–12.4%) (262/2360) during the study period. A further 312 patients with known diabetes were admitted. The prevalence of undiagnosed diabetes was highest in the 65–74-years age group. The HbA_{1c} test cost was $152 per new diagnosis of diabetes. Conservatively assuming an annual incidence of undiagnosed diabetes of 0.8%, the ongoing cost of testing hospitalised patients would be $2100 per new diagnosis of diabetes. RPG testing was not sensitive or specific in diagnosing diabetes. Patients were poorly compliant with the post-discharge OGTT (27% completion rate).

Conclusions: HbA_{1c} is a simple, inexpensive screening test that can be automated using existing clinical blood samples. Hospital screening for diabetes needs to be coupled with resources for management in the community.

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The prevalence of diabetes is 7.4% in Australia.[1] This continues to increase with an annual incidence of 0.8% in adult Australians.[1] Diabetes is associated with excess mortality, major morbidities and substantial use of health care resources.[2] The early phase of diabetes is usually asymptomatic and can remain undetected for many years, with about half of these patients unaware they have the condition.[1,3] Treatment of diabetes, hypertension and dyslipidaemia reduces long-term complications.[3-5] These factors favour early detection of diabetes by screening.[6,7]

The prevalence of diabetes among hospitalised patients is about three times the community prevalence.[1,8,9] Furthermore, hospitalisation is a point of contact with the health care system. However, this opportunity for population screening is not currently recommended because glucose-based tests are confounded by stress hyperglycaemia.[10]

Screening for diabetes by measuring fasting plasma glucose (FPG) and/or using oral glucose tolerance tests (OGTTs) among high-risk individuals has been recommended since 1965.[11] Glycated haemoglobin (HbA_{1c}) testing was recently recommended by the International Expert Committee as the preferred test to diagnose diabetes and this has been adopted by the American Diabetes Association (ADA).[6,12] Diabetes defined by HbA_{1c} level predicts microvascular and macrovascular complications at least as well as diabetes defined by glucose testing.[3,4,13-15] HbA_{1c} testing is familiar to clinicians, as it is routinely used in clinical practice to guide treatment, and is the preferred biochemical marker of diabetes in clinical studies. HbA_{1c} levels are less affected by acute illness than plasma glucose levels, and are therefore more likely to be reliable in the hospital setting.[16] We hypothesised that HbA_{1c} levels could be used as an automated screening test in hospitalised patients for the diagnosis of diabetes.

The primary aims of this study were to estimate the prevalence of undiagnosed diabetes in hospitalised patients, to assess the utility of HbA_{1c} testing to screen hospitalised patients for diabetes, and to define the distribution of HbA_{1c} levels among patients with undiagnosed diabetes. A further aim was to perform indicative cost analysis to explore the hypothesis that HbA_{1c} testing at the time of hospitalisation is a cost-effective method to detect patients with undiagnosed diabetes.

METHODS

Participants and setting

This project was approved by the Flinders Clinical Research Ethics Committee. A prospective, observational study of all adult non-obstetric patients admitted to a tertiary teaching hospital in South Australia from 1 April to 30 June 2009 was conducted. For all patients, a random plasma glucose (RPG) level ⩾ 5.5 mmol/L on admission automatically triggered an HbA_{1c} test on the first blood sample drawn during routine clinical care (Box 1). Patients admitted more than once during the study period were assessed only on the basis of the first admission with RPG level ⩾ 5.5 mmol/L.

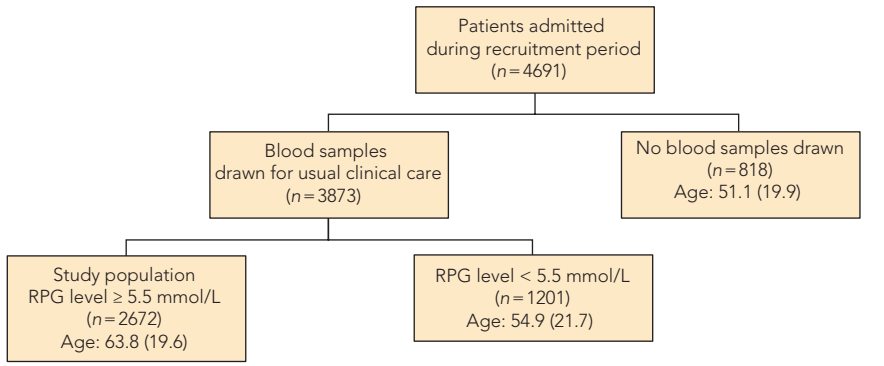
Demographic data (age, sex, ethnicity), admission data (length of stay, ward, treating specialty, reason for admission, diagnosis-related group) and additional laboratory data (RPG, serum creatinine, and haemoglobin levels) were obtained from hospital databases. Participants received usual care from their treating physicians. Treating physicians had access to admission RPG results but not to HbA_{1c} results, as this was not a recognised diagnostic test for diabetes in Australia.

A subset of patients was recruited for a postdischarge OGTT. All consenting participants were provided with an information sheet and request form for an OGTT 1 month after discharge. After 6 weeks, if no OGTT had been done, patients were sent a reminder letter and laboratory request form. After 3 months, a final reminder letter and request form were sent to patients who had not responded.

Laboratory analysis

Samples were batched for measurement of HbA_{1c} levels by high-performance liquid chromatography (PDQ, Primus Diagnostics,

1 Enrolment of study participants



Age is presented in mean (SD) years. RPG = random plasma glucose. ◆

Kansas City, Mo, USA) using boronate affinity chromatography (between-run coefficients of variation, 2.2% for HbA_{1c} 6.1% and 1.9% for HbA_{1c} 11.1%). Glucose samples were measured on a Roche P modular analyser (Hitachi High-Technologies Corporation, Tokyo, Japan) using the hexokinase/glucose-6-phosphate dehydrogenase assay (between-run coefficients of variation, 1.7% for glucose 4.9 mmol/L and 1.4% for glucose 15.7 mmol/L).

For OGTTs, patients were requested to attend their local phlebotomy centre for a blood test after an overnight fast, followed by 75 g of glucose administered orally over 5 minutes, with a second blood test 2 hours after glucose administration. Glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Diagnosis of diabetes

Patients were categorised as having known diabetes, undiagnosed diabetes or no diabetes. A patient was classified as having known diabetes if their discharge diagnoses included International Classification of Diseases (ICD-10) codes E10–E14. Patients were defined as having undiagnosed diabetes if they were not coded as having diabetes and their HbA_{1c} level was ⩾ 6.5% (48 mmol/mol), based on the International Expert Committee recommendation.[12] The HbA_{1c} results of patients with undiagnosed diabetes were provided to their general practitioner.

Cost analysis

Cost analysis was based on the cost of performing an HbA_{1c} laboratory test, which was $16.90 at the time of the study.[17] RPG tests were performed on all patients included in the study as part of routine clinical care, and were not included in cost analysis. The cost analysis was extended to include patients with RPG < 5.5 mmol/L (excluded from the study) using the conservative assumption that none of these patients had undiagnosed diabetes. The cost of screening all hospitalised patients for diabetes was estimated based on the community incidence of diabetes (0.8% per year) and assuming half are undiagnosed.[1]

Statistical analysis

Data were analysed using SPSS version 15.0 for Windows (SPSS Inc, Chicago, Ill, USA). Differences between groups were assessed by one-way analysis of variance (ANOVA) and a Scheffé test for parametric scaled variables, the Mann–Whitney *U* test with Bonferroni correction for non-parametric scaled variables and the χ^2 test for nominal variables. Post-hoc analyses were conducted for variables that had significant differences between groups. Area under the receiver operating characteristic (ROC) curve was used to assess the diagnostic value of RPG level for diabetes. $P < 0.05$ was considered statistically significant.

RESULTS

HbA_{1c} testing was conducted among 2672 patients. The study group was 93% white, comprised 48% women, and ranged in age from 18 to 102 years. The characteristics of the three groups classified by diabetes status are shown in Box 2. The prevalence of diabetes was 21.5% (95% CI, 19.9%–23.0%) among patients admitted to hospital with RPG ⩾ 5.5 mmol/L. Diabetes was previously undiagnosed among 262/2360 patients (11.1%; 95% CI, 9.8%–12.4%). There were 312 patients with known diabetes (11.7%; 95% CI, 10.5%–12.9%). The prevalence of undiagnosed diabetes was highest in the 65–74-years age group (Box 3). In our study, the prevalence of diabetes among hospitalised patients was three times higher than the community prevalence. Among the younger patients (25–34 years), the hospital prevalence of diabetes was 24 times higher than the community prevalence (Box 3).

Older age ($r = 0.08$; $P < 0.001$), increased RPG ($r = 0.41$; $P < 0.001$) and decreased GFR ($r = -0.07$; $P = 0.003$) correlated with undiagnosed diabetes. Sex and treating specialty did not correlate with undiagnosed diabetes. There was no significant difference in length of stay, number of admissions or discharge destination between those with and without undiagnosed diabetes. Among patients with known diabetes, the length of stay was longer compared with those with undiagnosed diabetes ($P < 0.001$).

Glycated haemoglobin and random plasma glucose levels

The HbA_{1c} levels of patients with no or undiagnosed diabetes are shown in Box 4. In addition to the 11% with unknown diabetes, a further 35% (822) had HbA_{1c} levels between 5.7% and 6.4%, classified as "increased risk for diabetes" by the ADA.[6] Among patients with no or undiagnosed diabetes, RPG levels ⩾ 11.1 mmol/L (World Health Organization definition) had a sensitivity of 28% and a specificity of 98% to diagnose diabetes. The area under the ROC curve for RPG level as a diagnostic test for diabetes was 0.78 (95% CI, 0.75–0.81).

Oral glucose tolerance test subset

Two hundred and fifty-nine patients were randomly selected to undertake an OGTT after discharge. Of these, 71 patients were unable to consent owing to cognitive impairment or unavailability at the times of investigator visits, and 26 patients declined participation, leaving a cohort of 162 patients consenting to undertake an OGTT. However, only 43 of these (27%; 95% CI 20%–33%) completed the OGTT. The ages of these 43 patients were not significantly different from the study population, but the mean HbA_{1c} (5.7%; 95% CI, 5.6%–5.9%) and RPG (7.4 mmol/L; 95% CI, 6.7–8.0) levels were lower than the study population. Four of these patients (9%) were diagnosed with diabetes by this test based on WHO criteria and five patients (12%) had HbA_{1c} levels ⩾ 6.5%. In two cases, the tests were concordantly positive and in 36 cases con-

2 Characteristics of hospital patients whose glycated haemoglobin levels were tested, according to diagnostic status*

	All patients ($n = 2672$)	Known diabetes ($n = 312$)	Undiagnosed diabetes ($n = 262$)	No diabetes ($n = 2098$)	P for difference†	P for difference‡
Age in years§	63.8 (19.6)	67.3 (16.0)	68 (15.3)	62.8 (20.5)	0.9	0.002
Female¶	1271 (47.6%)	146 (46.8%)	114 (43.5%)	1011 (48.2%)	na	na
Ethnicity¶					0.07	0.8
White	2483 (92.9%)	278 (89.1%)	250 (95.4%)	1955 (93.2%)		
ATSI	31 (1.2%)	12 (3.8%)	2 (0.8%)	17 (0.8%)		
Asian	25 (0.9%)	3 (1%)	3 (1.1%)	19 (0.9%)		
Other	30 (1.1%)	3 (1%)	2 (0.8%)	25 (1.2%)		
Not known	103 (3.9%)	16 (5.1%)	5 (1.9%)	82 (3.9%)		
HbA_{1c}, %**	6 (1.1)	7.6 (1.9)	7.4 (1.1)	5.6 (0.4)	0.2	< 0.001
RPG, mmol/L**	7.7 (3)	11.1 (5.4)	9.8 (3.7)	7.0 (1.5)	0.04	< 0.001
GFR, CKD-epi**	75.1 (30.7)	63.1 (34.1)	71.4 (26.5)	78 (29.8)	0.008	0.2
No. of admissions in 3 months**	1.2 (0.5)	1.3 (0.6)	1.2 (0.4)	1.2 (0.5)	0.1	0.8
Length of stay in days**	6.8 (10.6)	9.4 (13.5)	5.4 (9.4)	6.6 (10.2)	< 0.001	0.8
Admitting team¶					0.1	0.2
Medical	1065 (39.9%)	144 (46.2%)	116 (44.3%)	814 (38.8%)		
Surgical	666 (24.9%)	55 (17.6%)	54 (20.6%)	549 (26.2%)		
Intensive care	107 (4.0%)	19 (6.1%)	7 (2.7%)	81 (3.9%)		
Cardiology	473 (17.7%)	74 (23.7%)	54 (20.6%)	344 (16.4%)		
Stroke	99 (3.7%)	11 (3.5%)	12 (4.6%)	76 (3.6%)		
Other	262 (9.8%)	9 (2.9%)	19 (7.3%)	234 (11.2%)		
Discharge destination¶					na	na
Home	2101 (78.6%)	239 (76.6%)	208 (79.4%)	1656 (78.9%)		
Other hospital	404 (15.1%)	47 (15.1%)	40 (15.2%)	317 (15.1%)		
RACF	61 (2.3%)	9 (2.9%)	3 (1.2%)	49 (2.3%)		
Death	92 (3.4%)	14 (4.5%)	9 (3.4%)	69 (3.3%)		
Unknown	14 (0.5%)	3 (1.0%)	2 (0.8%)	7 (0.3%)		

ATSI = Aboriginal and Torres Strait Islander. GFR (CKD-epi) = glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. HbA_{1c} = glycated haemoglobin. na = not applicable. RACF = residential aged care facility. RPG = random plasma glucose.

* Results are shown as mean (SD) or no. (%). † P for difference between patients with undiagnosed diabetes and patients with known diabetes. ‡ P for difference between patients with undiagnosed diabetes and patients with no diabetes. § Analysis of variance (ANOVA) (age $F = 13.9$, df 2, $P < 0.001$) post-hoc comparisons by Scheffé test. ¶ Pearson χ^2 test with Bonferroni correction. ** Mann–Whitney U test with Bonferroni correction. ◆

cordantly negative. The low completion rate of the OGTT precluded meaningful statistical correlation of OGTT and HbA_{1c} results.

Cost analysis

The number needed to test (excluding those with known diabetes) to diagnose one patient with diabetes was nine (95% CI, 8.1–10.2). The assay cost per new diagnosis of diabetes was $152 in this selected and previously untested population. Testing all patients with admission blood tests regardless of RPG level would have cost about $250 per new diagnosis. Assuming an annual incidence of diabetes in hospitalised patients of 0.8%–2.4% (one- to threefold the community rate) and 50% of these undiagnosed, the cost of annual HbA_{1c} screening of every hospitalised patient would be between $1400 and $4300 per new diagnosis of diabetes.

Applicability of screening guidelines

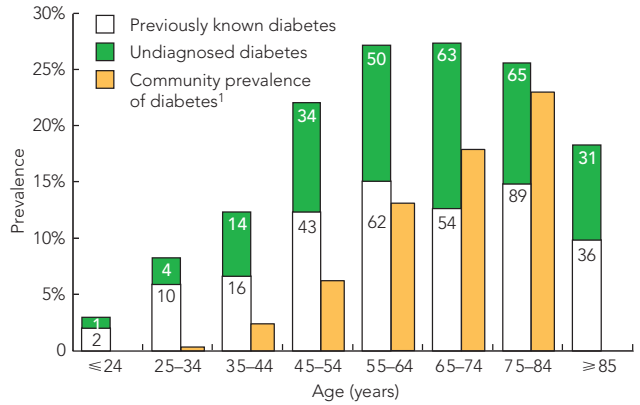
According to Australian guidelines,[18] 66/262 patients (25%) with undiagnosed diabetes and 422/2098 patients (20%) with no diabetes met criteria for screening, with a positive predictive value of 14% and a negative predictive value of 90% for patients with undiagnosed diabetes. Seventeen per cent of patients with undiagnosed diabetes indicated they do not have a regular GP.

DISCUSSION

We found that a high proportion of hospitalised patients with a RPG level ⩾ 5.5 mmol/L had undiagnosed diabetes. The prevalences of known and undiagnosed diabetes were about threefold higher than in the Australian community.[1,8,9] Among hospitalised patients younger than 55 years, the prevalence of diabetes was almost fivefold higher than in the community. We used the recent International Expert Committee recommended diagnostic threshold of HBA_{1c} levels ⩾ 6.5% to detect undiagnosed diabetes among hospitalised patients. A previous cohort study of unselected emergency admissions, which defined diabetes as an HbA_{1c} level ⩾ 6.2%, reported that 18% of patients had an HbA_{1c} level above this value.[8] In our study, 17% of patients had an HbA_{1c} level ⩾ 6.2%.

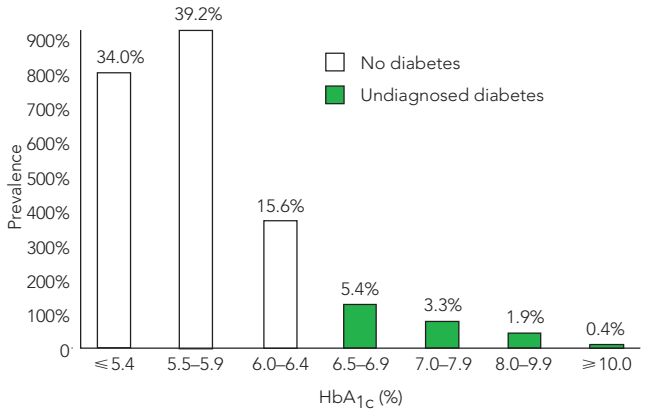
HbA_{1c} monitoring can be used as an automated screening test in hospitalised patients using blood samples drawn during usual clinical care. Potential benefits of an

3 Prevalence of diabetes among hospitalised patients, by age



The number in each group is shown within the columns. ◆

4 Distribution of glycated haemoglobin (HbA_{1c}) levels among patients with no or undiagnosed diabetes



automated HbA_{1c} screening program include low implementation costs and extensive coverage of a high-risk group. In contrast, glucose-based automated screening processes are unreliable due to unknown fasting status and stress hyperglycaemia.[8] Automated HbA_{1c} testing was easily implemented using existing blood samples and was an inexpensive method to diagnose diabetes in this patient cohort.

Although RPG testing is not recommended for diagnosing diabetes, evidence suggests RPG testing is commonly used for reasons of convenience.[5] In our study, RPG levels had low sensitivity in diagnosing diabetes; using the recommended RPG level of ⩾ 11.1 mmol/L would have missed 188 patients with diabetes. Using lower thresholds improves sensitivity, but compromises specificity. This is consistent with many other studies.[8,16,19]

Other studies used FPG testing and/or OGTT to diagnose diabetes in hospitalised patients and reported rates of undiagnosed diabetes from 2.6% to 9%.[20,21] The lower rates of diabetes in some studies may reflect the poor sensitivity of fasting glucose in this setting. We did not assess FPG levels in this study, but demonstrated that a post-discharge OGTT is unlikely to be an effective screening method. Despite a personal approach and two reminders, the completion rate of OGTTs was only 27%. Although other published studies have reported a higher completion rate (55%–58%), they have also noted poor compliance with this test.[22,23]

There is agreement about the need for screening and early intervention of diabetes. There is currently no recommendation to screen hospitalised patients in international guidelines.[6,7,18] Existing Australian screening guidelines would have led to testing of only 25% of patients with unknown diabetes in our study. This is consistent with previous reports that established risk factors are poor predictors of diabetes or impaired glucose tolerance among hospitalised patients.[19] Furthermore, 17% of patients with unknown diabetes in this study did not identify having a regular GP. This highlights the value of using hospitalisation as a point of contact with the health care system to screen patients who would otherwise be missed.

In any screening program, there is first-test bias and subsequent testing has lower yield. We estimated the likely ongoing yield from HbA_{1c} testing from the annual incidence of diabetes, 0.8%. Consistent with ADA recommendation, our results suggest that the yield from screening patients under 45 years of age will be low. However, the prevalence of diabetes in hospitalised patients under 45 years in our study is sevenfold higher than in the community and there may be greater potential benefit of screening in this cohort. Based on our findings, we believe the most practical approach to screening hospitalised patients for diabetes is to test HbA_{1c} level among all adult patients having blood tests on admission. For patients with known diabetes, this result is clinically important to guide discharge management. If local information technology systems permit, this could be further refined, for example, by excluding patients who have been tested within the past 12 months. We have shown HbA_{1c} screening is feasible, and, on face value, the screening costs per new diagnosis do not appear excessive. Cost-effectiveness of specific programs tailored to local environments should be the subject of further research.

A limitation of our study is that the diagnoses of known diabetes and comorbidities were based on coding data, which are underestimates of the true prevalence. However, this limitation does not apply to the incidence estimates used in our analysis. In our study, patients who did not have blood tests on admission or with RPG level < 5.5 mmol/L were excluded. Of patients with an RPG level just above this threshold (5.5–5.9 mmol/L), only 4% (24/587) had undiagnosed diabetes. Although the excluded patients are likely to be healthier than the study participants, the prevalence of diabetes in this group is unknown. A conservative estimate of the hospital prevalence of undiagnosed diabetes is 7.4% (assuming all patients with RPG levels < 5.5 mmol/L do not have diabetes).

There are limitations to the use of HbA_{1c} testing among hospitalised patients, particularly disorders of increased red cell turnover (eg, haemolytic disorders) and blood transfusion. However, these conditions are unlikely to be present in numbers that affect overall screening, and "first samples" are likely to be before transfusion.[3]

A hospital inpatient diagnosis of diabetes is only useful if patients receive adequate long-term management. Any automated laboratory-based screening program must be coupled to adequate resources to manage diabetes within the community. Further research into community integration should be conducted.

In summary, this study of 2672 patients with an RPG ⩾ 5.5 mmol/L admitted to a tertiary hospital over 3 months found undiagnosed diabetes in 11%. Automated HbA_{1c}

screening is easy to implement in a hospital setting using existing clinical blood samples. Screening hospitalised patients for HbA_{1c} levels is an inexpensive method of detecting undiagnosed diabetes. If adopted as a screening tool it would need to be coupled with adequate resources for follow-up and management of diabetes in the community.

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COMPETING INTERESTS

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