This is an author produced version of a paper published in:
Diabetes Research and Clinical Practice

Cronfa URL for this paper:
http://cronfa.swan.ac.uk/Record/cronfa26371

Paper:
http://dx.doi.org/10.1016/j.diabres.2016.01.023

This article is brought to you by Swansea University. Any person downloading material is agreeing to abide by the terms of the repository licence. Authors are personally responsible for adhering to publisher restrictions or conditions. When uploading content they are required to comply with their publisher agreement and the SHERPA RoMEO database to judge whether or not it is copyright safe to add this version of the paper to this repository.
http://www.swansea.ac.uk/iss/researchsupport/cronfa-support/
Title: Can HbA\textsubscript{1c} detect undiagnosed diabetes in acute medical hospital admissions?

Author: Susan E. Manley Kathleen T. O’Brien Diarmuid Quinlan Rachel A. Round Peter G. Nightingale Faazi Ali Aaron Liew Stephen D. Luzio Irene M. Stratton Graham A. Roberts

PII: S0168-8227(16)00072-3
DOI: http://dx.doi.org/doi:10.1016/j.diabres.2016.01.023
Reference: DIAB 6561
To appear in: Diabetes Research and Clinical Practice

Received date: 6-1-2016
Accepted date: 13-1-2016

Please cite this article as: S.E. Manley, Kathleen T. O’Brien, Diarmuid Quinlan, Rachel A. Round, Peter G. Nightingale, Faazi Ali, Aaron Liew, Stephen D. Luzio, Irene M. Stratton, Graham A. Roberts, Can HbA\textsubscript{1c} detect undiagnosed diabetes in acute medical hospital admissions?, Diabetes Research and Clinical Practice (2016), http://dx.doi.org/10.1016/j.diabres.2016.01.023

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
MAIN MESSAGES

• HbA1c can identify undiagnosed diabetes in white Caucasian, acute medical hospital admissions
• The specificity of HbA1c compared with OGTT for diagnosis of diabetes in acute medical admissions with possible diabetes symptoms/complications is equivalent to patients at risk of diabetes in the community but the sensitivity is lower
• The sensitivity of HbA1c for diabetes in hospitalised patients is higher when diagnosed on fasting plasma glucose rather than post glucose load on OGTT
• The discrepancy in diagnoses on HbA1c and OGTT may be explained at least in part by transient/stress hyperglycaemia resulting from acute illnesses
Can HbA1c detect undiagnosed diabetes in acute medical hospital admissions?

Running Title: HbA1c and OGTT in acute medical admissions

Keywords: HbA1c, OGTT, Diagnosis of diabetes, Acute medical admissions, Stress hyperglycaemia

Susan E. Manley a,b,*, Kathleen T. O'Brien c, Diarmuid Quinlan d, Rachel A. Round a, Peter G. Nightingale e, Fauzi Ali c, Aaron Liew f, Stephen D. Luzio g, Irene M. Stratton h, Graham A. Roberts c, i, j, k, l, **

*Joint first authors

a Diabetes Translational Research Group, Institute of Translational Medicine, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
b Divisional of Medical Sciences, University of Birmingham, Birmingham, UK
c Waterford Institute of Technology, Waterford, Ireland
d Department of General Practice, University College Cork, Ireland
e Wellcome Trust Clinical Research Facility, Institute of Translational Medicine, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
f Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
g Diabetes Research Group, Swansea University, Swansea, UK
h Gloucester Diabetic Retinopathy Research Group, Gloucestershire Hospitals NHS Foundation Trust, Cheltenham, UK
i School of Medicine, University College Cork, Ireland
j Department of Epidemiology & Public Health, University College Cork, Ireland

Page 2 of 2
k College of Medicine, Swansea University, Swansea, UK

l Department of Endocrinology and Diabetes, University Hospital Waterford, Waterford, Ireland

** Corresponding author Dr Susan MANLEY at: Glucose Fructosamine & HbA1c Program (GFH), Diabetes Translational Research Group (DTRG), First Floor, Institute of Translational Medicine, Heritage Building (Queen Elizabeth Hospital), Mindelsohn Way, Edgbaston, Birmingham, B15 2TH, United Kingdom

E-mail address:susan.manley@uhb.nhs.uk
ABSTRACT
OBJECTIVE — To study hyperglycaemia in acute medical admissions to Irish regional hospital.
RESEARCH DESIGN AND METHODS — From 2005-2007, 2061 White Caucasians, >18 years, were admitted by 1/7 physicians. Those with diabetes symptoms/complications but no previous record of hyperglycaemia (n=390), underwent OGTT with concurrent HbA1c in representative subgroup (n=148). Comparable data was obtained for 108 primary care patients at risk of diabetes.
RESULTS — Diabetes was diagnosed immediately by routine practice in 1% (22/2061) [age 36(26-61) years (median IQ range)/ 55% (12/22) male with pre-existing diabetes/dysglycaemia present in 19% (390/2061) [69(58-80) years/ 60% (235/390) male]. Possible diabetes symptoms/complications were identified in 19% [70(59-79) years/ 57% (223/390) male] with their HbA1c similar to primary care patients [54(46-61) years], 5.7(5.3-6.0)%/39(34-42) mmol/mol (n=148) v 5.7(5.4-6.1)%/39(36-43) mmol/mol, p=0.35, but lower than those diagnosed on admission, 10.2(7.4-13.3)%/88(57-122) mmol/mol, p=0.001. Their fasting plasma glucose (FPG) was similar to primary care patients, 5.2(4.8-5.7) v 5.2(4.8-5.9) mmol/L, p=0.65, but 2hPG higher, 9.0(7.3-11.4) v 5.5(4.4-7.5), p<0.001. HbA1c identified diabetes in 10% (15/148) with 14 confirmed on OGTT but overall 32% (48/148) in diabetic range on OGTT.
CONCLUSION — HbA1c can play a diagnostic role in acute medicine as it
diagnosed another 2% of admissions with diabetes but the discrepancy in sensitivity shows that it does not reflect transient/acute hyperglycaemia from the acute medical event.

Keywords

HbA1c
Diagnosis of diabetes
Acute medicine
Oral glucose tolerance test
Stress hyperglycaemia
INTRODUCTION

Diabetes mellitus is a serious disease causing premature illness and death [1]. It can be asymptomatic for many years allowing serious diabetes related complications to develop [2]. Hospitalised patients are up to three times more likely to have diabetes (diagnosed or undiagnosed) than those in the community [3, 4] with acute hospital admissions rising in affluent countries in line with the aging population [5-7].

Hyperglycaemia can be related to the particular acute medical event for which the patient is hospitalised [8]. In evolutionary terms, it is protective improving survival by allowing increased entry of glucose into crucial cells [9]. During hospitalisation, it is still debatable as to whether tight blood sugar control improves patient outcomes and is financially beneficial [10]. As hypoglycaemic episodes may be more problematical [11,12], different plasma glucose targets are recommended for patients with diabetes in these circumstances [13].

Glucose measurement is essential on admission to hospital as this high risk group may not have been screened systematically in the community. Hyperglycaemia, a common response to stress associated with acute illness [9], leads to poorer outcomes for patients by increasing morbidity and mortality [14-16] and lengthening hospitalization. It has been recognised as a major independent predictor of both in-hospital congestive heart failure and mortality [15, 17].

Current hospital practice involves blood glucose measurement using near patient or laboratory testing on admission with follow-up for certain patients in hospital and further testing after discharge. The American Diabetes Association (ADA) Clinical Practice Recommendations for 2015 suggest using HbA₁c to identify hospitalised patients with undiagnosed diabetes [10]. Other existing guidelines for acute coronary
syndrome include using HbA1c for diagnosis of diabetes although how widely they have been adopted is uncertain [8, 18].

As the uptake of HbA1c as a diagnostic test in asymptomatic patients in the community has been considerable in the UK, [19, 20], it is now important to assess its usefulness in acute medical admissions. In this study, OGTT were performed in 390 unselected, acute medical admissions identified with symptoms or possible complications of diabetes but no prior diagnosis of glucose dysregulation. They were admitted to one of the five busiest emergency hospitals in the Republic of Ireland providing high level services e.g. renal dialysis and cardiac catheterization to around 480,000 people.

HbA1c measurement in i) a representative subgroup of admissions with possible diabetes symptoms/complications undergoing OGTT (148/390), ii) 20/22 newly diagnosed cases of diabetes treated immediately on admission, and, iii) 108 patients at risk of diabetes referred for OGTT in primary practice, provides a unique opportunity to compare tests for hyperglycaemia in a hospital setting and in the community.

SUBJECTS

Ethical committee approval was obtained from the Ethics Committees of Waterford Regional Hospital and Waterford Institute of Technology and complies with the current revision of the Declaration of Helsinki.

This prospective, cross-sectional study was conducted between 1st June 2005 and 31st December 2007 and comprises consecutive, unselected, emergency, medical admissions to Waterford Regional Hospital, Ireland, (n=14,432), Fig 1a. All acute medical admissions (including cardiovascular disease) presenting to one of seven rostered consultant physicians were studied, (n=2,061/14%). A small number of
patients were newly diagnosed with diabetes on admission (n=22/1%) and treated immediately. Demographic data i.e. age, sex, ethnicity, reason for admission and diagnosis-related group were obtained from hospital databases, Table 1.

Patients at high risk of diabetes at a primary care practice in Glanmire, Co Cork, straddling both suburban and rural areas, were referred in 2007 and 2008 for OGTT performed according to routine guidance with simultaneous HbA1c measurement in 108 patients. Fig.1b.

**MATERIALS AND METHODS**

Inpatients requiring 75g OGTT (n=390/19%) were identified by the consultant physician on the post-call ward round within 24 hours of admission. The criteria defined in the study for eligibility for OGTT because of possible symptoms or complications of diabetes were a) clinical evidence or history of diabetes complications i.e. macrovascular disease - coronary heart, cerebrovascular or peripheral vascular disease or microvascular disease - nephropathy, retinopathy and neuropathy or b) risk factors for altered glucose states i.e. obesity, hypertension or dyslipidaemia, but no prior diagnosis of hyperglycaemia.

No patients refused blood sampling during the study with an OGTT performed by the inpatient phlebotomy service on the ward either immediately if fasting or after a 12 hour, overnight fast supervised by ward nursing staff.

**Laboratory measurements**

Venous blood was collected for glucose determination into serum tubes (Greiner Bio-One Vacuette 2.5ml K3EDTA) either on admission to hospital or during the OGTT. Glucose was measured in a routine laboratory on a Beckman LX 20 chemistry...
analyser (Beckman Coulter Inc) using a glucose oxidase method. Results were obtained within 2 to 4 hours of receipt of blood samples following routine procedures for emergency/critical care. HbA1c was measured within a week of admission or OGTT by ion exchange, high performance liquid chromatography (IE HPLC) in EDTA blood using IFCC-calibrated Menarini 8160 Variant Mode analyser (CV 2.0% at 40 mmol/mol and 1.3% at 92 mmol/mol with IFCC reference interval 20-42 mmol/mol/DCCT 4-6%). Blood samples from patients in the community were sent to the laboratory at University Hospital Cork for routine measurement of glucose on Olympus analysers and HbA1c using IFCC-calibrated Tosoh G7/G8 IE HPLC analysers, IFCC reference interval 20-42 mmol/mol/DCCT 4-6%. No patients with abnormal haemoglobin were included in the study.

Statistical analysis

Data were entered onto Microsoft Excel, double checked and analysed using SPSS version 15.0 for Windows (SPSS Inc, Chicago, Ill, USA) and PASW Statistics 18 (SPSS Inc., Chicago, Illinois, US). The Mann–Whitney U test was used to generate p values in Tables 1 and 2. Both subgroups of patients undergoing OGTT with accompanying HbA1c measurement were tested and found to be representative of the group as a whole.

Random or casual plasma glucose was defined as in the diabetic range if ≥11.1 mmol/L. For fasting plasma glucose, diabetes was defined as plasma glucose ≥7.0 mmol/L and impaired fasting glucose (IFG) as 6.1-6.9 mmol/L. Two hour plasma glucose ≥11.1 mmol/L was defined as diabetes with impaired glucose tolerance 7.8-11.0 mmol/L [21]. Diabetes was defined as HbA1c ≥ 48 mmol/mol/6.5% according to WHO 2011 criteria [22] and prediabetes as HbA1c 42-47 mmol/mol/6.0-6.4%, [23].
For the combined group of acute medical admissions comprising those newly
diagnosed with diabetes on admission and those with diabetic symptoms and
complications, the sensitivity of HbA1c was estimated by a weighted average of the
sensitivities of the two component groups. The weights used were the numbers of
diagnoses of diabetes that would be expected for each component group within the
study group of 2061 admissions if the calculated sensitivities were representative.
Based on a similar assumption, the specificity of the group with diabetic symptoms
and complications was used as an estimate of the specificity of the combined group.
Receiver operating characteristic (ROC) curves were produced for i) the combined
group, ii) the subgroup of acute medical admissions with possible symptoms or
complications of diabetes and iii) the primary care patients at high risk of diabetes.
Fisher’s Exact test was applied for comparisons of sensitivity and specificity.

RESULTS

Dysglycaemia in acute medical admissions

During the 30 month study period between 2005 and 2007, 2061 (14%) out of 14432
inpatients, all white Caucasian, were treated by one of seven admitting consultant
physicians, Fig. 1a. The burden of dysglycaemia was considerable with 22 (1%)
diagnosed with diabetes according to routine hospital practice immediately on
admission (aged 36(26-61) years, median (IQ range), 55% male (12/22); 9 Type 1
diabetes and 13 Type 2 diabetes). Diagnoses of diabetes, IGT or IFG were established
prior to admission in 390 patients (19%), aged 69(58-80) years, 60% (235/390) male.
A further 390 (19%), aged 70(59-79) years, 57% (223/390) male, had possible
symptoms or complications of diabetes on admission and underwent OGTT according
to study protocol. No routine diagnoses, symptoms or evidence of complications of
diabetes were present in 1233 (60%) of the acute medical admissions. Patients were excluded from the study, 26 (1%), if aged <18 years, pregnant or diagnosed with endocrine disorders i.e. Cushing’s disease, acromegaly, phaeochromocytoma or hyperthyroidism.

Admissions with possible diabetes symptoms or complications

The subgroup of 148/390 (38%) admissions undergoing OGTT with HbA1c measured for clinical reasons, Fig.1a, Table 1, were representative of the group as a whole with no significant differences between the variables. Similarly so, for the subgroup of 108/250 (43%) white Caucasian patients at risk of diabetes undergoing OGTT in primary care, Fig. 1b, who were younger than corresponding inpatients at 54(46-61) v 70(59-79) years, p=0.001, Table 1.

Glycaemic markers in those newly diagnosed with diabetes

Plasma glucose was 19.3 (11.8-27.4) mmol/L in patients diagnosed with diabetes immediately on admission and 6.4 (5.6-7.4) mmol/L in patients identified with possible symptoms or evidence of diabetic complications. Likewise, HbA1c was 88 (57-122) mmol/mol or 10.2 (7.4-13.3)%, and 39 (34-42) mmol/mol or 5.7 (5.3-6.0)%, p<0.001, Table 1. HbA1c identified diabetes in 18/20 (90%) of those inpatients diagnosed with diabetes immediately on admission.

HbA1c in at risk patients in hospital and from the community

HbA1c in inpatients with diabetes symptoms/complications was similar to GP patients at risk of diabetes who had not undergone an acute medical event, 39(36-43) mmol/mol or 5.7(5.4-6.1)%, p=0.35, Table 1. In the inpatient group, 15/148 (10%) had HbA1c ≥48 mmol/mol or 6.5% and, similarly, 17/108 (16%) GP patients, p=0.19,
Table 2.

On OGTT, 32% (48/148) of inpatients with possible symptoms or complications were diagnosed with diabetes by OGTT compared with 10% (15/148) on HbA1c, Table 2, a reflection of acute hyperglycaemia induced by the medical emergency. In total, 70% (103/148) of inpatients had abnormal glucose status in response to a glucose load as 37% (55) had IGT. No inpatient displayed IFG only. In comparison, in the GP population, 73% (79) were normoglycaemic, 5% (5) had IFG, 10% (10) IGT and 13% (14) were diagnosed with diabetes, p<0.001.

Distribution of HbA1c and glucose

Probability density functions demonstrate clearly the differences in HbA1c between those diagnosed with diabetes immediately on admission, and symptomatic inpatients or at risk patients in the community, Fig. 2. The HbA1c probability density functions for symptomatic inpatients and at risk patients in the community are very similar, with sharp bell shaped curves with maximum heights of 0.77 and 0.74 at 40 mmol/mol and are skewed to the right with slight traces up to approximately 100 mmol/mol. The corresponding curves for fasting plasma glucose are super-imposable. The HbA1c curve for inpatients diagnosed immediately on admission is displaced to the right with the flattened bell curve (maximum 0.09) extending from 40 mmol/mol to 180 mmol/mol HbA1c. HbA1c >120 mmol/mol was present in 5 out of 20 patients newly diagnosed with diabetes on admission (with HbA1c measured routinely) but not detected in admissions with possible symptoms/complications or primary care patients.

The probability density functions for 2h plasma glucose demonstrate the nature of hyperglycaemia resulting from acute medical incidents with a shift to the right for
inpatients with a peak at 8.5 mmol/L compared 5 mmol/L for GP patients, Fig. 2.

Sensitivity and specificity of HbA\(_1c\) for diabetes

The ability of HbA\(_1c\) to diagnose diabetes in GP patients was comparable to OGTT with the sensitivity being 93% (13/14) and specificity 96% (90/94), Fig. 3. In the acute medical admissions studied, the specificity of HbA1c for diagnosis in those diagnosed immediately and those with possible symptoms or complications of diabetes was 99%, \(p=0.20\), but the sensitivity was significantly lower at 38%, \(p<0.001\). In those with possible symptoms or complications only, the sensitivity was 29% and specificity 99%. The sensitivity was higher for those diagnosed on fasting plasma glucose than for those diagnosed on 2h plasma glucose only at 63% (5/8) versus 23% (9/40), \(p=0.037\).

DISCUSSION

Hospitals face an ongoing challenge on how to differentiate hyperglycaemia in inpatients. The ADA has moved the focus of diagnostic HbA\(_1c\) testing from asymptomatic patients in the community, to the large number of patients who remain undiagnosed in settings such as emergency or other hospital wards [10]. In addition to previously diagnosed or undiagnosed diabetes, hyperglycaemia in acutely ill patients may be induced by insulin resistance resulting from the stress of an acute medical event, or result from diabetes induced by glucotoxic drugs such as corticosteroids or antipsychotics.

In the white Caucasian patients at high risk of diabetes studied, the distribution of fasting plasma glucose on OGTT and HbA\(_1c\) was similar in acute admissions and primary care patients, Fig 2. The specificity of HbA\(_1c\) for diabetes was high in both populations justifying its use for diagnostic testing in hospital admissions, Fig.3.
However, the sensitivity was lower in inpatients because of the increased prevalence of raised 2h plasma glucose on OGTT following the acute medical incident but when was examined in terms of fasting and 2h plasma glucose, HbA1c reflected fasting plasma glucose better.

In most hospitals random plasma glucose is measured immediately on admission but the protocol for HbA1c testing is uncertain. The ADA suggests adding HbA1c measurement for patients with previously diagnosed diabetes not tested in the previous 2 to 3 months and also for those patients at risk of undiagnosed diabetes but this guidance is at the level of expert opinion only. The range of HbA1c found in this study on admission to hospital or referral from primary care indicate that some patients may have had raised blood glucose levels for some time. No cases of undiagnosed diabetes presented with HbA1c >120 mmol/mol from those with possible diabetic symptoms/complications or primary care but 25% of those diagnosed immediately on admission had values >120 mmol/mol considered to be the trigger for urgent referral in the UK [19]. Audit data from an ethnically diverse UK region demonstrated that one in 200 HbA1c results was above 120 mmol/mol and one in five patients had undiagnosed diabetes [20].

Use of HbA1c in these circumstances should improve the outcome for individual hospital patients. Its introduction requires assessment of i) the economic and financial situation by country, ii) the practical implications for the laboratory and point of care service, iii) the relationship of glucose to HbA1c for different ethnic groups, and iv) the effects of medical conditions or drugs on the accuracy of HbA1c relative to glucose [24-26]. The use of HbA1c for diagnostic purposes in the community has been well received in the UK because of its practicality with laboratory requests for HbA1c more than doubling since its introduction, glucose decreasing accordingly and requests for
OGTT rare [27].

There is not a perfect correlation between glucose and HbA1c around the diagnostic cut-off points. Previous studies have shown that HbA1c <37 mmol/mol (or 5.5%) and >58 mmol/mol (or 7.5%) correlate with OGTT at a 95% level but not so highly between 5.5% and 7.5% [28]. However, this data was analysed before the recent recalibration downwards of Tosoh and Bio-Rad analysers [29]. The lack of correlation around the diagnostic threshold may be attributed to normal variation in red blood cell turnover [30, 31]. The specificity and sensitivity of HbA1c reported in this paper for the white Caucasian patients in primary care may reflect the prevalence of undiagnosed diabetes within the Irish population at the time of the study i.e. 2007 to 2008.

Certain medical conditions/drugs in individual patients can also affect red blood cell turnover. HbA1c has been reported to be depressed by 20 mmol/mol in liver patients being assessed for transplantation [27] and up to 40mmol/mol in a patient with polycythaemia rubra vera [32]. There is not much quantitative evidence on the conditions that may compromise the accuracy of HbA1c relative to glucose outlined by WHO in 2011 when recommending HbA1c for diagnosis [22].

Only one HbA1c result was available for this study but the American Diabetes Association has now suggested a more measured approach to confirmation of diagnoses. They suggest repeats only when feasible or within 3 to 6 months if around the diagnostic threshold [10] rather than within two weeks. In patients with very high HbA1c, HbA1c should be repeated immediately with an accompanying glucose measurement. Although the IE HPLC analysers used in both hospital laboratories reported IFCC calibrated HbA1c results, it was reported in 2014 that the Tosoh IE
HPLC analysers have a positive bias of +2.4(2.2) mmol/mol or 0.22(0.20)%, mean difference and SD, compared to the IFCC secondary reference method and Menarini IE HPLC analyser a negligible bias of -0.4(1.2) mmol/mol or 0.04(0.11)% [29].

Being able to discern whether a patient has stress hyperglycaemia is important as it is associated with worse outcomes for patients [33-35]. HbA1c testing cannot identify recent transient episodes of hyperglycaemia given the half-life of red blood cells of 2 to 3 months. Only 29% (14/48) of inpatients with possible complications or symptoms with diabetes identified on OGTT had the diagnosis confirmed by HbA1c as opposed to 93% (13/14) of those from the community.

HbA1c can identify undiagnosed diabetes depending on the level provide assistance on whether treatment is required immediately or later during the hospital stay, or whether referral to primary care for their diabetes management is adequate. In addition to the 1% of white Caucasian inpatients diagnosed immediately with diabetes by routine methods of the time, another 2% (40/2061) would have been diagnosed by measuring HbA1c on admission in those with possible symptoms or complications.

Comprehensive information needs to be documented in discharge letters to enable primary care to continue to provide suitable diabetes care. It should include data on glycaemic status – i) HbA1c, glucose and in some cases fructosamine if HbA1c is not suitable, ii) advice on the management of glycaemic control in newly diagnosed patients and those previously diagnosed, and iii) the requirements for follow up of patients with any possible symptoms/complications. It is important to ensure that no unnecessary anti-hyperglycaemic treatment is continued in patients with transient hyperglycaemia caused by an acute medical event.

In conclusion, this study provides evidence on the use of HbA1c testing in hospital to
identify patients with undiagnosed diabetes. It highlights the need for local, national and international guidance to ensure appropriate treatment plans for all patients with diabetes and to provide the required follow up if stress hyperglycaemia or possible symptoms or complications of diabetes are evident on hospitalisation.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICTS OF INTEREST

Conflicts of interest: none.

CONTRIBUTORSHIP STATEMENT

S.E.M helped to develop the study design interpreted data, wrote and critically reviewed the manuscript; K.T.O’B developed the study design, acquired hospital data, analysed data initially and drafted the initial manuscript; D.Q. collected the data from patients at risk of diabetes in the community; R.A.R. prepared the manuscript; P.G.N. analyzed and interpreted data, and critically reviewed the manuscript; F.M.A. performed the OGTT and critically reviewed the manuscript; A.L. critically reviewed the manuscript; I.M.S. provided statistical expertise and critically reviewed the manuscript; G.A.R. designed and performed the study, and critically reviewed the manuscript. The guarantor is Dr Graham Roberts.

ACKNOWLEDGMENTS
The authors would like to thank Dr Sandip Ghosh for academic support.
REFERENCES


2. International Diabetes Federation: Global Guideline for Type 2 Diabetes.


7. World Health Organization; Hospitals in a changing Europe -


10. American Diabetes Association Clinical Practice Recommendations 2015.


FIGURE LEGENDS

Figure 1a
Flowchart for acute medical admissions identifying patients diagnosed with diabetes immediately and patients undergoing OGTT because of symptoms or complications of diabetes.

Figure 1b
Flowchart outlining patients in the community at risk of diabetes undergoing OGTT at GP practice.

Figure 2
Probability density functions for HbA1c in patients newly diagnosed with diabetes on admission to hospital or with possible symptoms/complications of diabetes. Also for glucose on OGTT in inpatients with possible symptoms/complications of diabetes and high risk patients referred to GP.
Grey GP referrals at risk of diabetes n=108; Turquoise Acute medical admissions with possible symptoms or complications of diabetes n=148; Green Acute medical admissions diagnosed with diabetes immediately n=20
HbA1c solid lines; FPG -----; 2hPG on OGTT ……

Figure 3
Receiver operator curves for use of HbA1c for diagnosis of diabetes in i) Grey line 108 patients at risk of diabetes diagnosed on OGTT by GP, ii) Purple line 22 acute medical admissions newly diagnosed routinely with diabetes and 390 with possible symptoms or complications (data extrapolated from OGTT subgroup) and iii) Turquoise line subgroup of acute medical admissions with possible symptoms or complications of diabetes undergoing OGTT (n=148). Arrows indicate cutpoint for diagnosis of diabetes ≥48 mmol/mol or 6.5% followed by sensitivity (%) and specificity (%).
Table 1—HbA1c at OGTT in acute medical admissions with possible symptoms or complications of diabetes and patients at high risk of diabetes from general practice

<table>
<thead>
<tr>
<th></th>
<th>Acute medical admissions with possible symptoms/ complications of DM</th>
<th>GP patients at high risk of diabetes</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>148</td>
<td>108</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>70 (59–79)</td>
<td>54 (46–61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White Caucasian (%)</td>
<td>148 (100%)</td>
<td>108 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Male (%)</td>
<td>93 (63%)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>Reason for admission to hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>85/57%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>19/13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>11/7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>6/4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>27/18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission*</td>
<td>6.4 (5.6–7.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fasting plasma glucose*</td>
<td>5.2 (4.8–5.7)</td>
<td>5.2 (4.8–5.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>2h plasma glucose*</td>
<td>9.0 (7.3–11.4)</td>
<td>5.5 (4.4–7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)*</td>
<td>39 (34–42)</td>
<td>39 (36–43)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)*</td>
<td>5.7 (5.3–6.0)</td>
<td>5.7 (5.4–6.1)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

* Median (IQ range)
<table>
<thead>
<tr>
<th>Status</th>
<th>HbA1c % (mmol/mol)</th>
<th>Status</th>
<th>HbA1c % (mmol/mol)</th>
<th>p value for HbA1c Prevalence</th>
<th>p value for prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions</td>
<td>GP referrals</td>
<td>Admissions</td>
<td>GP referrals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>5.7 (5.3–10.7)</td>
<td>5.5 (5.3–5.7)</td>
<td>0.75</td>
<td>104 (70%)</td>
<td>72 (67%)</td>
</tr>
<tr>
<td>Pre-diabetes</td>
<td>6.1 (6.0–6.3)</td>
<td>6.1 (6.0–6.3)</td>
<td>0.96</td>
<td>29 (20%)</td>
<td>19 (18%)</td>
</tr>
<tr>
<td>DM</td>
<td>7.0 (6.7–8.0)</td>
<td>8.0 (7.1–9.5)</td>
<td>0.08</td>
<td>15 (10%)</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>DM both</td>
<td>7.1 (6.7–8.2)</td>
<td>8.3 (7.3–9.6)</td>
<td>0.056</td>
<td>14 (9%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>DM HbA1c only</td>
<td>6.5 (50–64)</td>
<td>7.1 (6.6–8.7)</td>
<td>0.60</td>
<td>1 (1%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>DM OGTT only</td>
<td>5.8 (5.4-6.0)</td>
<td>5.7</td>
<td>1.00</td>
<td>34 (23%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>DM on OGTT</td>
<td>NG</td>
<td>IFG only</td>
<td>-</td>
<td>6.0 (5.5–6.6)</td>
<td>-</td>
</tr>
<tr>
<td>DM on OGTT</td>
<td>IGT only</td>
<td>5.7 (5.4–6.5)</td>
<td>0.31</td>
<td>47 (32%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>DM on OGTT</td>
<td>IFG &amp; IGT</td>
<td>5.7 (5.0–6.3)</td>
<td>0.14</td>
<td>8 (5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>DM on OGTT</td>
<td>DM on FPG</td>
<td>6.0 (5.6–6.7)</td>
<td>&lt;0.001</td>
<td>48 (32%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>DM on OGTT</td>
<td>DM on 2hPG</td>
<td>6.9 (5.8–10.2)</td>
<td>0.37</td>
<td>8 (5%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>DM on OGTT</td>
<td></td>
<td>6.0 (5.6–6.7)</td>
<td>&lt;0.001</td>
<td>47 (32%)</td>
<td>12 (11%)</td>
</tr>
</tbody>
</table>
3442 acute medical admissions to an Irish regional hospital between 2005 & 2007

2041 (60%) admitted by one consultant physician

1217 (36%) admitted by other E consultant physicians

450 (13%) previous diagnosis of DM, IGT or IFG

22 (1%) newly diagnosed with DM on admission

309 (9%) eligible for OGTT because of diabetic symptoms or complications

26 (1%) aged <18 or with endocrine disorders excluded

1213 (60%) with no diabetic symptoms or complications

148 (38%) with OGTT & HbA1c measured for clinical reasons

242 (62%) with OGTT but no HbA1c

48 (32%) DM on OGTT

55 (37%) IGT on OGTT

0 (0%) NOG on OGTT

45 (30%) IG on OGTT

Figure