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Title: Can HbA_{1c} detect undiagnosed diabetes in acute medical hospital admissions?

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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 HbA_{1c} detect undiagnosed diabetes in acute medical hospital admissions?

Running Title: HbA_{1c} and OGTT in acute medical admissions

Keywords: HbA_{1c}, OGTT, Diagnosis of diabetes, Acute medical admissions, Stress hyperglycaemia

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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.

The specificity of HbA1c in 2061 admissions was similar to primary care, 99% v 96% , p=0.20, but sensitivity lower, 38% v 93%, p <0.001 (63% on FPG/23% on 2hPG, p=0.037, in those with possible symptoms/complications).

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

HbA_{1c}

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 HbA_{1c} to identify hospitalised patients with undiagnosed diabetes [10]. Other existing guidelines for acute coronary

syndrome include using HbA_{1c} for diagnosis of diabetes although how widely they have been adopted is uncertain [8, 18].

As the uptake of HbA_{1c} 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.

HbA_{1c} 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 HbA_{1c} 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. HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} ≥ 48 mmol/mol/6.5% according to WHO 2011 criteria [22] and prediabetes as HbA_{1c} 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 HbA_{1c} 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, pheochromocytoma or hyperthyroidism.

Admissions with possible diabetes symptoms or complications

The subgroup of 148/390 (38%) admissions undergoing OGTT with HbA_{1c} 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, HbA_{1c} 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. HbA_{1c} identified diabetes in 18/20 (90%) of those inpatients diagnosed with diabetes immediately on admission.

HbA_{1c} in at risk patients in hospital and from the community

HbA_{1c} 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 HbA_{1c} \geq 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 HbA_{1c}, 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 HbA_{1c} and glucose

Probability density functions demonstrate clearly the differences in HbA_{1c} between those diagnosed with diabetes immediately on admission, and symptomatic inpatients or at risk patients in the community, Fig. 2. The HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}. HbA_{1c} > 120 mmol/mol was present in 5 out of 20 patients newly diagnosed with diabetes on admission (with HbA_{1c} 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 HbA_{1c} 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, HbA_{1c} reflected fasting plasma glucose better.

In most hospitals random plasma glucose is measured immediately on admission but the protocol for HbA_{1c} testing is uncertain. The ADA suggests adding HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} >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 HbA_{1c} results was above 120 mmol/mol and one in five patients had undiagnosed diabetes [20].

Use of HbA_{1c} 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 HbA_{1c} for different ethnic groups, and iv) the effects of medical conditions or drugs on the accuracy of HbA_{1c} relative to glucose [24-26]. The use of HbA_{1c} for diagnostic purposes in the community has been well received in the UK because of its practicality with laboratory requests for HbA_{1c} more than doubling since its introduction, glucose decreasing accordingly and requests for

OGTT rare [27].

There is not a perfect correlation between glucose and HbA_{1c} around the diagnostic cut-off points. Previous studies have shown that HbA_{1c} <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 HbA_{1c} 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. HbA_{1c} 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 HbA_{1c} relative to glucose outlined by WHO in 2011 when recommending HbA_{1c} for diagnosis [22].

Only one HbA_{1c} 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 HbA_{1c}, HbA_{1c} should be repeated immediately with an accompanying glucose measurement. Although the IE HPLC analysers used in both hospital laboratories reported IFCC calibrated HbA_{1c} 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]. HbA_{1c} 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 HbA_{1c} as opposed to 93% (13/14) of those from the community.

HbA_{1c} 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 HbA_{1c} 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) HbA_{1c}, glucose and in some cases fructosamine if HbA_{1c} 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 HbA_{1c} 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.

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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.

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ACCEPTED MANUSCRIPT

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REFERENCES

1. IDF Diabetes Atlas, sixth edition 2013.
2. International Diabetes Federation: Global Guideline for Type 2 Diabetes. *Diabetes Res Clin Pract.* 2014;104(1):1-52.
3. Wexler DJ, Nathan DM, Grant RW et al. Prevalence of elevated hemoglobin A1c among patients admitted to the hospital without a diagnosis of diabetes. *J Clin Endocrinol Metab* 2008;93:4238-44.
4. Inoue K, Matsumoto M, Akimoto K. Fasting plasma glucose and HbA1c as risk factors for type 2 diabetes. *Diabet Med* 2008;25:1157-1163.
5. Organization for Economic Cooperation and Development, OECD Health Data 2009 (Paris: OECD, Nov. 2009); Organization for Economic Cooperation and Development, OECD Health Care Quality Indicators Data 2009 (Paris: OECD, Nov. 2009).
6. The Economist Intelligence Unit Limited 2009. Healthcare strategies for an ageing society.
7. World Health Organization; Hospitals in a changing Europe - www.euro.who.int/document/e74486.pdf.
8. NICE National Institute for Health Care Excellence. [Hyperglycaemia in acute coronary syndromes \(CG130\)](#) Oct 2011.
9. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* 2009;373:1798-1807.
10. American Diabetes Association Clinical Practice Recommendations 2015. *Diabetes Care* 2015; 38 (Suppl. 1):S80-S85.
11. Egi M, Bellomo R, Stachowski E et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc* 2010;85:217-24.

12. Krinsley JS, Keegan MT. Hypoglycaemia in the critically ill: How low is too low? *Mayo Clin Proc* 2010;85:215-6.
13. Egi M, Finfer S, Bellomo R. Glycemic control in the ICU. *Chest* 2011;140:212-20.
14. Umpierrez GE, Isaacs SD, Bazargan N et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002;87:978-82.
15. Capes SE, Hunt D, Malmberg K et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;355:773-8.
16. Sung J, Bochicchio GV, Joshi M et al. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. *J Trauma* 2005;59:80-3.
17. Shore S, Borgerding JA, Gylys-Colwell I et al. Association between hyperglycemia at admission during hospitalization for acute myocardial infarction and subsequent diabetes: insights from the veterans administration cardiac care follow-up clinical study. *Diabetes Care* 2014;37:409-418.
18. Corbett SJ. Hyperglycaemia in acute coronary syndromes: summary of NICE clinical guideline 130. *Heart* doi:10.1136/heartjnl-2012-302421.
19. John WG. Expert Position Statement. Use of HbA_{1c} in the diagnosis of diabetes mellitus in the UK. The implementation of World Health Organization guidance 2011. *Diabet Med* 2012;29:1350-7.
20. Dowd RP, Round RA, Mason CL, Manning PW, Nightingale PG, Hanif W et al. Hyperglycaemia and Diabetic Ketoacidosis in Patients Presenting to Hospital with HbA_{1c} >13.1%/120 mmol/mol but No Previous Diagnosis of Diabetes. *Diabetes* 2014; 63 Suppl 1: A634 (Abstract type: Publish only 2501-PO).

21. World Health Organization 2006. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation.
22. Report of a World Health Organization Consultation: Use of glycosylated haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus. *Diabetes Res Clin Pract.* 2011;93:299-309.
23. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327-34.
24. Sacks DB, Arnold M, Bakris GL et al; National Academy of Clinical Biochemistry. Position statement executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 2011;34:1419-23.
25. Manley SE, Mason CL, Round RA et al. Is HbA_{1c} suitable for monitoring glycaemic control in patients with unusual haemoglobins or other haematological disorders? *Diabet Med* 2010; 27(Suppl. 1):161,P426.
26. Vracar S, Bhattacharjee D, Manning PW, Round RA, Nightingale PG, Stratton IM et al. HbA_{1c} depressed relative to random plasma glucose in patients with cirrhosis of the liver. *Diabetes* 2014; 63(Suppl. 1): A356. Poster presentation no 1365-P.
27. Dowd RP, Manning PW, Ahmed N, Mason CL, Round RA, Nightingale PG et al. Post introduction of HbA_{1c} as a diagnostic test: consequences for requesting and reporting. *Diabet Med* 2015;32(Suppl. 1):163,P440.
28. Manley S, Nightingale P, Stratton I, et al. Diagnosis of diabetes: HbA_{1c} versus WHO criteria. *Diabetes & Primary Care* 2010;12:87-96.

29. Manley SE, Hikin LJ, Round RA, Manning PW, Luzio SD, Dunseath GJ et al. Comparison of IFCC-calibrated HbA_{1c} from laboratory and point of care testing systems. *Diabetes Res Clin Pract.* 2014;105:364-72.
30. Cohen RM, Franco RS, Khera PK et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA_{1c}. *Blood* 2008;112:4284-91.
31. Simmons D, Hlaing T. Interpretation of HbA_{1c}: Association with mean cell volume and haemoglobin concentration. Personal communication submitted to *Diabet Med*.
32. HbA_{1c} in diabetes. Case studies in IFCC units. Gough S, Manley S, Stratton I. (Editors) Wiley-Blackwell March 2010.
33. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359–67.
34. Malmberg K, Norhammar A, Wedel H et al. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999;99:2626–32.
35. Clement S, Braithwaite SS, Magee MF et al; American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. [Erratum in *Diabetes Care* 2004;27:856 and *Diabetes Care* 2004;27:1255]. *Diabetes Care* 2004;27:553–91.

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—*HbA_{1c} at OGTT in acute medical admissions with possible symptoms or complications of diabetes and patients at high risk of diabetes from general practice*

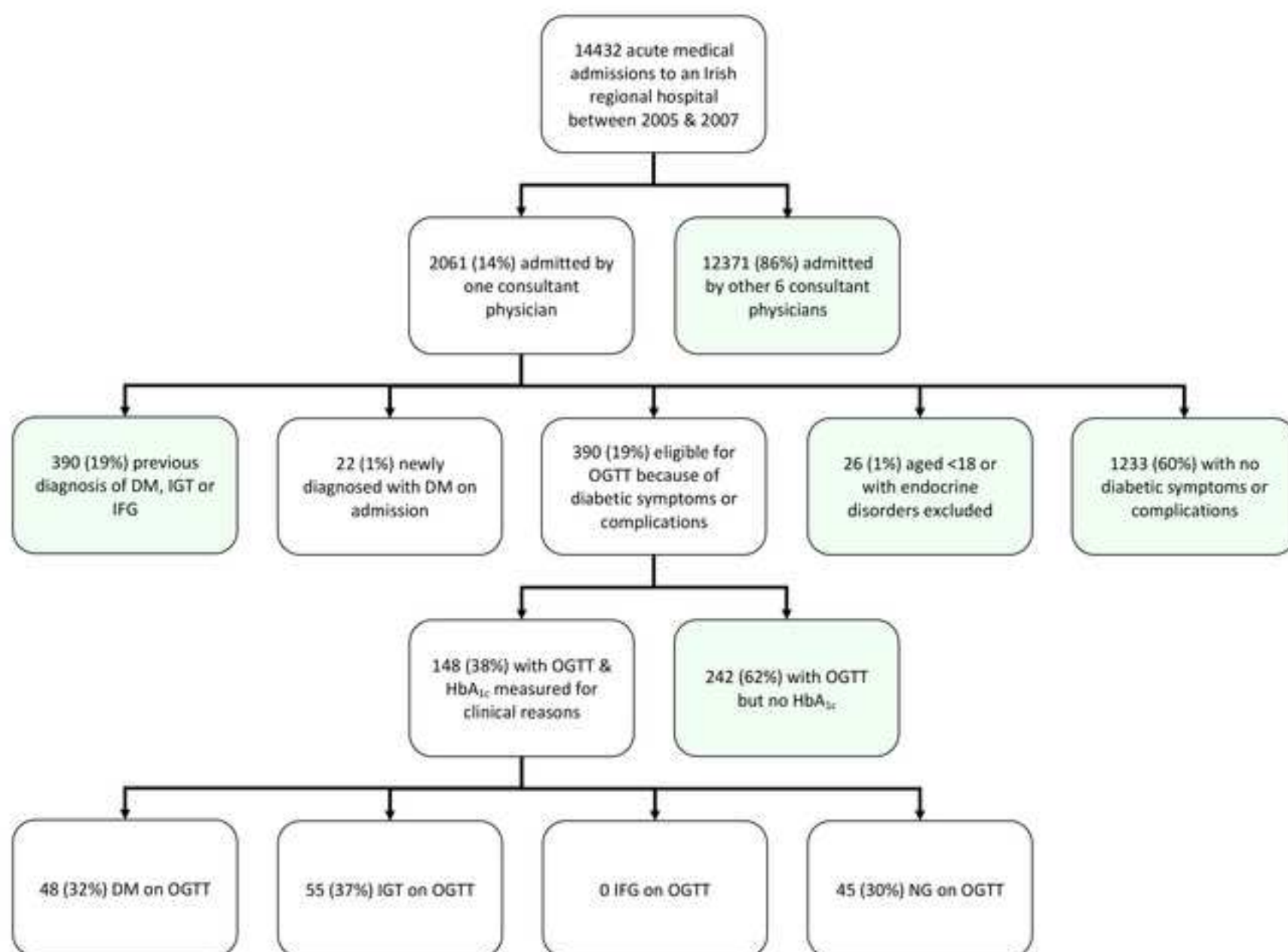
	Acute medical admissions with possible symptoms/ complications of DM	GP patients at high risk of diabetes	p value
N	148	108	-
Age (years)*	70 (59–79)	54 (46–61)	<0.001
White Caucasian (%)	148 (100%)	108 (100%)	1.00
Male (%)	93 (63%)	NA	-
Reason for admission to hospital			
CVD	85/57%	-	-
Stroke or TIA	19/13%		
Respiratory	11/7%		
Endocrine disorders	6/4%		
Other (%)	27/18%		
Plasma glucose (mmol/L)			
Admission*	6.4 (5.6–7.4)	-	-
Fasting plasma glucose*	5.2 (4.8–5.7)	5.2 (4.8–5.9)	0.65
2h plasma glucose*	9.0 (7.3–11.4)	5.5 (4.4–7.5)	<0.001
HbA _{1c} (mmol/mol)*	39 (34–42)	39 (36–43)	0.35
HbA _{1c} (%)*	5.7 (5.3–6.0)	5.7 (5.4–6.1)	

* Median (IQ range)

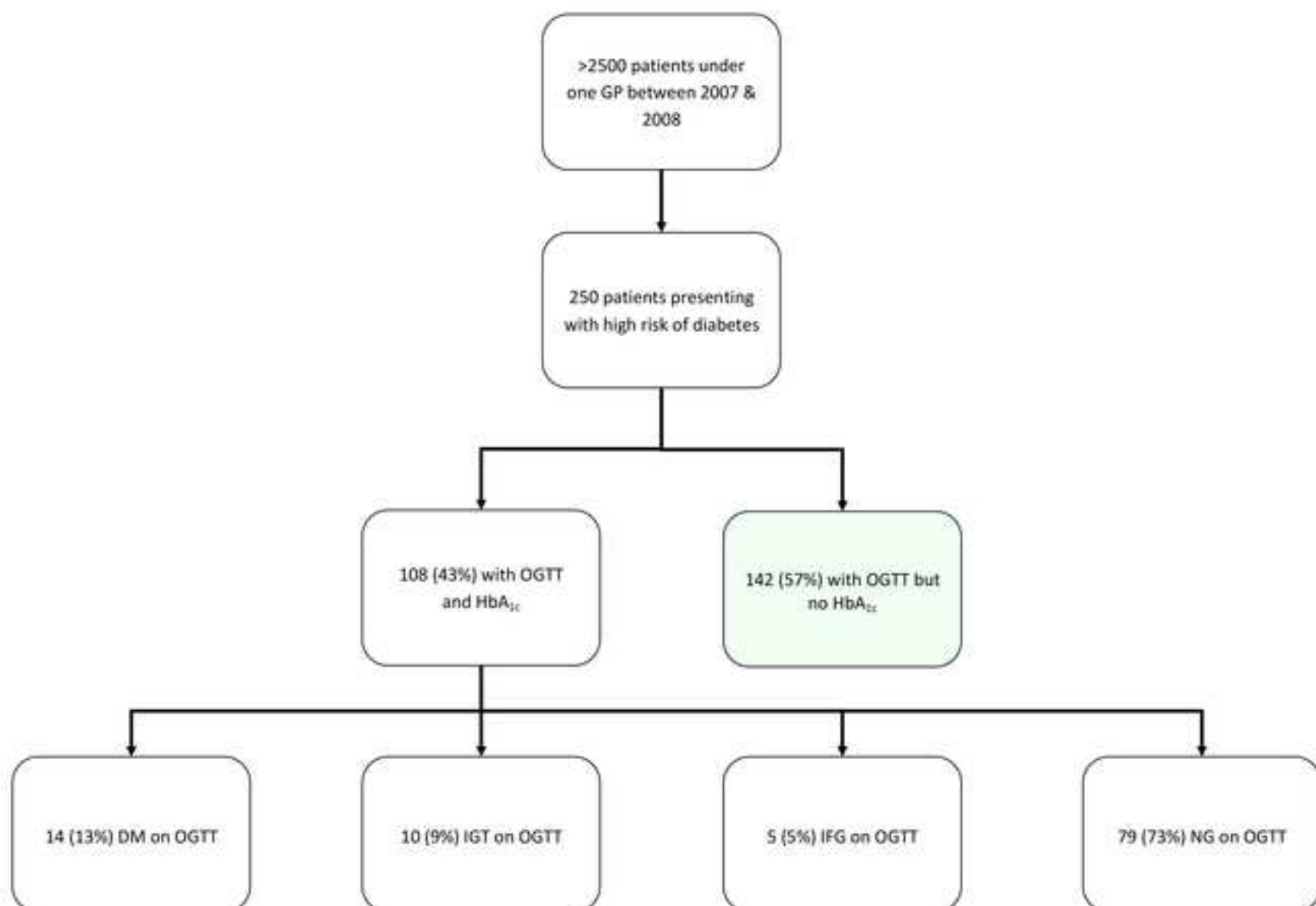
Table 2—Glycaemic status on OGTT and HbA_{1c} ≥6.5% or 48 mmol/mol in acute medical admissions and GP referrals in white Caucasian patients from Ireland
Median (IQ range)

Status	Admissions n=148	GP referrals n=108	<i>p</i> value for HbA _{1c}	Admissions n=148	GP referrals n=108	<i>p</i> value for prevalence
	HbA _{1c} % mmol/mol	HbA _{1c} % mmol/mol		Prevalence	Prevalence	
On HbA_{1c}						
Normal	5.7 (5.3–10.7) 39 (34–93)	5.5 (5.3–5.7) 37 (34–39)	0.75	104 (70%)	72 (67%)	0.59
Pre-diabetes	6.1 (6.0–6.3) 43 (42–45)	6.1 (6.0–6.3) 43 (42–45)	0.96	29 (20%)	19 (18%)	0.75
DM	7.0 (6.7–8.0) 53 (50–64)	8.0 (7.1–9.5) 64 (54–80)	0.08	15 (10%)	17 (16%)	0.19
DM both	7.1 (6.7–8.2) 54 (50–66)	8.3 (7.3–9.6) 67 (56–81)	0.056	14 (9%)	13 (12%)	0.54
DM HbA _{1c} only	6.5 / 48	7.1 (6.6–8.7) 54 (49–72)	0.60	1 (1%)	4 (4%)	0.17
DM OGTT only	5.8 (5.4–6.0) 40 (36–42)	5.7 39	1.00	34 (23%)	1 (1%)	<0.001
On OGTT						
NG	5.6 (5.2–5.8) 38 (33–40)	5.6 (5.3–5.9) 38 (34–41)	0.21	45 (30%)	79 (73%)	<0.001
IFG only	-	6.0 (5.5–6.6) 42 (37–49)	-	0 (0%)	5 (5%)	0.013
IGT only	5.7 (5.4–6.0) 39 (36–42)	5.9 (5.5–7.0) 41 (37–53)	0.31	47 (32%)	6 (6%)	<0.001
IFG & IGT	5.7 (5.0–6.3) 39 (31–45)	6.2 (5.9–6.8) 44 (41–51)	0.14	8 (5%)	4 (4%)	0.77
DM	6.0 (5.6–6.7) 42 (38–50)	8.2 (7.1–9.6) 66 (54–81)	<0.001	48 (32%)	14 (13%)	<0.001
DM on FPG	6.9 (5.8–10.2) 52 (40–88)	8.2 (7.1–9.6) 66 (54–81)	0.37	8 (5%)	14 (13%)	0.042
DM on 2hPG	6.0 (5.6–6.7) 42 (38–50)	8.5 (7.6–9.6) 69 (60–81)	<0.001	47 (32%)	12 (11%)	<0.001

Figure



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