Title: Point-of-care testing as a tool for screening for diabetes and prediabetes.

Running title: Screening for prediabetes

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Abstract

Aim To determine the utility of finger prick point of care blood glucose testing (POCT) for the detection of dysglycaemia

Methods A fasting POCT and an oral glucose tolerance test (OGTT) with laboratory assays were performed as part of the baseline screening for 5309 participants enrolled in Te Wai o Rona Diabetes Prevention Strategy. Participants were aged 46 ± 19 y with no self reported diabetes. Dysglycaemia including diabetes were defined using World Health Organisation (WHO) criteria. Agreement between the two fasting plasma glucose measurements and their screening properties (with sensitivity and specificity for cut points) were compared using receiver operator characteristic analysis.

Results 3225 participants had both capillary and venous fasting blood sampled within 30 minutes and then had OGTT. New diabetes was found in 161 participants (5.0%) and prediabetes in 414 (IGT 299, 9.3% IFG 115 3.6%). The mean difference in capillary and venous measures was 0.02 mmol/l (95%CI -0.04-+0.01; limits of agreement –1.37 -1.33 mmol/l). Capillary POCT was a poorer predictor of dysglycaemia and IGT and new diabetes (area under curve (AUC) 0.76 and 0.71) than venous laboratory analysis (AUC 0.87 and 0.81 respectively). Optimal screening criteria was best at a venous glucose of 5.4 mmol/litre; 77% sensitivity/specificity.

Conclusions POCT significantly underestimated the true blood glucose at diagnostic levels for diabetes. POCT cannot be recommended as a means of screening for or diagnosing diabetes or prediabetes.

Keywords Point of Care, dysglycemia, detection, prediabetes, Indigenous health, sensitivity, specificity

Abbreviations POCT, point of care testing; OGTT, oral glucose tolerance test; WHO, World Health Organisation; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; AUC, area under the curve; ROC, receiver operating characteristic; BMI, body mass index

Introduction

The use of point-of-care testing glucose meters (POCT) for monitoring blood glucose concentration in the management of diabetes is well established. A major advantage of POCT is ease of use, convenience, and accessibility. The analytical performance of most available glucose meters has been extensively evaluated with recent studies showing acceptable clinical accuracy and good correlations with laboratory analysers [1-3]. Clinical accuracy is defined as providing results that lead to the same clinical management or outcome for a patient. The industry standard, ISO/FDIS 15197 however, allows for up to 20% deviation from true blood glucose concentrations.

Despite the widespread acceptance and use of POCT in the management of diabetes, recent evidence suggests they are still not suitable (or accurate enough) for the diagnosis [4, 5] or screening for dysglycaemia including diabetes [6]. This is supported by international guidelines and recommendations [4, 7] which state that since higher quality laboratory glucose measurements for diagnostic purposes are readily available in most cases, it is important to demand the same quality from POCT. However, laboratory measurements through oral glucose tolerance test (OGTT) and venous blood samples are not always easily obtained due to time, expertise, professional attitudes and cost (eg in under-resourced countries). WHO suggest POCT where it is not feasible to obtain venous samples and undertake an OGTT. No recent research has investigated the diagnostic accuracy and use of modern glucose meters in large populations “in the field".

Fasting venous plasma glucose has limited utility when screening for diabetes [8-12] and dysglycaemia. Comparisons of the test characteristics of POCT with venous blood sampling and laboratory analysis in screening for and diagnosing diabetes, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are required to help inform current policy and assess the utility of modern POCT.

Te Wai o Rona Diabetes Prevention Strategy, a randomized cluster controlled trial of intensive lifestyle change, recruited 5309 participants [13]Baseline assessments included venesection and POCT.

The aim of this study is to determine in a large cohort, (i) the accuracy of a modern POCT glucose meter and whether it is suitable for screening for dysglycaemia (diabetes, IGT or IFG) and (ii) the utility of a fasting venous sample for screening.

Methods

Those invited were self-identified Maori aged ≥28 years on 30th September 2004, without known diabetes and resident within the boundaries of the Waikato District Health Board, and the tribal area of Ngati Tuwharetoa in the neighbouring Lakes District Health Board. Members of households with at least one Maori resident, Maori with past gestational diabetes mellitus or with 2 parents with known diabetes, were also considered eligible. Those terminally ill, unfit to sign a consent form or with known diabetes were excluded. Recruitment (5/2004-3/2006) occurred through health, community and media channels. Transport to the screening venue was provided. The trial is Australasian Controlled Trials Registry registered (ACTRN012605000622606), approved by local ethics committees (Northern Y Regional Ethics Committee) with all participants giving signed consent.

Fasting attendance was requested. On arrival at the screening venue,fasting and known diabetes status were ascertained. The finger was cleaned and warmed, and the blood droplet obtained using a Softclix Pro disposable lancet, an Accu-chek Advantage meter and strips (Roche Diagnostics, Mt Wellington, New Zealand. The glucose measurement range was 0.6-33.0 mmol/L. Whole blood values were reported. Care was taken to ensure insertion of the correct code key and that all strips had the same batch number. A phlebotomist sampled venous blood into a fluoride tube for glucose. A 75g oral glucose

load was given and a second blood sample taken for glucose measurements two hours later. Samples were centrifuged, separated and refrigerated within 30 minutes on site using a mobile laboratory. Standardised duplicate anthropometric measurements were recorded after the fasting sampling, and before the two-hour sample. Measurements were repeated if beyond a specified tolerance level.

Glucose was measured using the Hitachi 911 (Hitachi Limited, Tokyo, Japan). All assays were within target limits specified by the RCPA Quality Assurance Program. These assays were carried out by the Waikato District Health Board Laboratory which has IANZ ISO9002 Accreditation. Criteria for diabetes, IGT and IFG followed WHO criteria for venous and capillary samples [14]

Statistics

Data were analysed using SPSS, version 14.0 (SPSS Inc, Chicago, Ill, USA). Data are summarised by mean±SD and percentage. Mean difference (bias) between POCT capillary blood analysed by the Accu-Chek glucose meter and the laboratory measure of venous plasma glucose and limits of agreement were determined using the Bland-Altman technique [15]. Concordance between POCT and laboratory measurements was assessed using the method of Lin[16]. Receiver operating characteristic (ROC) curves, plots of sensitivity and specificity of the test for each value of the POCT and venous laboratory measurements enabled determination of screening, optimal and diagnostic cut-offs.. The area under the curve is 1.0 if the test can perfectly discriminate and 0.5 if there is no discrimination. The p value for the curve tests if the area is significantly different to 0.5. The utility of fasting plasma glucose to differentiate dysglycaemia was also examined using ROC-analysis. A p-value of <0.05 was considered significant.

Results

Of the 5309 participants enrolled in Te Wai o Rona Diabetes Prevention Strategy, 3225 completed the full OGTT and had a concurrent POCT glucose. Those who had the POCT glucose and OGTT on the same day were slightly older and had a higher BMI than those who were not fully tested (Table 1). Of the 3225, the OGTT diagnosed 115 (3.6%) with IFG only, 299 (9.3%) with IGT and 161 (5.0%) with new diabetes. Of those with IGT 78 (26.1%) also had IFG.

There was no apparent bias in fasting blood glucose between POCT and venous laboratory samples (Figure 1). The mean difference between the capillary and venous sample was -0.02±0.69mmol/l (95%CI -0.04 to 0.00; limits of agreement –1.37 to 1.37 mmol/l). However, the venous and POCT sample correlation was moderate (Pearson r = 0.70, p <0.0001, concordance correlation coefficient =0.69). The correlation with the two hour sample was greater for the venous sample (0.66 95%CI 0.64-0.68) than the POCT 0.52(95%CI CI 0.50-0.55). There was a tendency for the POCT glucose to be lower when venous blood glucose was ≥7 mmol/l; for the 115 participants at these levels, POCT underestimated the venous value by 0.44±1.03 mmol/l, and the agreement was moderate (Pearson r = 0.76, p <0.0001, concordance correlation coefficient =0.72). If a fasting venous glucose ≥7 mmol/l is the criterion for diagnosis of diabetes, then the POCT would have correctly identified 84/115 (73%) with a venous glucose above 7mmol/l. (Figure 2). This equates to an overall sensitivity of 0.57 and specificity of 0.98 with a positive likelihood ratio of 31.7.

Of those newly diagnosed with diabetes, 23% had a POCT value <6.1 mmol/l and 57% ≥7mmol/l. When fasting venous glucose cut-points were examined, 14% had a venous value <6.1 mmol/l and 71% ≥7 mmol/l. Venous fasting sampling alone therefore did not identify 29% (n=46) with new diabetes. Of those with new diabetes or IGT: 56% had a

POCT value <6.1 mmol/l and 20% ≥7mmol/l. When the fasting venous glucose cut-point 6.1 mmol/l was examined 44% had a fasting glucose <6.1 mmol/l and therefore 56% (258) required an OGTT to identify IGT or diabetes.

The utility for screening for any dysglycaemia was then examined. Sensitivity and specificity were also poor from the POCT as shown in Table 2. In 308 (12%) participants POCT value was <6.1 mmol/l but the venous was ≥6.1 mmol/l. For those with dysglycaemia the misclassified participants were 3 years older than those correctly classified and the misclassified women but not men had a smaller BMI and waist.. At a threshold of ≥5.6 mmol/L for the POCT, n=882 (27.3%) would be sent for further testing but 216 (37%) with dysglycaemia would remain unidentified (POCT<5.6 mmol/l). With an action point for further testing at ≥6.1 mmol/l on the POCT, 44% of those with dysglycaemia would have been missed.

The area under the ROC curve for any dysglycaemia was 0.76 (95% CI 0.74-0.79) for the POCT glucose and 0.866 (95% CI 0.85-0.89) for venous laboratory glucose. Utility of various cutoffs derived from this curve are shown in Table 3. Only 2/3 would be recognised as correctly having dysglycaemia with a cut point of 6.5mmol/L.

The area under the ROC curve for IGT and diabetes by POCT was 0.74 (95% CI 0.71-0.76) and 0.81 (95% CI 0.79-0.84) when the venous laboratory glucose was used. The optimal screening criteria for IGT and diabetes (where sensitivity equalled specificity) was at 5.4 mmol/l using POCT (68% sensitivity/specificity) and 5.4 mmol/l using venous glucose (77% sensitivity/specificity).

Discussion

To our knowledge this report is only one of two [17] studies this decade to examine the usefulness of POCT in an indigenous or other population at high risk of Type 2 diabetes.

We show that this first pass screening procedure had low utility even in conjunction with other observations e.g. BMI and waist for informing advice for further, more rigorous tests. Others (eg Cohen, [3, 18]) call for more stringent quality control of studies using POCT and indicate that precision may not be acceptable. The observed 73% concordance of the POCT value in those with fasting venous glucose levels of >7 mmol/l is similar to that observed on repeating an OGTT in people with diabetes[19]. Similarly the 12% discordant rate for a fasting glucose <6.1 mmol/l is in the range expected. Given the urgency[20] and cost implications for practical field methods to inform primary health care for purposes of prevention, monitoring and identifying those at risk we believe venous blood should only be used unless there is no alternative. In such settings, individuals with a negative screen need to be informed that the test does not exclude the presence of diabetes, IFG or IGT. This poor sensitivity is due to both the reliance upon the use of a fasting sample and the POCT itself.

Our analysis is limited by the fact that the testing was only undertaken once – we therefore do not have any precision data on either the POCT or the OGTT. While the mean fasting glucose concentrations by the 2 methods were remarkably similar, there was a great deal of individual variation. Temporal and physiological [21] variation in blood glucose, variation in instrument precision and differences between plasma and whole blood glucose means that the use of cut-off criteria will always have some diagnosed with a disease on one day and not meeting the diagnostic criteria on the next time of testing and vice versa. The Accu-Chek Advantage meter measures whole blood capillary glucose levels which is adjusted by a factor to coincide with laboratory reports of plasma glucose level which is ~11%[7, 22] higher than that of whole blood. This is likely to vary between individuals eg with haematocrit [22] which can influence the measurement. We

used only one type of meter but others have found similar magnitudes of bias with other meters[3].

The strategy of screening all members of a high risk population for diabetes with POCT and then applying a diagnostic test is appealing. Based on our analysis we can say that this course of action is unlikely to save time and money. Even in this high risk population, the positive predictive value is low, supporting the view that POCT is not good enough for screening. The poor sensitivity when screening for such an important chronic disease raises the question whether this test should be advocated as it is, at present, in pharmacies and other health clinics where there is not a clear understanding of what the values obtained really mean[4] and the need for confirmation with an OGTT [2, 4, 5, 18, 23-26] still applies.

In pragmatic terms to get people to report to a screening site, fasting in the morning and then to wait quietly for two hours after drinking the oral glucose can increase participant burden. The relatively high uptake here shows that this is possible in indigenous and other high risk populations. Other benefits of finger-prick samples are their relative ease in collection compared with venous samples particularly in the obese, an issue of growing importance. Trained phlebotomists were required for venous sampling, although the ability to collect capillary samples for the laboratory may be of use[27].

There are a small number of potential biases in this study. The focus upon an ethnic group with a high prevalence of diabetes (and hence a higher prior probability of dysglycaemia), does imply high applicability to most other populations with a high prevalence of diabetes, among whom screening using POCT may appear tempting. Applicability to low risk populations (mainly of European descent) can not be commented upon. The loss of those who did not attend fasting or stay for the full OGTT would have an unpredictable impact on the results, as would the fact the participants were part of a

trial. While in many studies, the potentially more health conscious attend for trials [28, 29], in this cohort, many of those who attended were those attending to support another family member, or to use this as an opportunity to be tested for diabetes rather than through primary care. Additionally given that the capillary blood sample was always followed by the venous blood sample there could be different states of anxiety associated.

Conclusion

While it has been argued that POCT is useful for the diagnosis and exclusion of diabetes [17], our findings suggest that its use for both diabetes and pre-diabetes is too inferior to standard laboratory measures to be recommended for use. Not to make the additional effort required for venous testing could be deemed inadequate care. If used to speed up the diagnostic process for those with particularly high glucose concentrations, contemporaneous use of venous sampling is required.

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Table 1 Subject characteristics according to testing status

	Tested on same day (Mean ± SD)	Not tested same day (Mean ± SD)	P value (unpaired t-test)
Female, n	2065	1299	
Age, y	49 ± 13	45 ± 13	>0.0001
BMI $kg.m^{-2}$	32.9 ± 7.6	32.0 ± 7.8	0.001
Waist, cm	98.5 ± 16.8	96.6 ± 16.6	0.002
Male, n	1115	785	
Age, y	49 ± 13	46 ± 13	>0.0001
BMI $kg.m^{-2}$	32.7 ± 6.7	32.5 ± 6.7	0.5
Waist, cm	106.1 ± 16.6	105.9 ± 17.7	0.8

Table 2 Utility in screening for dysglycaemia (n=3225)

Classification	Fingerprick POCT*	Venous sample Laboratory testing	Same classification both tests	% agreement venous with POCT
Prediabetes=FPG† >=6.1mmol/litre				
Normoglycaemic	2743 (85.1%)	2650 (82.2%)	2435	91.9%
Dysglycaemia	482 (14.9%)	575 (17.8%)	267	46.4%
Diabetes				
Action point=POCT* 5.6 mmol/litre				
Normoglycaemic	2343 (72.7%)	2650(82.2%)	2127	80.3%
Dysglycaemia	882 (27.3%)	575 (17.8%)	359	62.4%
Diabetes				

*POCT = Point of care testing; †FPG = Fasting plasma glucose

Table 3 Cut-off points and utility of finger prick point of care test for identifying dysglycemia (fasting venous laboratory measurement of glucose ≥6.1mmol/l)

Cut-off point	Value (mmol/l)	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio
POCT				
Screening*	4.2	0.97 (0.97, 0.98)	0.07 (0.06, 0.08)	1.2
Optimal†	6.2	0.44 (0.65, 0.68)	0.94 (0.93, 0.94)	7.4
Diagnostic‡	6.5	0.31 (0.29, 0.33)	0.98 (0.97, 0.98)	13.7

*Rate of true positives is maximised; †Optimises rate of true positives while minimising rate of false positives; ‡Maximises specificity while optimising sensitivity