

Evaluation of a Self-Administered Oral Glucose Tolerance Test

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OBJECTIVE—To assess the feasibility of using a disposable, self-administered, capillary blood sampling oral glucose tolerance test (OGTT) device in a community setting.

RESEARCH DESIGN AND METHODS—Eighteen healthy and 12 type 2 diabetic volunteers underwent six 75-g OGTTs using a prototype device in the following three settings: unaided at home (twice); unaided but observed in clinic (twice); and performed by a nurse with simultaneous laboratory glucose assays of 0- and 120-min venous plasma samples (twice). The device displayed no results. A detachable data recorder returned to the clinic provided plasma-equivalent 0- and 120-min glucose values and key parameters, including test date, start and end times, and time taken to consume the glucose drink.

RESULTS—The device was universally popular with participants and was perceived as easy to use, and the ability to test at home was well liked. Device failures meant that 0- and 120-min glucose values were obtained for only 141 (78%) of the 180 OGTTs performed, independent of setting. Device glucose measurements showed a mean bias compared with laboratory-measured values of +0.9 at 5.0 mmol/L increasing to +4.4 at 15.0 mmol/L. Paired device glucose values were equally reproducible across settings, with repeat testing showing no training effect regardless of setting order.

CONCLUSIONS—Self-administered OGTTs can be performed successfully by untrained individuals in a community setting. With improved device reliability and appropriate calibration, this novel technology could be used in routine practice to screen people who might need a formal OGTT to confirm the presence of impaired glucose tolerance or diabetes.

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A screening mechanism that identifies those with, or who are at risk for development of, diabetes might allow more targeted use of public health resources for early treatment and prevention of diabetes complications (1,2).

The current gold standard for diagnosing diabetes is the oral glucose tolerance test (OGTT), but it is resource-intensive. Individuals are required to attend a clinical facility where a health care professional can draw venous blood samples at times 0 and 2 h after an oral 75-g anhydrous glucose challenge. The need for clinic-based trained

staff and for laboratory access limit the availability of OGTTs for large-scale screening initiatives because of cost and the inconvenience for the individual, with travel to a clinic and possible time off work being barriers to compliance.

To overcome these issues, a novel disposable electronic OGTT device has been developed. This device is provided in the form of a stand-alone kit containing everything required to perform an OGTT with simple written and pictorial instructions. It uses capillary blood samples, which are not retained, and it does not

display any results. Instead, a detachable data recorder that contains no patient identifiers is forwarded to a central reading center. Here, a readout of the test results is obtained and matched to the individual concerned using each recorder's unique serial number.

We have performed a proof-of-concept study to determine whether it might be feasible for untrained individuals to use this novel device to perform OGTTs in a community setting.

RESEARCH DESIGN AND METHODS

This was an investigator-led, single-center, randomized, open-label, three-setting, crossover device trial, with replicate testing in each setting. It received ethical approval from the South East London Research Ethics Committee 3 and complied with The World Medical Association Declaration of Helsinki (1964) and its amendments and clarifications, the European Union Clinical Trials Directive (2001/20/EC), and ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). All participants provided written informed consent.

Participants

Eighteen healthy individuals and 12 individuals with type 2 diabetes were recruited via local advertisements and from the Oxford Centre for Diabetes, Endocrinology, and Metabolism research recruitment register. To be eligible, participants needed to be at least 18 years of age with sufficient vision and reading comprehension to follow instructions written in English. Diabetic participants needed to have been undergoing stable therapy for 3 months before enrollment, with diet alone or metformin monotherapy. Healthy individuals with previous experience of finger pricking techniques or who had undergone a previous OGTT were excluded, as were those who were pregnant or planning a pregnancy or receiving therapies known to significantly affect glucose levels, e.g., high-dose corticosteroids.

Device

Prototype electronic OGTT devices (SmartGRA) were provided by Smart-Sensor Telemed (Abingdon, U.K.) as part

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of a stand-alone kit containing written and pictorial user instructions, a printed user guide, a premixed 75-g glucose drink (Biofile, Turku, Finland), four sterile lancets (Vitrex Medical A/S, Herlev, Denmark), tissues, and an adhesive finger bandage. The device consisted of a number of integrated components, which included 0- and 120-min glucose dehydrogenase biosensors, a clock with an interactive timer, a temperature sensor, a light-emitting diode and a beeper for alerts, and a detachable wireless-enabled data recorder encoded with a unique serial number.

Using both pictorial and written instructions, the device guided participants through the steps required to perform a correctly timed glucose tolerance test. Once the device had been activated by pushing the “on” button, participants were instructed to use a lancet to obtain a capillary blood sample for placement on the 0-min glucose sensor. They were then instructed to consume the entire glucose drink before pushing a “set” button to signal this had been completed. The next instruction was to rest without eating, drinking, or smoking for 2 h. At the 2-h time point, the beeper sounded, alerting the participant to use a second lancet to obtain a capillary blood sample for placement on the 120-min glucose sensor. To complete the test, the participant was then instructed to snap-off the data recorder and return it to the clinic. The remainder of the kit, including the now blood-stained glucose sensors, was disposed of in household waste.

Data recorders received by the clinic were read electronically by a near-field wireless scanning device to obtain 0- and 120-min glucose values and key parameters, including the test date, start and end times, and the time taken to consume the glucose drink.

Study design

Participants were required to undergo two OGTTs in each of three different settings. In the home setting, participants were asked to use the kit unaided by following the printed and pictorial instructions. In the observed setting, participants were asked to use the kit unaided while being observed by a research nurse. Nurses were instructed not to assist with the procedure or to answer any queries unless absolutely necessary to avoid a complete failure to perform the test. Any observed difficulties or interventions required were recorded and scored using a prepared checklist. In the

nurse-run setting, a trained research nurse performed the OGTT using the kit and also took simultaneous 0- and 120-min venous plasma samples for laboratory assay of glucose. Participants were allocated at random by an automated system to their individual sequence of test settings, stratified for diabetes status.

The two OGTTs within each setting were required to be performed no less than 2 days and no more than 7 days apart. Participants were instructed to follow their usual diet and exercise pattern on the day before every OGTT and to have nothing to eat or drink (except water) after 10:00 P.M. Patients using metformin were asked to delay their morning dose on test days until the OGTT was completed. Participants were strongly advised to have a light meal after every OGTT to avoid possible rebound hypoglycemia, with meals provided in the observed and nurse-run settings. They also were informed about potential adverse events, including discomfort related to finger pricks, bruising or discomfort at venepuncture sites, or symptoms consistent with hypoglycemia, and were asked to record any occurrences in a study diary.

User acceptability was assessed with an adapted validated device satisfaction questionnaire (Appendix 1) (3) and by means of focus groups. The questionnaire was administered after the first OGTT in each setting. Focus groups were conducted once all OGTTs had been completed and were moderated by a clinician (H.C.P.) and diabetes specialist research nurse (S.W.). Sessions, recorded digitally, used a question map of open-ended questions designed to identify emerging themes rather than to test predetermined hypotheses. Topics discussed included, but were not limited to, the following: 1) understanding of the kit and its limitations; 2) purpose of the kit; 3) convenience, difficulty, or barriers to the use of the kit; and 4) any anxieties or worries about using the device.

Outcomes

The primary objective was to assess the degree to which the two 0- and two 120-min glucose values measured by the device were repeatable in the home and observed settings compared with repeatability obtained in the nurse-run setting as the control arm. A secondary objective was to assess whether repeatability improved with OGTTs performed in successive settings, i.e., a possible training effect.

Bias and precision of device-measured capillary glucose values obtained in the nurse-run setting were assessed by comparing them with the simultaneous laboratory-measured venous plasma values.

User acceptability was analyzed by using focus group transcripts to develop codes identifying recurring themes, similar patterns, or distinctions supported by individual quotations. The themes were not predetermined and were not referred back to the focus group participants.

Statistical analysis

For this proof-of-concept study, a sample size of 30 participants was estimated to be sufficient to reliably exclude an unacceptable lack of repeatability in 0- or 120-min glucose levels obtained in the home or observed settings compared with the nurse-run settings.

Baseline characteristics were summarized for the overall population and by diabetes status using mean and SD for continuous variables and using percentages for categorical variables. Reproducibility of device-measured glucose values within each setting was assessed using their coefficient of variation (4). Descriptive statistics were presented by period and setting. Exploratory inferential analyses of 0- and 120-min device-measured glucose values were performed using a linear mixed-effects model (5) to provide 95% CIs for adjusted means and within-subject SDs. The model accounted for fixed effects of the sequences, periods, and settings, as well as for a random effect of subjects within sequences with an unstructured covariance matrix to allow estimation of different variance components for each setting. Because the mixed model uses all available data, the estimated SDs produced are generally slightly lower than those derived by descriptive statistics. To estimate the training effect, variance components for each period were estimated using a similar model in which the random effects were grouped by period instead of setting.

The agreement between nurse-run device-measured and laboratory-measured glucose values was assessed using the Bland-Altman limits of agreements method, accounting for multiple measurements of glucose per subject (6). For this analysis, four pairs of data from each subject (device versus laboratory 0- and 120-min glucose values on replicate days) were considered simultaneously.

Responses to the device satisfaction questionnaire were tabulated, summarized,

and reported overall by diabetes status and by test setting. Focus group transcripts were analyzed for recurring themes and supportive quotations were identified. Both these assessments of user acceptability were performed in an exploratory fashion and no formal statistical analyses were undertaken.

The trial was designed, implemented, and analyzed by the authors, who had sole access to the data and wrote and reviewed the paper.

RESULTS—Between 1 April and 15 June 2011, 73 potentially eligible participants were invited by mail to participate in the study. Of the first 45 who responded, 11 were excluded (6 because of concomitant medications, 3 because of previous finger pricking experience, 2 participating in other trials), and 4 declined to participate. Baseline characteristics of the 30 participants enrolled (18 healthy individuals, 12 with type 2 diabetes) are listed in Table 1. Diabetic participants were older, had higher BMI, waist circumference, systolic and diastolic blood pressures, and were more likely to have a family history of diabetes. The healthy subjects were using no concomitant medications. The majority of diabetic participants were using an ACE inhibitor and a statin.

Table 1—Baseline characteristics of participants

	Diabetic subjects (n = 12)	Healthy subjects (n = 18)	All subjects (n = 30)
Age (years)	62 ± 9	40 ± 16	49 ± 17
Female	6 (50%)	11 (61%)	17 (57%)
Ethnicity			
Caucasian	11 (92%)	18 (100%)	29 (97%)
Black	1 (8%)	0 (0%)	1 (3%)
Family history of diabetes	7 (58%)	5 (28%)	12 (40%)
History of gestational diabetes	0 (0%)	0 (0%)	0 (0%)
History of cardiovascular disease	1 (8%)	0 (0)	1 (3%)
Duration of diabetes (years)	5 ± 3	N/A	N/A
BMI (kg/m ²)	29 ± 3	25 ± 4	26 ± 4
Waist circumference (cm)	102 ± 9	85 ± 11	92 ± 13
Systolic blood pressure (mmHg)	139 ± 14	116 ± 9	126 ± 16
Diastolic blood pressure (mmHg)	75 ± 13	70 ± 6	72 ± 10
Concomitant medications			
Beta-blocker	1 (8%)	0 (0%)	1 (3%)
Thiazide diuretic	4 (33%)	0 (0%)	4 (13%)
Angiotensin receptor blocker	2 (17%)	0 (0%)	2 (7%)
ACE inhibitor	8 (67%)	0 (0%)	8 (27%)
Aspirin	3 (25%)	0 (0%)	3 (10%)
Statin	8 (67%)	0 (0%)	8 (27%)
Corticosteroid	0 (0%)	0 (0%)	0 (0%)

Data are mean ± 1 SD unless indicated otherwise. N/A, not applicable.

Device performance

Of the 180 OGTTs performed, the prototype device produced 152 (84%) 0-min glucose values and 162 (90%) 120-min glucose values. The missing values meant that only 141 (78%) of the OGTTs could be interpreted, giving success rates of 76% (82/108) and 82% (59/72) in healthy subjects and diabetic participants, respectively.

Device bias and precision

Device-measured glucose values obtained in the nurse-run setting were consistently higher than simultaneous laboratory-measured values (Table 2). The Bland-Altman plot (Fig. 1) shows a progressive positive bias with decreasing precision (heteroscedacity) at higher glucose levels. A quadratic regression line indicates a bias of +0.9 at 5.0 mmol/L, increasing to +0.8 at 10.0 mmol/L, +4.4 at 15.0 mmol/L, and +11.8 at 20 mmol/L.

Reproducibility between trial settings

No consistent differences were seen for 0- and 120-min coefficients of variation for replicate device-measured glucose values between trial settings, overall, or for healthy and diabetic individuals separately (Table 3), i.e., no setting appeared to produce more consistent results than another. No training effect was seen

either, i.e., there appeared to be no improvement in reproducibility with repeated testing, regardless of the order in which the settings were allocated.

Adverse events

No serious adverse events occurred. Seven adverse events were identified in five participants. Six of these (four episodes of shakiness or fatigue in three participants and two episodes of increased pulse in one participant) were considered possibly related to the use of the device, particularly the glucose drink, because they could reflect an autonomic response to rapid changes in plasma glucose levels. All adverse events resolved on the same day.

User acceptability

The device satisfaction questionnaire (Appendix 1) did not identify any adverse psychological impact. The median score for items 1–14 was ≥4 (disagree or strongly disagree) in all settings, except for item 4 (“has taught me new things about diabetes that I did not know before”), which had a median response of 3 (not sure) in the home and observed settings. For item 15, assessing the difficulty of the test, >90% of the participants in each setting provided a score ≤2 on a scale of 1 (easy) to 7 (difficult).

Three focus groups were performed with 22 participants (10 with diabetes). A summary of the recurring themes identified is presented. Supportive quotations from focus group members for each theme are listed in Appendix 2. Overall, there were no discernable differences between the opinions of the participants with and without diabetes or between focus groups.

Ease of use. Participants universally reported that the device was easy to use. One participant remarked, “I cannot really see how somebody could make it more straightforward.” Participants reported that assistance was not required from another person to help complete the test, and commented that even if the first experience of the device was alone at home the test could still be completed without difficulty.

Device failure. This theme emerged from all three focus groups. Four participants (18%) reported device failure and one reported the failure of more than one device. Participants did not seem unduly disappointed that their devices failed.

Clarity of instructions. The instructions printed both on the device and on the

Table 2—Differences between device and laboratory-measured glucose values

	Time 0 min			Time 120 min		
	Device glucose (mmol/L)	Laboratory glucose (mmol/L)	Device – laboratory (mmol/L)	Device glucose (mmol/L)	Laboratory glucose (mmol/L)	Device – laboratory (mmol/L)
Diabetic subjects (n = 12)	8.1 (0.5)	7.7 (0.5)	0.4 (0.3)	18.5 (1.7)	13.1 (1.7)	5.4 (1.3)
Healthy subjects (n = 18)	5.0 (0.1)	4.6 (0.1)	0.4 (0.1)	6.2 (0.2)	4.4 (0.2)	1.8 (0.1)
All subjects (n = 30)	6.2 (0.4)	5.8 (0.4)	0.4 (0.1)	10.1 (1.2)	7.0 (1.2)	3.1 (0.6)

Data are mean (adjusted for setting-by-period interactions) and standard error.

accompanying booklet were deemed clear and helpful by all participants. Participant responses varied regarding whether they followed the instructions on the device or those on the booklet, but both were deemed clear and sufficient enough to allow an individual to complete the test at home without any further assistance or guidance.

First impressions. Participants generally felt that when they first encountered the device, it was complicated. However, this did not turn out to be the case once they had followed the instructions. One participant remarked, “When I first looked inside it I went ‘God, what is all this?’ I was a little bit intimidated at first but I read the booklet first and it was very simple from there on.” Others felt that the

device looked fragile and were worried about damaging it, particularly when detaching the data recorder to return it to the study coordinating center. Some participants also felt that the plain white box packaging was too clinical-looking and were intimidated by it.

Difficulties completing the test. Overall, participants had no difficulties performing the tests. The only issues of note seemed to be the need to fast for 2 h during the test, and for some participants the taste of the glucose drink was unpleasant. Several participants thought the test kit should contain a snack or treat that could be consumed at the end of the test. One participant, who had hearing difficulties, commented that he thought the beep could have been louder and several

participants said they thought the inclusion of a countdown timer would have been useful. A few participants struggled with using the lancets to draw blood and expressed surprise at how little blood was required to perform the test. Advice in the device instructions to warm hands by washing them in warm water before using the lancets was useful. Several participants commented that the box in which the device was contained was too large to fit through their mailboxes.

Testing at home. Participants liked being able to perform the test in their own homes and thought this was a major advantage of the device. Those who lived a long way from the clinic liked the convenience and others simply preferred the ability to perform the test in the comfort of their own homes.

Potential screening for diabetes concerns. Those participants without preexisting diabetes did not express increased worry about diabetes by taking part in the study, but several commented that it had made them more aware of and more interested in diabetes. For those participants with diabetes, some found that taking part in the study made them think about their diabetes more than they usually would.

CONCLUSIONS—This initial proof-of-concept trial demonstrates that the prototype device evaluated can be used to perform self-administered OGTTs in a community setting. No previous training or experience with obtaining capillary blood samples was required in our study population of native English speakers with limited ethnic diversity. The device, however, had not been calibrated correctly, showing increasing bias and reduced precision at higher glucose values. Poor build quality also meant that only approximately four out of five OGTTs performed gave usable results. The reproducibility between repeated tests in each setting, however, was consistent with those seen in other studies (7,8) representing both day-to-day biological variation and assay variation. The main finding was that the device universally was found to be easy to use and the home testing feature was well-liked. Importantly, self-testing for glucose tolerance did not increase anxiety.

One obvious application for a reliable and properly calibrated device would be to perform screening for dysglycemia in a public health setting. Cost-effective identification of abnormal glucose

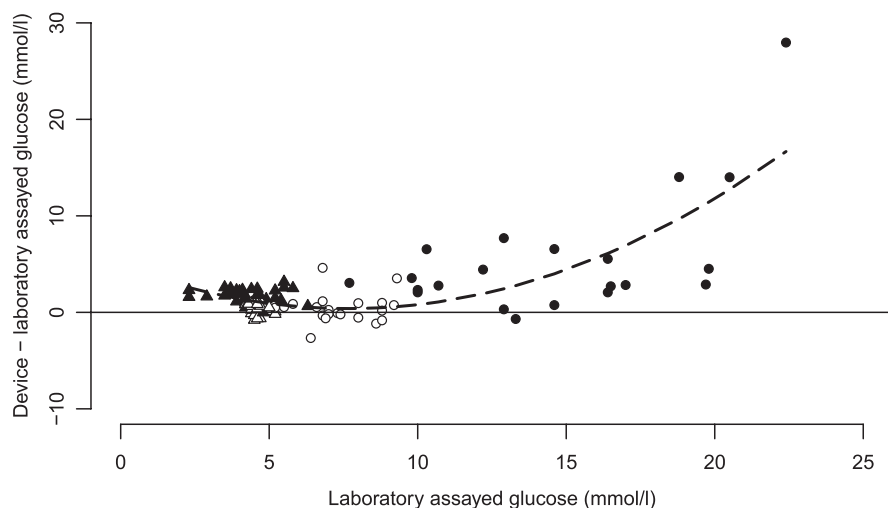


Figure 1—Bland-Altman plot, with quadratic model fitted line, showing relationship between device and laboratory-measured glucose values. White triangles indicate healthy subjects 0 min, black triangles indicate healthy subjects 120 min, white circles indicate diabetic subjects 0 min, and black circles indicate diabetic subjects 120 min.

Table 3—Reproducibility of device glucose measurements by time point, setting, and diabetes status

Time	Setting	Diabetic subjects		Healthy subjects		All subjects	
		Mean	CV	Mean	CV	Mean	CV
0 min	Home	7.7	9%	5.2	17%	6.3	14%
	Observed	8.1	19%	4.9	16%	6.2	18%
	Nurse	8.1	14%	5.0	7%	6.2	13%
120 min	Home	19.9	37%	6.3	19%	11.7	44%
	Observed	21.0	26%	5.9	22%	11.7	25%
	Nurse	19.7	23%	6.1	13%	11.6	25%

Means are adjusted for sequence, period, and setting by period interactions. CV, coefficient of variation.

metabolism has important implications for cardiovascular risk stratification and glucose management, with a growing body of evidence suggesting that earlier diagnosis and treatment of hyperglycemia are beneficial (9,10). At present, the utility of mass screening of asymptomatic individuals remains controversial (1,11), with most professional organizations advocating targeted screening for type 2 diabetes in high-risk populations (12,13). Recent guidelines have suggested that an $HbA_{1c} > 6.5\%$ can be used to diagnose diabetes but impaired glucose tolerance only can be detected using an OGTT (14). Also, the OGTT will remain an important method for diagnosing diabetes in many parts of the world where the use of HbA_{1c} is limited by common clinical conditions, e.g., hemoglobinopathies, anemia, the cost or availability of laboratory facilities, or the lack of trained staff to perform the test. At present, the cost of a mass-produced version of this device is unknown but is anticipated to be substantially less than the overall costs incurred in performing a standard OGTT (15–17).

In clinical practice, the device could provide a simple way to identify individuals likely to have diabetes or to be at high risk for development of the condition. These selected individuals could then undergo confirmative testing in an appropriate health care setting. Because the device delivers no glucose values or diagnostic information to the user, it does not circumvent any communication between the user and a health care provider who must interpret the results and offer appropriate counseling and treatment options as necessary.

The device also could prove useful as a research tool. Currently, there is ongoing global competition for >112,000 participants with impaired glucose tolerance or diabetes to enter 16

large-scale cardiovascular outcome trials (18). Many investigators are finding that screening mechanisms used in the past, e.g., hospital or individual practice database searches and local advertisements, can no longer deliver sufficient numbers of potential participants. Using properly calibrated production-quality versions of the device tested here might make it possible to screen for diabetes or impaired glucose tolerance rapidly and effectively in a larger community-based population. Alternatively, in a clinical trial requiring repeated OGTT monitoring of results, the device could provide a pragmatic alternative mechanism for collecting such data without the need for additional visits to the research site. The detachable data recorder of the device provides particular advantages in these settings because no blood samples or other biohazardous material need to be transported by mail, and the device augments efforts to maintain data privacy because it records no personal identifiers. Collected data only can be used by the coordinating center holding the device identification codes.

In conclusion, the device tested here potentially has significant practical benefits over the existing standard OGTT procedure. It is convenient, user-friendly, and can be operated without training or specialized laboratory facilities. Provided that the build quality and technical shortcomings can be remedied, the electronic OGTT device could be used successfully in routine practice for public health screening efforts or in the research environment.

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