Performance evaluation of a Self-Administered Home Oral Glucose Tolerance Test Kit in a Controlled Clinical Research Setting

RUNNING TITLE: Home OGTT

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CONFLICTS OF INTEREST

None

NOVELTY STATEMENT

- This study evaluates the performance of a novel, pre-production version of a home oral glucose tolerance testing device
- The device was easy to use, with an excellent device success rate and showed good agreement with 2 separate laboratory analysers in both normal glucose tolerance and glucose intolerance
- Our findings demonstrate that the device offers an alternative to clinic-based OGTT testing, with the potential for the test to be performed conveniently at home or in a community setting

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ABSTRACT

Aims: To evaluate the performance of the current, pre-production version of a novel Home OGTT device when administered by trained research nurses, compared to a reference laboratory glucose analyser and a second laboratory analyser, incorporating a sample processing delay to simulate normal practice.

Methods: One hundred women (19 to 48 years), with and without known glucose intolerance were recruited. Following an overnight fast, participants attended for a 75g OGTT. A fasting capillary sample was applied to the Home OGTT device with a corresponding venous sample collected and measured immediately on the reference YSI 2300 stat plus analyser, and following a 1 hour delay on the Randox Daytona plus analyser. The sampling process was repeated 2 hours after the oral glucose load.

Results: 97% of tested devices gave complete data for analysis. Good agreement was observed between the reference glucose analyser and the Home OGTT device, with the Home OGTT device displaying a small negative bias (-0.18mmol/l [-1.75 to 1.39] / -1.0% [-26.4 to 24.5]). When classified as normal glucose tolerant or glucose intolerant, the Home OGTT device showed 100% and 90% sensitivity and 99% and 99% specificity using FPG and 2 hour glucose respectively. Similar sensitivity (100% and 100%) and specificity (96% and 99%) for FPG and 2 hour glucose were observed using the secondary analyser.

Conclusions: The novel Home OGTT device was reliable and easy to use and showed excellent agreement with 2 separate laboratory analysers. The Home OGTT offers potential as an effective alternative for clinic-based OGTT testing.

INTRODUCTION

Traditionally, diagnosis of the various classifications of glucose intolerance has been achieved by performing an Oral Glucose Tolerance Test (OGTT) [1, 2]. More recently, measurement of glycated haemoglobin (HbA1c) has been employed as the diagnostic test [3-6], however there remain situations where HbA1c is not suitable for diagnosis, including its use in people with abnormal or variant haemoglobins, anaemia and conditions altering the lifespan of the red blood cell [7]. Many studies show HbA1c has poor sensitivity and specificity compared to OGTT for the detection of IGT, however performing an OGTT can be expensive, inconvenient and difficult to provide, and therefore measurement of HbA1c is often the only viable option.

In clinical settings where OGTT is the only recommended test, for example for gestational diabetes (GDM) in pregnancy and for cystic fibrosis related diabetes [8, 9], poor availability and accessibility of OGTT often leads to low compliance. A novel test kit has been developed that offers the potential for untrained individuals to perform an OGTT conveniently at home or in a community setting. The SmartSensor Telemed (SSt) Home OGTT device is an electronic device that has a wireless detachable data record that can be either returned for reading or scanned by smartphone with results uploaded to a Web based database for data processing and generation of test results. The Home OGTT device does not provide a result directly to the user. An evaluation of an early prototype version of this device has been described previously in 2013 [8], in people both with and without type 2 diabetes. While the device was well accepted by participants and showed good reproducibility across study visits, a positive bias was observed which increased at high glucose levels and there were a significant number of device failures. An editorial in the same edition of the journal suggested that if calibration and device failure rates were addressed, self-administered OGTT could impact future screening and diagnosis of diabetes [9].

The aim of this study was to evaluate the current version of the Home OGTT device, that has incorporated hardware and calibration improvements informed by the findings of the previous 2013 study [8]. The devices were tested in a study cohort similar to those at risk of GDM (except participants did not need necessarily to be pregnant), a population who could potentially benefit from the convenience offered by the device. The performance during an OGTT was compared to that of two different laboratory analysers; one measured immediately as the ‘reference’ result and a second processed and measured after a period of an hour, to more closely reflect the situation in a routine clinic.

PARTICIPANTS AND METHODS

This study was performed between April 2017 and June 2018 at the Joint Clinical Research Facility, ILS2, Swansea University, Swansea, UK, in compliance with Good Clinical Practice. Ethical approval was obtained from Wales REC 6 (17/WA/0079) prior to commencement of the study. All test procedures were carried out by research staff.

Participants

One hundred women aged 19 to 48 years inclusive, with and without known glucose intolerance and with a BMI $\geq$25 kg/m^2 were recruited into the study. The sample size of 100 participants was established following an interim statistical review of the data after 60 completed participants.

Home OGTT device

The Home OGTT devices were provided by SmartSensor telemed (Didcot, UK). The device consisted of 2 glucose dehydrogenase test strips (0 and 2 hour) with user activated buttons. The test procedure was driven by an integral clock and timer, with audible and visual prompts.

Each single-use, disposable device was stored in sealed packaging, and opened immediately prior to use. Full instructions to guide the user through the complete OGTT procedure were included. An example of the device with user instructions is shown in Figure 1. The process is similar to that described previously by Bethel et al [8]. Briefly, the device was activated by removing a protective cover over the 0 hour test strip and a capillary blood sample obtained using a lancet administered to the strip. After consuming the glucose drink, the 'set' button was pressed to begin the timer. After 2 hours, an audible alarm alerted the user to press 'stop' and repeat the sampling process with the 2 hour test strip. A further audible alarm confirmed the test was complete. Finally, the detachable data recorder was removed, scanned and the result automatically transferred to a secure Web based database.

Study procedure

All study procedures were performed by research nurses, fully trained in the use of the Home OGTT device. Following an overnight fast, all participants attended for a 75 gram OGTT. At time 0, a fingerprick capillary blood sample was applied to the 0 minute glucose sensor and the Home OGTT device timer initiated. From the same capillary sample, haematocrit was also measured (Hemo Control

Haemoglobin Analyser, EKF Diagnostics, Penarth, UK). At the same time, a corresponding venous blood sample was taken into a sodium fluoride /potassium oxalate vacutainer (Becton Dickinson, Berks, UK) for determination of plasma glucose on 2 laboratory analysers utilising glucose oxidase. Following the blood collection, a drink containing the 75g glucose (Polycal, Nutricia, Trowbridge, UK) was consumed. After 2 hours, the glucose sampling was repeated. Following this the detachable data recorder was removed, scanned and the result automatically transferred to a database.

Laboratory measurements

Venous blood in sodium fluoride / potassium oxalate, was immediately aliquoted into 2 separate tubes. The first tube was centrifuged immediately for 5 minutes and the plasma decanted and measured (YSI 2300 stat plus, Yellow Springs Instruments, Hants, UK). This YSI glucose value was considered the 'reference' value. The second tube was centrifuged for 5 minutes after a period of an hour, to simulate the delay in processing and measurement that may be expected in routine practice. This 'routine' sample was subsequently measured using a Randox Daytona Plus analyser (Randox Laboratories Ltd., County Antrim, UK). Daily internal quality control samples were run prior to any study samples (Assayed Chemistry Control Plus, levels 2 and 3, Randox Laboratories, County Antrim, UK).

Due to the difficulty in obtaining venous blood from a small number of participants, the reference YSI sample was prioritised and consequently fewer 'routine' samples were available for analysis using the Randox Daytona Plus analyser.

Data analysis

Method comparison was assessed using Bland Altman plots (absolute and relative bias) of the Home OGTT device versus the reference YSI values.

To view the results in a more clinical context, participants were categorised as normal glucose tolerant or glucose intolerant according to the WHO (2006) criteria. Agreement of the diagnoses generated using the Home OGTT device and the routine Daytona plus lab analyser with the reference YSI analyser were assessed using Receiver Operating Characteristics (ROC) curves (sensitivity and specificity) and positive and negative predictive values (PPV and NPV) [10].

RESULTS

Demographic characteristics

Mean (SD) age, BMI and haematocrit of the participants was 35.8 (7.84) years, 33.9 (5.97) kg/m^2 and 39.1 (4.07) % respectively. The measured glucose concentrations ranged from 3.13 to 23.2 (5.37 [4.71, 6.54]) mmol/l (median [25^{th},75^{th} percentiles) on the reference YSI analyser and from 3.25 to 20.47 (5.22 [4.64, 6.46]) mmol/l (median [25^{th}, 75^{th} percentiles]) on the Home OGTT devices.

Comparison of SST OGGT device with YSI analyser

Of the 100 Home OGTT devices used, 3 devices failed to generate one or both results (1 generated a fasting result only, one generated a 2 hour result only and 1 failed to generate either result), meaning a total of 98 fasting and 98 2 hour results were included for comparison.

Good agreement was observed between the reference YSI and Home OGTT device glucose, with a small negative bias (-0.18 mmol/l [-1.75 to 1.39mmol/l] and -1.0% [-26.4 to 24.5%]; absolute and relative mean [95% limits of agreement] bias, respectively) observed for the Home OGTT device compared to the YSI glucose values (Figure 2 A and B).

Diagnosis / Interpretation

Participants were classified as glucose intolerant by either fasting plasma glucose (FPG) $\geq$6.1 mmol/l or 2 hour plasma glucose (PG) $\geq$7.8 mmol/l or a combination of both (FPG$\geq$6.1 and/or 2 hour PG $\geq$7.8 mmol/l) by all analytical methods (Home OGTT device, YSI and Randox Daytona Plus), with the diagnosis using the YSI taken as the reference diagnosis.

The sensitivity and specificity of the Home OGTT device and Randox Daytona Plus analyser are shown in Table 1 and ROC curves shown in Figure 3. The Home OGTT device showed 100% and 90% sensitivity using the FPG and 2 hour glucose respectively, with corresponding specificity of 99% for both. Similar sensitivity (FPG and 2 hour PG 100%) and specificity (96% and 99%; FPG and 2 hour PG respectively) were observed with the Randox Daytona Plus.

Positive (PPV) and Negative (NPV) values for device and routine are shown in Table 2. Home OGTT device PPV and NPV all exceeded 90% versus the YSI diagnosis by FPG only, 2 hour PG only and combined FPG and 2 hour PG. For the Randox Daytona Plus, the respective PPVs were slightly lower but displayed NPVs of 100% for all diagnoses.

DISCUSSION

Although measurement of HbA1c is commonly used as a diagnostic test for diabetes, there remain situations where HbA1c is not suitable and an OGTT needs to be performed. In clinical settings where OGTT is the recommended test, for example for gestational diabetes in pregnancy and for cystic fibrosis related diabetes, poor availability and accessibility of OGTT often leads to low compliance. A novel test kit has been developed with the intention that untrained individuals can perform the OGTT conveniently at home providing a convenient alternative to a conventional clinic-based test. In this study, the performance of the novel Home OGTT device was evaluated in a cohort of overweight women of childbearing age and compared to the concentrations and diagnoses obtained using two separate laboratory analysers.

Out of a total of 100 tested devices, 97 generated both fasting and 2 hour results, illustrating the reliability and ease of use of the device in its present pre-production form. Across a wide glucose concentration range, the device performed well with good agreement with the reference glucose analyser, with a small negative bias observed for the Home OGTT device. When classed as glucose intolerant by the reference glucose analyser, the device displayed very high sensitivity and specificity for both fasting and 2 hour results. In addition, compared to the reference analyser, the device positive and negative predictive values were very high.

A previous study [8] using an earlier prototype version of the device demonstrated ease of use, both by nurses and untrained volunteers, however a significant device failure rate (22%) and positive bias (0.4 mmol/l and 3.1 mmol/l for fasting and 2 hour glucose respectively) which increased at higher glucose concentrations was observed. In our study the high device success rate and small overall bias, illustrates that the hardware and calibration changes implemented in these pre-production devices have resulted in a significant improvement in performance.

In routine practice during an OGTT, there is generally a delay between sample collection and processing and analysis in the laboratory. To simulate this delay, an aliquot of each collected venous sample was left unprocessed for a period of an hour, before centrifuging and analysing on a second glucose analyser (Randox Daytona Plus). Compared to the reference YSI diagnosis, the sensitivity and specificity of the routinely handled samples was equivalent to that of the Home OGTT device, with similar agreement observed.

The limitations of this study are that the evaluation was performed in a specific population, with the OGTT procedures performed by research nurses trained in the use of the device. This was to establish the improvements in performance characteristics of the current version of the device in a controlled setting, prior to testing under ‘real-life’ conditions. Further studies will be required to determine

whether the performance we have observed is comparable across a more diverse participant group, reflecting that of the overall population and also when the procedures are performed by the participants themselves, without input from research staff.

The excellent agreement between the Home OGTT device and laboratory analysers makes it an effective alternative for clinic-based OGTTs, and in particular in parts of the world where the use of HbA1c is limited by common clinical conditions, e.g., haemoglobinopathies, anaemia, the cost or availability of laboratory facilities, or the lack of trained staff to perform the test. As the device does not give glucose values or diagnostic information directly to the user, interpretation of the results will remain with the health care provider who can then offer the most appropriate advice or treatment options. The Home OGTT device is also easy to use giving the potential for a significant improvement in compliance with uptake. The SSt Home OGTT device offers a convenient, cost-effective route to detecting prediabetes and diabetes or as a research tool, being far more sensitive and specific than HbA1c and fasting glucose.

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Glucose intolerant by:		**Device**			**Routine lab analyser**	
	N	Sensitivity	Specificity	N	Sensitivity	Specificity
FPG (≥6.1mmol/l)	98	1.000	0.988	90	1.000	0.961
2 hour PG (≥7.8mmol/l)	96	0.900	0.987	83	1.000	0.986

Table 1 ROC analysis with sensitivity / specificity for both device and routine laboratory analyser compared to reference YSI diagnosis

Glucose intolerant by:	**Device**		**Routine lab analyser**	
	PPV	NPV	PPV	NPV
FPG (≥6.1mmol/l)	0.941	1.000	0.824	1.000
2 hour PG (≥7.8mmol/l)	0.947	0.974	0.933	1.000
FPG ≥6.1 and/or 2 hour PG ≥7.8mmol/l	0.909	0.973	0.850	1.000

Table 2 Positive (PPV) and negative (NPV) predictive values for both device and routine laboratory analyser compared to reference YSI diagnosis

FIGURE LEGENDS

Figure 1 Example of device including user instructions

Figure 2 Absolute (a) and relative (b) bias. Solid blue line = bias, broken lines = 95% limits of agreement.

Figure 3 ROC curves for Home OGTT device using (a) FPG (b) and 2 hour glucose and Randox Daytona Plus using (c) FPG and (d) 2 hour glucose respectively against reference YSI 2300 classification