

Clinical article

Title: Comparing the diagnosis of gestational diabetes using the oral glucose tolerance test and a designed breakfast in a randomised, cross-over trial

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Synopsis: The designed breakfast glucose profile provides a user-friendly, standardised, palatable and promising alternative option to diagnose gestational diabetes mellitus that merits further investigation.

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Abstract

Objective

This study compared a standardised, user-friendly designed breakfast (DB) to the 75g OGTT, comparing venous and capillary glucose values for the diagnosis of gestational diabetes.

Methods

A prospective, randomised, cross-over trial comparing the gold standard OGTT to a designed breakfast glucose profile (DBGP) in the diagnosis of gestational diabetes, was performed from March to December 2015. Fifty-one patients, attending the high-risk antenatal clinic at Tygerberg Hospital, were randomised to OGTT or DBGP at baseline. One week later, before intervention, the alternative test was performed. Fasting and 2-hour, venous and capillary values were measured. Patients qualified for screening on risk factors: previous gestational diabetes, previous unexplained intra-uterine death, previous macrosomic baby, booking BMI $>40 \text{ kg/m}^2$, age >40 years, affected first degree relative, susceptible family origin (Asiatic), acanthosis nigricans and polycystic ovarian syndrome.

Results

Fasting and 2-hour capillary glucose values measured during the OGTT correlated significantly with laboratory venous samples (Pearson's 0.74; $p < 0.001$ at both time intervals). The 2-hour capillary glucose values obtained for the DB showed satisfactory correlation to the current gold standard OGTT (Pearson's 0.54; $p < 0.001$).

Conclusions

The designed breakfast glucose profile provides a user-friendly, sufficiently accurate, promising alternative to diagnose GDM that deserves further investigation.

Introduction

The obesity pandemic is challenging healthcare in general with obstetrics disproportionately affected. Low and middle-income countries (LMICs) are in a period of epidemiological disease transition, experiencing the “double burden” of infectious diseases and under-nutrition, as well as chronic lifestyle diseases such as obesity. In South Africa 69% of women aged 20 years or older are overweight or obese.[1] Obesity together with advancing maternal age, decreasing levels of physical activity, and poor diets with high caloric content have continued to increase the incidence of gestational diabetes mellitus (GDM).

Robust studies, study groups and international bodies have proclaimed the negative effects of poor glycaemic control during pregnancy advocating timely diagnosis and stricter management to curb the morbidity associated with GDM.[2,3] Consensus has not been reached on whether to employ universal or selective screening and which specific test to use. However, with ever-increasing numbers and finite resources, particularly in LMICs, obstetric clinics must apply pragmatic policies. The true incidence of GDM in South Africa is also not known. This is partly because of the utilization of selective screening and the different cut-off values used by different obstetric units across the country.

In the Western Cape Province of South Africa, the provincial guideline lists risk factors for GDM and directs selective screening. [4] It offers two options for diagnostic testing, the first being a formal oral glucose tolerance test (OGTT), using 75grams of dextrose with fasting and 2-hour venous glucose values. The OGTT is unpleasant and requires laboratory facilities. The alternative glucose profile (GP) which is performed in the clinic, comprises a fasting capillary glucose measurement, consumption of a non-standardised glycaemic load (patient's

breakfast) and a 2-hour capillary glucose measurement. The GP is easy to perform and is regularly used at the Tygerberg Hospital, but a recent study found that the breakfast meals varied widely in carbohydrate content.[5] This provoked the search for a standardised, readily available, user-friendly, "designed breakfast" (DB). The Future Life Excel[®] meal was identified as the ideal product to use as it was available on local tender, available to all community-care clinics and could easily be pre-measured to contain 75 grams carbohydrate. The aim of this study was to compare the capillary glucose profile utilizing the DB to the 75g OGTT. Capillary samples obtained during the OGTT were also compared with laboratory measured plasma glucose levels.

Materials and methods

This prospective, randomised, cross-over study was performed in the High-Risk Antenatal Clinic at Tygerberg Hospital, a secondary and tertiary referral centre in the Western Cape Province of South Africa, from March 2015 to December 2015. The provincial guideline advocates selective screening, listing established risk factors for the development of GDM. These included previous gestational diabetes, previous unexplained intra-uterine death, previous macrosomic baby > 4,5 kg, body mass index at booking >40 kg/m², maternal age >40 years, a first degree relative with diabetes, family origin with a high prevalence of diabetes (Asiatic), acanthosis nigricans and polycystic ovarian syndrome.

Patients with known pre-gestational diabetes mellitus and patients on chronic medication known to adversely affect glucose homeostasis were excluded from study participation.

This study planned to recruit 50 women at high risk of developing GDM. The number of women to be recruited was determined by the nature of the study and the available resources, including the time constraints of the principal investigator (a trainee specialist). Written informed consent

was obtained by the principal investigator. Computer-generated random numbers, in blocks of ten were placed in consecutive, opaque, sealed envelopes. Subjects were then randomly allocated to undergo either an OGTT or designed breakfast glucose profile (DBGP) at baseline. One week later, before any intervention (including dietary advice), the alternative test was performed in cross-over fashion with each subject acting as her own control. To limit any patient-initiated interventions, the results of the tests were not disclosed to the patient until both tests were complete.

The OGTT was performed using pre-measured 75 grams of dextrose dissolved in water and ingested orally within 10 minutes. Both venous and capillary samples were taken at fasting and two hours. Venous samples were drawn from the antecubital vein in a heparin-fluoride-containing vacuum tube, hand-delivered and processed within two hours in the hospital laboratory. Capillary samples were taken for comparison to venous values. A single HbA1C level was also collected at the first visit.

The meal utilized in this study was selected based on its favourable composition (75g carbohydrate with a fat and protein content below levels that may interfere with carbohydrate absorption) and the availability on local hospital tender.[5] During the DBGP, 125 grams of Future Life Excel® with one standard 6-gram sachet of white sugar (providing a total of 75 grams of carbohydrate) was mixed with water to achieve the patients desired consistency, resulting in a thick or thin "porridge". The DB content was pre-measured by a dedicated dietitian using a calibrated scale. Patients were instructed to consume the full portion within 10 minutes. Fasting and two-hour capillary samples were recorded. No venous samples were drawn.

All capillary samples were measured with the same Accu-chek Active® hand-held machine and measuring strip codes were confirmed before each measurement. Care was exercised to limit any contamination such as food or fluid that could affect the accuracy of the capillary sample. The finger used for the measurement was cleaned with an alcohol swab and thoroughly air-dried. Accu-check Active® device and test strips determine blood glucose concentration by reflectance photometry. The Roche® package insert states that the device is calibrated (corrected) to reflect plasma levels even though whole blood is applied to the test strip.

The fasting and 2-hour diagnostic values for true gestational diabetes were set at 5.6 mmol/l and 7.8 mmol/l respectively in accordance with the Western Cape and recently updated NICE-guidelines.[2,4] Only one high value was needed to test positive. Any measurement in keeping with overt diabetes according to the WHO-guidelines for non-pregnant individuals served as an exclusion criterion.

The primary outcomes were the correlations of the venous and capillary glucose values of the OGTT as well as the two-hour capillary values of the OGTT and the DBGP.

Patient information and data were entered onto a spreadsheet using Microsoft Excel®. Statistical analysis was performed using IBM SPSS version 24. Pearson's correlation and intraclass correlation coefficients, using an absolute agreement definition, were computed to assess relationships between variables. Statistical significance was assessed at the 0.05 level.

The study complied with the World Medical Association Declaration of Helsinki - ethical principles for medical research involving human subjects and was approved and registered by

the Human Research and Ethics Committee at the Faculty of Medicine and Health Sciences, Stellenbosch University (S13/10/205).

Results

All 58 patients approached to participate in the study consented. These were not consecutive cases but rather the first 58 eligible women when the principal investigator was available in the clinic for the duration of tests. Six patients were lost to follow-up and one was excluded due to a delay in performing the second tolerance test (interim period of 14 days). No patients were excluded due to the diagnosis of overt diabetes at the initial visit. The descriptive baseline data of the final 51 cases are shown in Table 1.

The screening risk factors that identified these women as candidates for the diagnostic tests were as follows: BMI ≥ 40 kg/m² (n=37; 73%), previous unexplained intra-uterine death (n=11; 22%), maternal age ≥ 40 years (n=6; 12%), first degree relative with diabetes (n=5; 10%) and previous macrosomic baby ≥ 4.5 kg (n=4; 2%). Nine patients (18%) had more than one risk factor. The time interval between the first and cross-over tests ranged from 5-9 days, median 7.

The correlations between venous and capillary measurements within the OGTT as well in between the two modalities are shown in Figures 1 and 2.

Although the primary outcomes were the correlations of the venous and capillary glucose values of the two tests, the diagnostic accuracies of the tests were also examined. The OGTT with venous sampling, the OGTT and the DBGP with capillary sampling identified five, six and seven cases of GDM respectively. When considering the OGTT with venous sampling as the

gold standard, three cases were missed by the DBGP, while four false positives were diagnosed, but three of the four false positives were due to higher measured fasting capillary values (Table 2).

In keeping with the finding of a significant correlation between venous and capillary sampling, the OGTT with capillary sampling performed well at the diagnostic threshold for true GDM. Only a single case of GDM diagnosed with a borderline elevated fasting venous value at 5.6 mmol/L was missed. When looking at 2 hr tolerance values, the OGTT capillary sampling identified all the positive cases. Two false positives were, however, identified with the respective corresponding negative venous sample values 7.7 mmol/L and 6.9 mmol/L respectively.

Due to small numbers in the positive group, the interpretation and value of sensitivities and specificities when comparing the tests are of limited value and should be interpreted with caution. (Sensitivity 25%; Specificity 96%; PPV 33% and NPV 94% for 2hr DBGP capillary glucose versus gold standard 2hr OGTT venous sample).

No patient had an HbA1c measurement that met the WHO diagnostic criteria for overt diabetes mellitus in non-pregnancy i.e. all measured HbA1C's were $\leq 6.5\%$. Amongst the patients who met diagnostic criteria for GDM based on the gold standard OGTT, HbA1C values ranged between 5.5 and 6.3 (mean 5.8%) as shown in Table 2.

Discussion

The need for a pragmatic diagnostic modality in the current environment of economic pressure and an obesity pandemic is great. This study compared the current "gold standard" OGTT to

the designed breakfast glucose profile (DBGP) and showed satisfactory correlation between capillary and venous samples within and between the two modalities.

There are few studies on incidence and risk factors for GDM in sub-Saharan Africa and heterogeneity is high. In the index study the DBGP identified five cases (9.8%) of GDM in a study population considered to be at high risk of dysglycemia and where selective screening was mostly driven by obesity. In other studies, the incidence of GDM approximates 14% when high-risk women were studied. [6,7] The current incidence of GDM in South Africa is unknown.

The landmark Hyperglycaemia and Adverse Pregnancy outcome study (HAPO) published in 2002 [3] was a robust study that examined pregnancy outcomes in 23 316 women whose plasma glucose levels were ≤ 5.8 mmol/L fasting and < 11.1 mmol/L 2hrs after a 75g oral glucose load. The study reported a strong correlation between increasing maternal glucose levels at 24-32 weeks' gestation and a range of adverse maternal and fetal outcomes. No specific plasma glucose value above which the risk of adverse pregnancy outcomes was markedly increased was found, but instead revealed a continuum of risk with increasing maternal glucose levels. Diagnostic criteria are thus necessarily arbitrary cut-offs based on an odds ratio for adverse outcome. Two large randomized intervention studies confirmed the observations of the HAPO trial by clearly demonstrating the benefits of treatment for both mother and foetus at mild glucose elevations in later gestation.[8,9] Lifestyle modification formed the basis of therapy in both studies, with pharmacological intervention only required in a minority of study subjects. In the index study, the difference between "positive" and "negative" values were mostly small and the focus should thus rather be on the range of values rather than absolute diagnostic cut-offs.

The significant correlation between the venous and capillary glucose values employed simultaneously as part of the OGTT and the subsequently capillary values in the DBGP demonstrate the potential use of user-friendly, capillary sampling in a clinical setting. The outcome of the tests as a whole at the proposed diagnostic thresholds did, however, differ and may modify the subset of women diagnosed as having GDM. The OGTT capillary samples showed excellent correlation with the 2hr venous measurements identifying 100% of the GDM cases. The DBGP capillary sampling performed less well, confirming the diagnosis of GDM based on the 2hr sample in only one out of the four cases, but the numbers are small.

The formal OGTT is globally accepted as the gold standard despite the fact that published evidence outside of, and during pregnancy revealed intra-individual variability and poor reproducibility.[10–12] A South African study by Bonongwe et al also questioned the reproducibility of the OGTT during pregnancy and proposed fasting glucose values to be more reliable.[13] In the index study, fasting glucose measurements identified a different subset of women with GDM compared to those identified by the 2hr OGTT samples. This finding is not unique to pregnancy, but has been observed in the general population as well,[14] and fasting glucose values are known to vary considerably in a single person from day to day.[15,16] Therefore, the current position requiring only one positive value (either fasting or 2hr) may be questioned.

The documented poor reproducibility of test results may explain why the capillary values of the DBGP did not correlate as well as the capillary samples done simultaneously with the venous sampling during the OGTT. Thus, at the low diagnostic thresholds currently adopted for diagnosing GDM, this might not necessarily reflect a diminished ability of the DBGP to assess glucose tolerability in accordance with the 75g OGTT standard as the time interval between

OGTT and DBGP was 5-9 days. Rather this could be interpreted as inherent inter-test variability.

The danger of missed treatment opportunities versus the cost of over diagnosis of GDM must be considered as well. Correct diagnosis and timely intervention helps optimize outcomes for mothers and foetuses. Point of care results for diagnosis and management, by using capillary sampling either as part of the OGTT or DBGP, eliminate the need for laboratory equipment and staff, expenses related to transportation (and potential loss of income) and the need for additional visits.

Limitations of this study include the small sample size, the resultant low positive rate for GDM and that no formal cost analysis was performed. Although study subjects were specifically instructed not to make any dietary adaptations in the one week interval between the two tests, the possibility of patient initiated dietary changes cannot be ruled out with absolute certainty.

The numbers in the index study are too small to draw firm conclusions but the more palatable designed meal showed statistically significant correlation with the gold standard OGTT for the diagnosis of GDM and should therefore be investigated further as an alternative with merits.

Author contributions

The main author recruited the patients, obtained written informed consent and collected all samples. All the authors were involved in the planning, protocol development and submission, data interpretation and final composition of the article.

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Conflict of interest

None to declare

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Table 1: Descriptive baseline data (n = 51)

Age (years)	31.5 (19 – 44)
Gravidity	3 (1 – 7)
Parity	2 (0 – 5)
BMI kg/m ²	42 (19 – 62)
• Normal n(%)*	2 (4)
• Overweight n (%)*	4 (8)
• Obese n (%)*	45 (88)
• Obese Class 3: BMI > 40 n(%)*	37 (73)
Hypertension n(%)	4 (7.8)
Gestation (weeks)	26 (22 - 29)

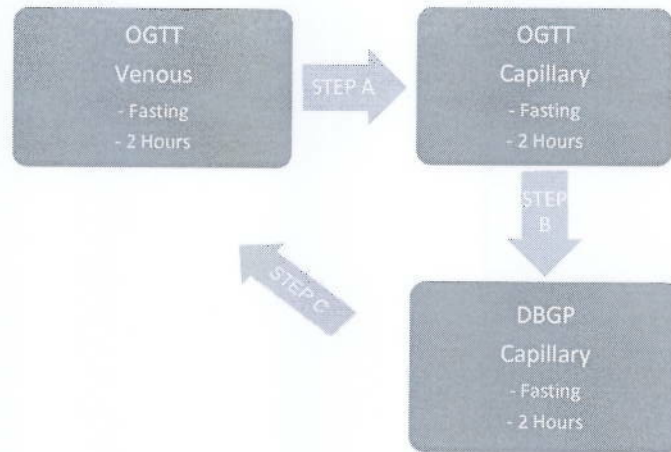
Data expressed as median (range); n (%) where specifically indicated; BMI = body mass index *Classification of adult underweight, overweight and obesity adapted from WHO 1995, WHO, 2000 and WHO 2004.[17]

Table 2: Venous and capillary glucose measurements in subjects with GDM by either test

Subjects	OGTT (fasting)		DBGP (fasting)	OGTT (2-hour)		DBGP (2-hour)	HbA1C (%)
	Venous	Capillary	Capillary	Venous	Capillary	Capillary	
1	4.7	4.4	5.1	8.6	7.8	5.6	5.8
2	4.7	5.6	4.0	6.4	7.4	4.7	4.8
3	3.9	4.6	4.6	7.7	9.2	7.9	5.2
4	4.4	4.4	4.9	9.2	9.2	8.8	5.6
5	5.4	4.9	5.8	6.2	7	6.5	5.6
6	4.7	5.4	5.1	6.3	6.9	8.2	5.5
7	4.1	*	3.7	8.7	*	6.5	5.7
8	4.7	5.4	5.8	7.1	7.4	7.3	5.8
9	5.6	4.1	4.6	5.4	6.3	4.4	5.5
10	6.3	6.4	5.8	8.4	10.5	7.3	6.3
11	4.3	4.7	5.6	6	6.2	6.6	6.2
12	5.1	5.4	5.3	6.9	8.6	6.8	5.6
Mean	4.8 ± 0.7	4.6 ± 0.7	5.0 ± 0.7	7.2 ±	7.2 ± 1.4	6.7 ± 1.3	5.6 ± 0.4
±SD				1.2			

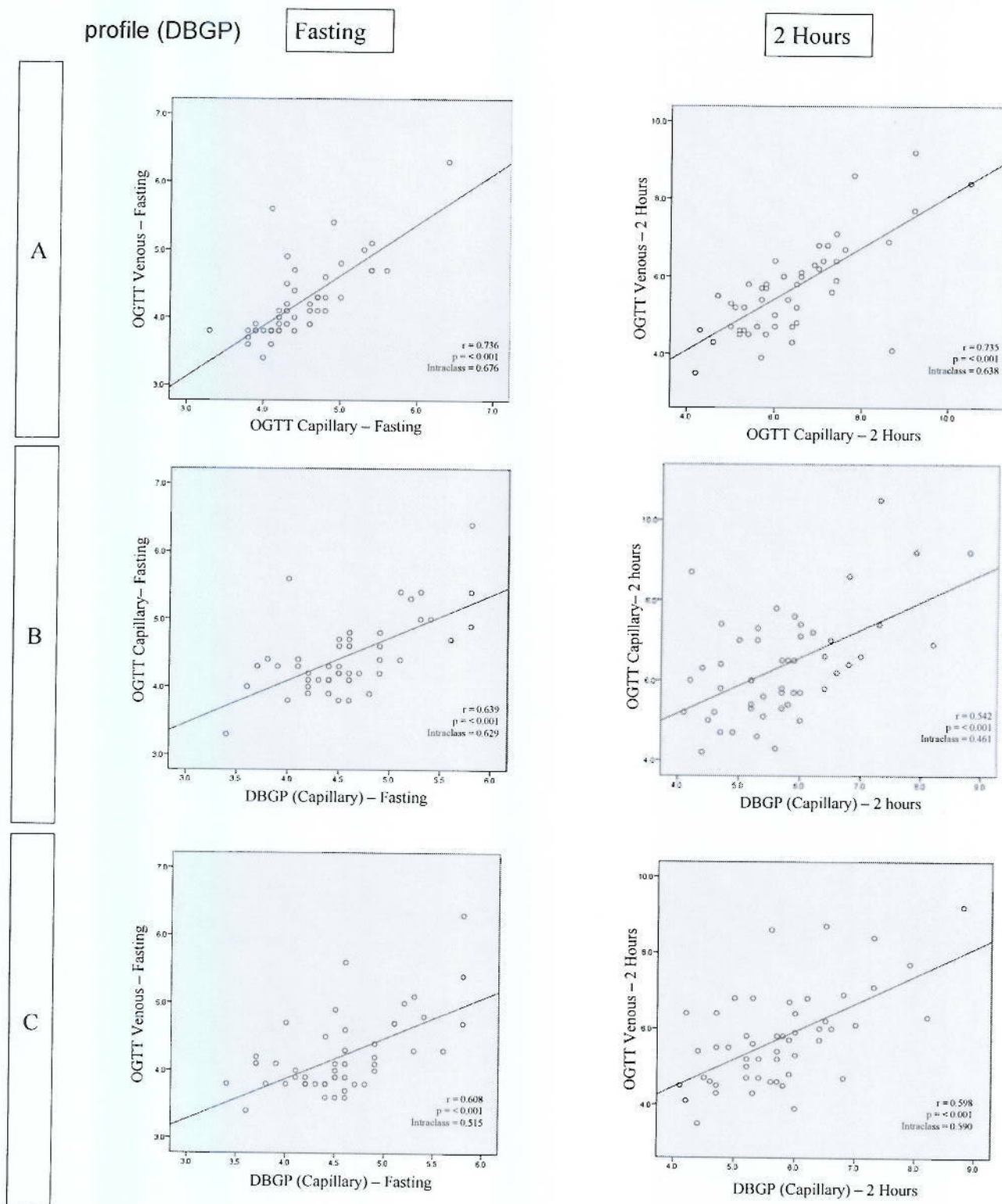
*All values expressed in mmol/L; diagnostic values bold font; shaded rows GDM based on gold standard OGTT with venous sampling; * = missing value*

Figure 1: Order of comparison illustrated.



Note: Step A: Comparing venous to capillary during the same OGTT. Step B: Comparing capillary values during OGTT with capillary values in DBGP. Step C: Comparing venous values during OGTT with capillary values from DBGP.

Figure 2: Scatter plots comparing fasting and 2-hour venous and capillary values during the oral glucose tolerance test (OGTT) and designed breakfast glucose profile (DBGP)



A) OGTT Venous vs OGTT Capillary. B) OGTT Capillary vs DBGP Capillary. C: OGTT Venous vs DBGP Capillary

Note: Pearson's correlation coefficients (r) as well as intraclass correlation coefficients (Intraclass) were used to limit bias.