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# Oral Glucose Tolerance Test (OGTT): Undeniably the First Choice Investigation of Dysglycaemia, Reproducibility can be Improved

*Dahiru Saleh Mshelia, Sani Adamu and Rebecca Mtaku Gali*

## Abstract

Type 2 diabetes mellitus accounts for  $\approx 90\text{--}95\%$  of those with diabetes, about 50% of those with type 2 diabetes are unaware and it can remain undiagnosed for up to 12 years,  $\geq 25\%$  of people have evidence of microvascular complications at diagnosis. The consequences of diabetes can be reduced by screening and early interventions. Urinalysis as a screening test is limited by its low sensitivity ranging from 21% and 64%, though has high specificity ( $>98\%$ ), it has a place where no other procedure is available. Fasting plasma glucose though recommended as a universal screening and diagnostic test for diabetes mellitus, a changed in the diagnostic criteria was made when this did not give corresponding hyperglycaemic impact compared to the OGTT results, bringing a complex and variable effect on the prevalence of diabetes and on subjects diagnosed. To date the searching to finding the corresponding FPG to what is normal or IGT is still ongoing. FPG testing poorly identify early signs of dysglycaemia. This is due to the difficulty ensuring compliance with instructions about fasting, FPG represents glucose handling during the moment of fasting period only and is affected easily by short-term lifestyle changes, FPG has diurnal variation, higher in the morning than in the afternoon, these may cause serious misclassifications. OGTT do indicates the pathophysiology responsible for diabetes better as it provides information on what happens in the postprandial state when the functional capacity of pancreatic  $\beta$ -cell is crucial. It accurately detects changes in post-prandial glycaemia that tend to precede changes in fasting glucose. OGTT is the gold standard for the diagnosis of GDM and the only means of identifying people with IGT and WHO placed emphasis on the OGTT as the “gold standard”, in diagnosis of dysglycaemia. Reproducibility can be improved remarkably when patient preparation, a forvariable atmosphere during the procedure, standardized sampling protocol, sample handling, and analysis are given high attention. Measurement of A1c equals the assessment of hundreds of FPG levels and also captures postprandial glucose peaks. Regrettably, it has been shown that 44% of people with newly diagnosed diabetes with OGTT had A1c  $<6.0\%$  and that a stronger correlations with plasma glucose is better in subjects with known diabetes, but not in the general population. A1C values just above the upper limits of normal require OGTT to be correctly interpreted; it is not available in many part of the world. Finally, A1c can not diagnose IFG and IGT to disclose high-risk subjects for

diabetes. In conclusion an OGTT is undeniably the best test in investigation of dysglycaemia, either with the intention of testing for pre-diabetes, type 2 diabetes, or for gestational diabetes mellitus.

**Keywords:** Dysglycaemia, T2DM, GDM, Screening, Urinalysis, Fasting Plasma Glucose, OGTT, A1c

## 1. Introduction

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

The diabetes epidemic is accelerating in the developing world and Type 2 diabetes has been recently reported in children and adolescents [1]. This is likely to increase further the burden of chronic diabetic complications worldwide. Diabetes is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life. These can be reduced by screening and early interventions (prevention or treatment).

## 2. Classification of diabetes mellitus

Several distinct types of diabetes mellitus exist and are caused by a complex interaction of genetic and environmental factors, however, assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. Therefore understanding the pathogenesis of the hyperglycaemia and to treat it effectively is more important. It can therefore simply be classified as presented below [2–4].

**Type 1 diabetes** ( $\beta$ -cell destruction, either immune-mediated or Idiopathic), accounts for only 5–10% of those with diabetes mellitus, usually leading to absolute insulin deficiency. The immune-mediated has strong HLA associations, linkage to DQA and DQB genes and is influenced by DRB genes, while the idiopathic has no known aetiology, has permanent insulinopenia, prone to ketoacidosis, has no evidence of autoimmunity, strongly inherited and is not HLA associated.

**Type 2 diabetes** (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance), accounts for  $\approx 90$ –95% of those with diabetes, and most patients are obese and/or have an increased percentage of body fat with predominant abdominal region distribution, ketoacidosis seldom occurs spontaneously. Patients may have normal or elevated insulin levels, though still less with respect to degree of hyperglycaemia, thus insulin secretion is defective and insufficient to compensate for insulin resistance. This type of diabetes is frequently associated with a high genetic predilection compared to the autoimmune form of type 1 diabetes, yet the genetics are complex and not obviously defined.

**Gestational diabetes mellitus (GDM)** [4]: Defined as any magnitude of glucose intolerance with onset or first recognition during pregnancy, whatever modalities of treatment use or whether the condition lingers after index pregnancy. It includes unrecognized glucose intolerance antedating or begun in the index pregnancy. It complicates  $\approx 4\%$  of all pregnancies in the USA, with prevalence ranging

from 1 to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes. Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester.

**Other specific types of diabetes [4]:**

- a. **Genetic defects of the  $\beta$ -cell:** Fair numbers of diabetes are affiliated with monogenetic defect in  $\beta$ -cell function, referred to maturity onset diabetes of the young (MODY) and are characterised by impaired insulin secretion with minimal or no defects in insulin action. Inherited in an autosomal dominant pattern
- b. **Genetic defects in insulin action:** These are rare causes of diabetes sequel to genetic abnormalities of insulin action. The metabolic flaws amalgamated with mutations of the insulin receptor may traverse from hyperinsulinaemia and modest hyperglycaemia to severe diabetes and some may have acanthosis nigricans, women may be virilized and have enlarged, cystic ovaries. Leprechaunism and Rabson-Mendenhall syndromes are two paediatric syndrome with mutations in the insulin receptor gene
- c. **Diseases of the exocrine pancreas:** Any process that diffusely injures the pancreas can cause diabetes, ranging from infections, trauma, metabolic, and rarely neoplasm
- d. **Endocrinopathies:** Several hormones (growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones as noted in acromegaly, Cushing's syndrome, glucagonoma, Pheochromocytoma, respectively can cause diabetes
- e. **Drugs or chemical-induced diabetes:** Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves but they may precipitate diabetes in individuals with insulin resistance
- f. **Infections:** Certain viruses have been associated with  $\beta$ -cell destruction; eg. Congenital rubella, Coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the diabetes
- g. **Unknown forms of immune-mediated diabetes:** In this variety, two conditions are known, others may occur. The stiff-man syndrome distinguished by inflexible axial muscles with painful spasms. Patients routinely present with high titers of the GAD autoantibodies, and roughly one-third will develop diabetes
- h. **Other genetic syndromes sometimes associated with diabetes:** Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus, eg., Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterised by insulin-deficient diabetes and the absence of  $\beta$ -cells at autopsy

**Prevalence and burden of diabetes mellitus, Table 1.**

Diabetes burden goes beyond individual but extends to families and society as a whole. It has huge consequences affecting both national productivity and economies particularly in the low- and middle-income countries when considering the projection for the year 2025.

- a. The prevalence is increasing and is projected to reach pandemic proportions over the next 10–20 years.
- b. By the year 2025, diabetes population will reach 333 million –90% will have Type 2 diabetes.
- c. There will be disproportionate in the developed and developing countries, 42% (increase from 51 to 72 million) and 170% (increase from 84 to 228 million), respectively
- d. Thus, >75% of all people with diabetes will be in the developing countries, as compared to 62% in 1995, over a period 30 years
- e. Without interventions to halt the increase in diabetes, there will be at least 629 million people living with diabetes by 2045.
- f. In most Western societies, the overall prevalence has reached 4–6%, and is as high as 10–12% among 60–70-year-old people.
- g. High blood glucose causes almost 4 million deaths each year, and the IDF estimates that the annual global health care spending on diabetes among adults was US\$ 850 billion in 2017.
- h. The annual health costs caused by diabetes and its complications account for around 6–12% of all health-care expenditure.
- i. The ADA estimated the national costs of diabetes in the USA for 2002 to be \$US 132 billion, increasing to \$US 192 billion in 2020.

**Table 1.**  
*The BURDEN of Diabetes Mellitus [5–8].*

Determinates of increasing prevalence of diabetes mellitus may be summarized as: Rising levels of overweight/obesity; increasing age of life expectancy in the general population; decreasing age of onset of type 2 diabetes; increasing number diagnosed due to decreased level of fasting plasma glucose; improved methods of health records; and increasing number of detection by practice-based screening and greater public awareness.

**3. Need for screening for dysglycaemia**

About 50% of those who have diabetes are unaware since the most prevalent form [9], Type 2 diabetes, can remain undiagnosed for many years, up 12 years [10], ≥25% of people have evidence of microvascular complications at diagnosis [11–13] and individuals with undiagnosed T2DM are at significantly higher risk for macrovascular complications than the nondiabetic population. Therefore, the magnitude of the epidemic increase in diabetes, particularly among younger age group including children, its serious long-term consequences, the high prevalence of undiagnosed diabetes and the proportion of cases with evidence of complications at diagnosis, coupled with complex treatment requirements that are difficult and costly to implement, undoubtedly create a strong imperative for screening, making the prevention of diabetes a critical public health goals. Since 1997 some major clinical trials examined whether lifestyle changes or pharmacologic interventions would prevent or delay the development of diabetes in populations at high risk [14–16]. These trials achieved 25–60% reduction in development of diabetes and the largest reduction by lifestyle modification and thiazolidinediones [14–16], though a lesser reduction (25—30%) were achieved with other drugs [16]. These must be emphasized particularly in the developing countries where the expected increase is disproportionately higher.

**3.1 Considerations in screening of a disease in general**

The term screening should be based on the WHO principles of screening document [17]. Screening is offered to individuals at sufficiently high risk of a particular disorder to be informed for further directives. These are usually carried out on



asymptomatic individual and are often initiated by medical personnel or authorities. Screening will not only benefit the individual but the society at large.

Although it is desirable to have a test that is both highly sensitive and highly specific, this is usually not possible. Only a valid, reliable and reproducible test in a population is recommended. This requires uniform procedures and methods, standardized techniques, properly functioning equipments, well trained personnel, and quality assurances are necessary to achieve these properties. Screening for dysglycaemia requires three-stages: (a) selection from the general population using practice registers or self-completed questionnaires amongst at high risk; (b) Testing blood glucose, eg OGTT; and (c) confirmation (or not) of raised blood glucose noted in stage (b) above using the same method of glucose testing. The biochemical tests currently available are blood glucose (Fasting blood glucose or OGTT), blood HbA1c or blood fructosamine measurements or urine glucose measurements. Each screening test needs a designated and pre-determined threshold or “cut point” that defines high risk.

WHO adapted 10 criteria that still serve as foundation for much of the discussions surrounding screening programs and are as indicated in **Table 2** [17].

The above criteria is not focus on the test itself but the disease and every criterion should be present for a given screening test to improve the health of the population.

3.2 Applying these qualities to dysglycaemia screening

The main reasons for the current interest in screening for T2DM can be summarized as follows [18]; which undauntedly fulfills the WHO principles of screening” document [17]

- a. Type 2 diabetes is becoming more common and many with the condition, about  $\geq 30\%$ , are undiagnosed [19]
- b. The rising prevalence of T2DM world-wide [18], the seriousness of the immediate effects and long-term complications of T2DM are alarming
- c. That there is a long, latent, asymptomatic period in which the condition can be detected [20]
- d. Many of newly referred cases of T2DM already have evidence of the microvascular complications of diabetes

a. The prevalence of disease to be screened for must be high in that particularly population to increase sensitivity of the test	e. There should be a suitable test or otherwise that is acceptable to the population
b. There must be an acceptable treatment for patient with the disease	f. The natural history of the disease should be adequately understood
c. Methods for diagnosis and treatment should not only be available but affordable	g. There should be an agreed policy on whom to screen and treat as a patient
d There must be a recognized latent or early symptomatic period	h. The cost of case-finding should be economically balance with attended objective of treatment
	i. Screening should be a continuous process for that particular population

**Table 2.**  
*The following criteria should available for disease to qualify for screening [17].*

- e. There have been advances in risk scoring, screening methods and more convenient methods of blood testing using HbA1c in non-fasting state
- f. Diabetes care is advanced, including screening for detection of complications early enough and a wider range of treatments for glycaemia and its complications
- g. Evidence supporting the efficacy of intensive blood glucose control [20, 21], blood pressure control [22], blood lipid control [23], and these development of CVD in T2DM
- h. Increasing pressure from professional organisations, lay groups and from some of the members associations of IDF to institute screening for type 2 diabetes if only to further highlight the increasing prevalence and public health importance of the condition
- i. Individuals with IGT have increased risk of CVD and on average, 11% of people with pre-diabetes develop type 2 DM each yr. (1.5–4%) and in 10 yrs. and 50% higher risk of CVD, this can be prevented or delayed by Life style and/or pharmacologic interventions.

### **3.3 However not everybody is convinced that it is worthwhile screening for type 2 DM and their views are**

- a. Some of the NSC criteria for screening programme are not met [18]
- b. A 13-year follow-up in health measures or cardiovascular morbidity showed no advantage after screening for diabetes
- c. The ADDITION trial did not show any benefit after applying intensified management
- d. Up to now there is yet to be a perfect screening test for dysglycaemia
- e. If other cardiovascular risk factors are assessed and addressed, the benefits of screening for hyperglycaemia are modest in terms of further reducing cardiovascular risk
- f. The proportion of undiagnosed diabetes has probably been reduced by opportunistic screening

Although there are advances in screening for and treatment of type 2 diabetes, the policies and practices do have profound consequences for individuals, health systems and society in general [18].

### **3.4 Consequences for individuals' include**

- a. The time and other resources necessary to undergo the screening and diagnostic tests may not be there particularly for the poor [18]
- b. The fair of unknown on both the test outcome, the reflection on societal views, the cost of treatment and what is said about the disease in the society is

grave. These may include occupational discrimination and/or increased costs or difficulty in obtaining insurance

### **3.5 The consequences on the health system and society as a whole are**

1. The costs and other consequences particularly on primary health care system of carrying out screening and confirmatory test may be huge and unattainable [18]
2. The additional costs of starting treatment early of diabetes and preventions and/or its complication
3. Since there is no perfect screening test yet, consequences of false negative and false positive results are inevitable and is grave
4. Any loss of production as a result of the earlier diagnosis of the condition (from absence from work or reduced job opportunities, for example)

### **3.6 The potential benefits of early detection of T2DM are**

- a. Not only boost life span but also the quality resulting from a diminish severity and occurrence of instantaneous effects or prevention or slow diabetes long-term complications [18]
- b. Increase savings and allow redistribution by reduced levels of care required for diabetes complications (reduction in hospital admissions and length of stay)

## **4. Methods use for screening of dysglycaemia**

### **4.1 Urinalysis**

The usefulness of urinary glucose as a screening test is limited because of the low sensitivity ranging from 21% and 64% with specificity >98% in studies which included performing OGTT in the entire study population or a random sample of negative screeners. Despite this, urine glucose testing may have a place in low resource settings where no other procedure is available. This is particularly so when the prevalence of undiagnosed diabetes is likely to be high [23, 24]. Urine should be protected from direct sunlight, add 5 ml glacial acetic acid to preserve glucose in the urine otherwise up to 40% may be lost after 24-hr storage at room temperature [25]. Keeping samples on ice-water slurring during collection is also recommended [26]. However, this may not be feasible in rural areas of developing countries; it is therefore recommended that urinalysis should be done immediately after urine collection in such situations.

### **4.2 Blood glucose estimation**

Plasma glucose estimation has high intraindividual biological variability (4–14%). This is accounted for by method of sample collection and storage, lifestyle measures while preparing for sample collection like exercise, calorie restriction and difficulty in ensuring fasting state. About 3–8 mg/dl/hr. of glucose is lost in a sample kept at room temperature. Therefore, in interpreting blood glucose test result, the



need to be conversant with causes of intraindividual and interindividual variation of blood glucose is necessary. Such variability can be grouped as

- a. The biological variability is substantially greater than analytical variability
- b. Analytical imprecision  $< 3.3\%$
- c. Bias  $< 2.5\%$
- d. Total error  $< 7.9\%$
- e. Glucose assay  $\sim 4\%$
- f. Biological CV  $6.9\%$

On the basis of biological variation, glucose analysis having analytical imprecision  $3.3\%$ , bias  $2.5\%$ , and total error  $7.9\%$ , may produce classification errors, although imprecision is usually low at the diagnostic decision limits. It is also believed generally that glucose assay is highly reproducible across laboratories, however, a recent survey conducted in 6,000 US laboratories clearly documented a significant bias in glucose assessment in as many as  $41\%$  of them, yielding a misclassification of glucose tolerance in  $12\%$  of subjects [27]. The coefficients of variation of A1c, FPG, and 2-h PG were demonstrated to be  $3.6\%$ ,  $5.7\%$ , and  $16.6\%$  respectively [28], reflecting both biological and analytical variability.

Preanalytical processing of blood samples can markedly affect the results of plasma glucose readings because ongoing glycolysis by erythrocytes and leukocytes prior to centrifugation lowers its concentration [29, 30]. A study reported  $5\text{--}7\%$  [ $0.6\text{ mmol/L}$  ( $10\text{ mg/dl}$ )] an average rate of glycolysis per hour [31]. This varies with the glucose concentration, temperature, white blood cell count and other factors [32], *for example*, it has been estimated that pre-analytical variability of FPG is  $5\text{--}10\%$  and the within day-day variability is  $12\text{--}15\%$ . Glycolysis can be attenuated by inhibition of enolase with sodium fluoride ( $2.5\text{ mg fluoride/ml}$  of blood) or, less commonly, lithium iodoacetate ( $0.5\text{ mg/ml}$  of blood). A citrate tubes should be use if a delay in centrifugation is expected because citrate more rapidly inhibits glycolysis [30]. It should be noted that although fluoride maintains long-term glucose stability, the rates of decline of glucose in the first hour after sample collection in tubes with and without fluoride are virtually identical [31]. Currently, both WHO and ADA recommend that for preanalytical processing for plasma glucose measurements involves venous blood collection into sodium fluoride (NaF) tubes with placement in ice-water slurry prior to centrifugation within 30 min of sample collection [33, 34]. The benefit of this policy is demonstrated in the following studies: An observed increase rate of GDM from  $11.6\%$  to  $20.6\%$  on changing to a protocol of centrifuging blood collected into NaF tubes within 10 min of venipuncture compared to delayed centrifugation was noted [35]. A study in Ireland showed a 2.7-fold higher ( $38.1\%$  compared with  $14.2\%$ ) when the ADA preanalytic protocol was followed compared with the previous standard practice of collecting blood into NaF tubes, leaving them at room temperature, and centrifuging after collection of all three samples [36]. Similarly, the impact of long delays in centrifugation for OGTT samples collected in NaF tubes on GDM diagnosis in Western Australia was estimated to be an under diagnosis rate of  $62\%$  [37]. In HAPO, a reference study for GDM, blood samples for all glucose measurements were collected into NaF tubes, placed in ice-water slurry immediately after phlebotomy, and kept that way until they could be centrifuge and separated [38].

### 4.3 Specimen for glucose estimation

Glucose can be measured in whole blood, serum, or plasma, but plasma is recommended for diagnosis. It can also be measured in capillary, venous or arterial blood. It is essential that in a repeat sampling for confirmation of blood glucose result, the same type of sampling used previously must be used. The molality of glucose (i.e., amount of glucose per unit water mass) in whole blood and plasma is identical. Although red blood cells are essentially freely permeable to glucose, the concentration of water (kg/L) in plasma is 11% higher than that of whole blood depending on the haematocrit, increasing to 15% at a haematocrit of 0.55 and decreasing to 8% at a haematocrit of 0.30 [39]. Therefore, glucose concentrations in plasma are 11% higher than whole blood if the haematocrit is normal. Glucose concentrations in heparinized plasma are reported to be 5% lower than in serum [40]. This may be caused by water shifting from red blood cells to plasma sequel to effect of anticoagulants. In feed (OGTT) state capillary glucose is higher by about [mean of 1.7 mmol/L (30 mg/dL), equivalent to 20–25%] than in venous blood, *but the mean difference in fasting samples is only 0.1 mmol/L (2 mg/dL) [41].*

### 4.4 Fasting plasma glucose (FPG): a tool in screening for dysglycaemia

In 1997, ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [42] recommended universal use of FPG for screening and diagnosis of diabetes mellitus because of its ease of administration, convenience, acceptability to patients, and lower cost in comparison to the OGTT and also based on assumption that the measurement reproducibility would be better. Since the goal and premise of diabetes management is the prevention of diabetes-associated complications, and this goal is best achieved when the disease is diagnosed at an early stage, the committee lowered the diagnostic threshold of FPG from 7.8 mmol/L to 7.0 mmol/L and also created a new category, defined as individuals exhibiting FPG levels between 6.1 and 6.9 mmol/L, called impaired fasting glucose (IFG) to describe the zone between the upper limit of normal FPG and the lower limit of the diabetic FPG. The IFG was believed at that time to be analogous to the zone between the upper limit of a normal 2-hr plasma glucose and the lower limit of the diabetic 2-hr plasma glucose described by IGT and was adapted by WHO in 1999 [43]. The FPG of 6.1 mmol/L was adopted by both ADA [44] and WHO [43] as the upper limit of “normoglycaemia” because this is the level above which first-phase of insulin secretion is lost in response to intravenous glucose and is also the level at which there is associated progressively greater risk of developing micro- and macrovascular complications.

In 2003, the ADA reviewed its diagnostic criteria when it found out that the FPG stated in the earlier classifications does not give corresponding hyperglycaemic impact compared to the OGTT results. The threshold for IFG was lowered from 6.1 mmol/L to 5.6 mmol/L [44] dependent on ROC curve analysis indicating that a cut-point of 5.4–5.5 mmol/L gives the best combination of sensitivity and specificity for predicting future diabetes, and this consequently increased the overall prevalence of IFG approximately three- to four-fold, though WHO and IDF maintained this as FPG 6.1–6.9 mmol/L. To date the searching to finding the corresponding FPG to what is normal or IGT is still ongoing.

Although both IGT and IFG are associated with resistance to insulin and increased insulin secretion, they do not identify identical patient populations and are not equivalent in predicting development of T2DM or cardiovascular events [45]. People with isolated IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with isolated IGT have

normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance [46]. Individuals with isolated IFG have reduction in both first-phase (0–10 min) during IVGT and early phase (first 30 min) during OGTT insulin secretion but maintained the late-phase (60–120 min) response during OGTT, while Isolated IGT apart from having defect in early-phase insulin secretion in response to OGTT also has a severe deficit in late-phase insulin secretion [47].

The prevalences of IFG and IGT varies widely, varied considerably among different ethnic groups [48], differ significantly in their age and sex distribution; and increase with advancing age. IGT is more frequent in women than in men [49]. A study of 1,245 Italian telephone company employees followed for 11.5 years found that, unlike baseline IGT, baseline IFG did not predict progression to DM, and the categories only overlapped 40% of the time [48]. The natural history of both IFG and IGT is variable, with approx 25% progressing to diabetes, 50% remaining in their abnormal glycaemic state, and 25% reverting to NGT over an observational period of 3-5 years [50, 51].

#### **4.5 Advantages of using FPG in screening for dysglycaemia**

American Diabetes Associated did not recommend OGTT to be used commonly in the diagnosis of type 1 and 2 diabetes because it was thought that if FPG is appropriately use it will identify almost the same number of dysglycaemia in the population as the OGTT, and that OGTT is not practicable in routine practice and in many studies OGTT is found to be poorly reproducible, with an estimated rate of only about 50–66% [52].

#### **4.6 Disadvantages of FPG in screening for dysglycaemia**

The fasting blood glucose testing in nondiabetic persons poorly identify early signs of dysglycaemia because high postprandial glucose marks the journey of first signs of abnormal glucose regulation and this best predict cardiovascular outcome. Fasting is not really the central issue and it seems to be overemphasized in diagnosing dysglycaemia.

One problem well known in the measurement of FPG in population studies is the difficulty in ensuring that all the participants have complied with the instructions about fasting [53]. Consequently, some participants with completely normal glucose homeostasis might have been misclassified into impaired fasting glucose category or, more rarely, even into a diabetes category. More so, FPG represents glucose handling during the moment of fasting period only (particularly so, of that moment of blood sampling), and this is affected easily by short-term lifestyle changes such as over activity, stress and drug ingestions. Therefore under these conditions subjects may be classified wrongly if only FPG is used. Knowledge of intraindividual variability of FPG concentrations is essential for meaningful interpretation of patient values. A study of healthy individuals [mean glucose, 4.9 mmol/L (88 mg/dL)] exhibited within- and between-subject CVs of 4.8–6.1% and 7.5–7.8%, respectively [34]. Recent evidence revealed a diurnal variation in FPG, with mean FPG higher in the morning than in the afternoon, indicating that many cases of undiagnosed diabetes would have been missed in patients seen in the afternoon [54]. A study with repeated OGTT in 31 nondiabetic adults at 48-hr intervals, demonstrated FPG varied by 10% in 22 participants (77%) and by 20% in 30 participants (97%) [44]. Similarly, in population studies of subjects with newly diagnosed diabetes showed a wide distribution of FPG, ranging in one study from <5.0 mmol/L to >30.0 mmol/L [55]. As a consequence, the sensitivity of the OGTT is naturally higher, given the current criteria.



The change in the diagnostic procedure has brought a complex and variable effect on the prevalence of diabetes and on subjects diagnosed. Many studies have reported that FPG and 2-hr plasma glucose do not identify the same people as having diabetes. The difference between the prevalence of diabetes based on the FPG and 2-hr criteria varied from  $-4.0\%$  to  $13.2\%$  in the 16 European survey in the DECODE study. In that study [56], of the 1517 people with newly diagnosed diabetes, 40% met only the FPG criterion, 31% met only the 2-hr criterion and 29% met both criteria. In the DECODA study [49], of 1215 subjects with diabetes by either criterion, only 449 (37%) met both criteria, of the 995 subjects with 2-hr  $\geq 11.1$  mmol/L, 546 (55%) had non-diabetes FPG value, and of the 669 subjects with FPG  $\geq 7.0$  mmol/L, 220 (33%) had non-diabetes 2-hr value. In the two studies the concordance rate ranges between 29–37%. In the NHANES study data cited in the 1997 ADA report showed 38% of subjects with newly diagnosed diabetes using only ADA criteria were missed when OGTT was carried out in the same population [42]. An even larger discrepancy was observed for the categories of IFG and IGT. In DECODA study, more than three quarter ( $\geq 3/4$ ) of the subjects with IGT would be classified as normal if only the FPG criteria is used. Degree of hyperglycaemia, age, sex, BMI and ethnicity influence the concordance. The severer the hyperglycaemia the better the agreement between the two criteria. It might therefore be appropriate to use the FPG alone in subjects with clinical symptoms of diabetes to confirm. It is inappropriate to use it as the only test in the general population for epidemiological purposes, or in cohort with slightly higher glycaemia but without any symptoms because a large proportion of subjects diagnosed by 2-hr criteria would not be identified by the FPG particularly in Asians. In 1999, WHO recommended retaining the use of OGTT for epidemiological purposes, and this appears to be particularly important for the Asian population. The 2-hr criterion is more sensitive in the elderly and fasting criterion in the mid-aged. Barrett-Conner, et al. [57] reported that 70% of women and 48% of men aged 50–89 years had new diabetes diagnosed solely by elevated 2-hr plasma glucose. Similarly, in the Early Diabetes Intervention Program study [58], 24% and 50% of subjects with OGTT-confirmed diabetes had FPG levels between 5.5 and 6.0 and 6.1–6.9 mmol/L, respectively. Still in a further study, an isolated elevation of 2-hr glucose (2-hr glucose  $\geq 11.1$  mmol/L and FPG  $< 7.0$  mmol/L) identified as high as 65% (61/94) of those with newly diagnosed diabetes while 76% (644/845) who were normal by fasting blood glucose were identified with IGT and these individuals carry high risk of cardiovascular disease events [59]. A recent report showed that even if the concordance between the WHO and ADA criteria increased with this lower cutoff of IFG, 29% of patients with diabetes revealed by an OGTT and 57% with IGT would still have remained undiagnosed using FPG [59]. All individuals with IFG should have an OGTT, as a significant number (approximately 5%, but up to 20%, in some populations) will already have diabetes by 2-hr post challenge criteria [60], so why delaying diagnosis, why not start with OGTT in the first place.

Impaired glucose tolerance (IGT), not diagnosed with FPG estimation, is associated with risk of cardiovascular events almost as high as in subjects with diabetes which is not similarly observed in people with IFG necessitating ADA to lowered the threshold for IFG from 6.1 mmol/L to 5.6 mmol/L in order to detect more subjects with pre-diabetes [61]. Consequently, with regards to the assessment of the risk of mortality and cardiovascular disease events, these discrepancies are crucially important. Therefore, in screening programs, clinical research, and population-based epidemiological studies, where participants often lack diabetes symptoms or complications, an OGTT is commonly used to detect diabetes, thus adding to the diabetic “pool” an equal-sized group of subjects with unrecognized diabetes and it is misleading trying to assess glucose homeostasis without information on post-prandial glucose metabolism.

In conclusion, although in clinical practice the OGTT is often regarded as a cumbersome, time-consuming, and patient-unfriendly procedure, for a more detailed and sensitive assessment of the glucose dysmetabolism, the oral glucose tolerance test (OGTT) is the best.

## **5. Oral glucose tolerance test (OGTT): undeniably the best choice investigation for dysglycaemia**

The OGTT is a non-physiological procedure required to unveil a highly compensated derangement in insulin's handling of glucose metabolism [62]. It requires administration of glucose solution to a patient who has indication for investigation of glucose dysmetabolism. Although more sensitive diagnostic test than FPG, the OGTT is affected by a number of factors that result in less acceptable reproducibility. Therefore OGTT requires that any influence in glucose handling must be eliminated or minimize where result should reflect patient's internal milieu, to increase reproducibility. Subsequently, patient preparation, a favorable atmosphere during the procedure, standardized sampling protocol, sample handling, and analysis are paramount. OGTT or 2-hr post-glucose levels do indicate the pathophysiology responsible for diabetes better than any other glycaemic parameter as it provides information on what happens in the postprandial state, when glucose is high in the system and when the functional capacity of pancreatic  $\beta$ -cell is crucial. Normal blood glucose levels 2-hr after glucose load indicate a good  $\beta$ -cell capacity, whereas high levels document an impairment of  $\beta$ -cell function [63]. This means that only 2-hr OGTT PG can provide reliable information on the key pathophysiological defect of dysglycaemia or providing advice regarding the correct therapy to overcome it.

### **5.1 Advantages of OGTT in screening for dysglycaemia**

The oral glucose tolerance test has a long history [64] but from time to time had to endure considerable criticism. One review pointed out that the considerable number of variables involved results in both poor reproducibility and difficulties in interpretation [65]. In spite of this the oral glucose tolerance test survives and for routine use in the diagnosis of diabetes mellitus it is not replaceable (Undeniably). The OGTT detects changes in post-prandial glycaemia that tend to precede changes in fasting glucose. In fact, inability to respond appropriately to a glucose challenge, i.e., glucose intolerance, represents the fundamental pathologic defect in diabetes mellitus and OGTT is currently the gold standard for the diagnosis of diabetes. The OGTT is vital for the characterization of metabolic syndrome, the metabolic actions of cardiovascular and metabolic drugs, and natural progression from prediabetes to T2DM. OGTT is extensively used as a sensitive indicator of GDM. Therefore, OGTT is an important Lab tool in preclinical studies as it provides an indication of the relative roles of insulin secretion and insulin resistance in the progression of glucose intolerance.

The OGTT allows all of the normal stages of insulin secretion and glucose processing to take place in sequence without causing stress or trauma to the subject. The OGTT is the most robust means of establishing the diagnosis of diabetes and provides a more comprehensive assessment of dynamic glucose handling. Thus, the OGTT more accurately mirrors daily life. OGTT is much more sensitive in identifying the loci of insulin resistance and its modulation by different interventions. Thus, the OGTT is useful as a research tool, yields laboratory data with greater relevance to the prevention and treatment of human disease. It is the reference method for the assessment of glucose tolerance, despite the notoriously poor



reproducibility of the test (CV = 50%) for 2 h blood glucose. Some of these cause of variations can be minimized with adequate attention to physical activities, dietary preparation and taking care of sample collection at the 2-hr sample (sampling must be done within 5 minutes of 120 minute [66]. The WHO (1999) placed emphasis on the OGTT as the “gold standard”, with both fasting and 120-min values being taken into consideration [67]. This is by no means a mistake. Only when an OGTT cannot be performed should the diagnosis rely on fasting levels. Other hormones and metabolites can be measured during OGTT, not just glucose and insulin, eg., the OGTT is the primary test used for the diagnosis of GH hypersecretion.

OGTT is the only means of identifying people with IGT, and IGT is an essential diagnostic step, especially when FPG is within the normal range, as these subjects are at high risk not only for type 2 diabetes, but in particular for cardiovascular disease. The main clinical significance of IGT are [68]: (1) It is a risk factor for type 2 diabetes, about 20–50% of subjects with IGT develop type 2 diabetes over 10 years; (2) It predisposes individual to cardiovascular disease (CVD); and (3) It is a component of the metabolic syndrome and its consequences. IGT when identified and subsequently managed will prevent or delayed progression to type 2 diabetes mellitus. It has been indicated by recent studies [69–71] that persons classified with IGT using WHO criteria have increased risk of cardiovascular disease, however many of these subjects do not have impaired fasting glucose (IFG) by the new ADA criteria. Furthermore, the OGTT by WHO criteria identifies diabetes in 2% more individuals than does FPG using ADA criteria [70], although diabetic individuals who are identified by both abnormal FPG and 2-h OGTT have a higher risk of premature death than those with only an increased FPG concentration [71]. More so, fasting plasma glucose alone fails to diagnose in about 30% of cases of diabetes diagnosed by OGTT. OGTT establishes whether an IFG subjects has normal 2hPG and only the simultaneous information obtained from 2hPG (OGTT) allows the screening to become effective. An important matter here is that people with IGT who cannot be identified by either FPG or A1c have  $\approx 40\%$  increased mortality compared with normoglycaemic subjects and lifestyle intervention in these individuals can prevents progression to type 2 diabetes and may reduce their mortality risk to the level observed among normoglycaemic population. These prevention benefits do not exist for A1c or FPG, and this evidences should not be forgotten when deciding the approaches to identify intermediate dysglycaemia. We should therefore make OGTT a priority in an attempt to diagnose hyperglycaemia as early as possible.

Thus, using solely FPG, would deceitfully reassure a large proportion of individuals as having NGT, without warning them on the benefits of preventive treatment. Epidemiological studies showed that A1c and plasma glucose (FPG and/or 2-hr OGTT) identify partially different groups of diabetic subjects. While A1c  $\geq 6.5\%$  identifies only  $\approx 30\text{--}40\%$  newly diagnosed patients with diabetes [72], a larger percentage was detected by FPG ( $\approx 50\%$ ), and more so by 2-hr PG ( $\approx 90\%$ ).

These findings are based on several recent studies, including the 2003–2006 NHANES study demonstrating only 30% of diabetic individuals were detected by A1c  $\geq 6.5\%$ , 46% by PFG  $\geq 126$  mg/dl, and the IRAS demonstrated 32%, 45%, and 87%, respectively) [73] indicating OGTT is superior. However, the pivotal issue on OGTT is its low reproducibility which is significantly represented by physiologic contexts of the test. The plasma glucose during OGTT are influenced by both insulin sensitivity and secretion, however, impact of other factors particularly incretins, neural responses to nutrient ingestion, gastrointestinal motility and gastric emptying are also important. These factors differ significantly between individuals and are part of non-modifiable factors that govern post-load glucose metabolism and plasma glucose concentration, and are difficult to measure in every

individual undergoing OGTT. Finally, all trials aimed at type 2 diabetes prevention included IGT subjects [74, 75], who could not be possibly recognised without OGTT, seems therefore evident that the routine execution of OGTT is presently the one and only possible answer (Undeniably) [76].

## 5.2 Disadvantages of OGTT

### 5.2.1 Factors why OGTT may not be the first choose in screening for dysglycaemia

- a. Biological variation which may account for about 5.7% of available blood glucose value
- b. Variable effects of administration of hyperosmolar glucose solution on gastric emptying, eg, nausea, vomiting, osmotic diarrhea, abdominal distension. Flavoring with sugar-free lemon and chilling increases palatability and may reduce nausea.
- c. More cost and time, Cumbersome, unfriendly procedure for patients
- d. Because of the OGTT's high variability and low sensitivity, epidemiological studies based on a single OGTT may overestimate the prevalence of diabetes by as much as 16%

Due to the number of limitations, the OGTT should be undertaken on two separate occasions before the results are considered abnormal (unless the initial results are grossly abnormal). It has high intra-and interperson variability. This may be due to a number of factors, including diet and exercise during the days before the test, caffeine use, smoking, medications, and stress. However, with careful patient preparation the impact of these modifiable factors can be markedly reduced resulting in improved reproducibility. These modifiable factors can be placed into three categories:

- a. When preparing patient for test: duration of fast; prior carbohydrate intake; medications (e.g. thiazide, oral contraceptives and corticosteroids); trauma; intercurrent illness; age; physical activity.
- b. Glucose given: quantity of glucose ingested; volume of administration; and rate of ingestion.
- c. Fasting sample: posture; anxiety; caffeine; smoking; physical activity; stress, and time of the day

This shows that with proper patient preparations spanning through history taking and physical examination and appropriate patient education will highly improve the reproducibility of OGTT, hence care must be taken of the factors [65, 77] in **Table 3** during patient preparation.

An increase in the volume or decrease in the osmolality of a meal may result in an increase in the rate of gastric emptying and in a subsequent increase in glycaemia. Gastric emptying has implications for the reproducibility of the OGTT. It was twice observed that the faster an OGTT meal is emptied from the stomach, the higher the resulting postprandial glycaemia level. About 30%, 19.8% and 14% differences in postprandial glucose after the dilution of 75-g (present study), 50-g and 25-g tolerance tests was noted, respectively [77]. The dilution effect is noted

a. The OGTT is a non-physiological procedure and the interperson variability is rather high.	e. Other factors are: Lack of adequate patient preparations, Diet
b. Analytical and biological variability	f. Exercise during the days before the test
c. Use of different samples(eg; venous and capillary for a repeat or during same procedure	g. Caffeine use, Smoking, Medications, Stress
d. Biological variation is been found to be up to 20–35%—these can be minimized by stringent careful attention to the protocol	h. Changed in ambient temperature
	i. Volume of the glucose solution
	j. Others are: gastric emptying, Intestinal absorption, the gastrointestinal hormonal stimulus to insulin release, the liver, and the pancreatic islets.

**Table 3.**  
*Causes of variability in OGTT results.*

more between 90 and 180 minutes post-glucose solution ingestion. It is possible therefore that some of the earlier reports of poor reproducibility of the test may be attributable to a volume effect. The gastric emptying falls as the glucose concentration rises and this was demonstrated over a wide range of glucose concentrations [77]. It has been suggested that this is due to the stimulation of receptors in the duodenum sensitive to the osmotic pressure of the duodenal contents. The rate for gastric emptying in normal individuals lies between 40 and 80 minutes. Chronic pancreatitis does, however, causes overt diabetes in some patients, and most patients with this condition have impaired insulin secretion [78] even if this is not sufficiently severe to produce disturbances in carbohydrate tolerance. The liver, situated between the portal and systemic circulation, is in a position to influence oral glucose tolerance profoundly. Reproducibility can be improved by drawing Blood at the stipulated time or at least within  $\pm 5$  minutes and centrifuge sample within 45 minutes of drawing it to obtain plasma.

To improve the reliability of a test it should be conducted in the individual that appropriately require the test, hence OGTT reproducibility can be improved when it is conducted in the selected individuals noted in **Table 4**.

5.2.2 Patient’s preparation for conduct of OGTT, improving reproducibility

Interaction with patients before procedure is very important because one of the conditions leading to spurious result in patient investigation is lack of patient’s

1. Age > 45 yrs. (type 2 among 40-70 yr —7%, IGT—20%. In general pop—4.3%	11. Women with polycystic ovarian disease
2. Body Mass Index(BMI) >27 kg/m <sup>2</sup>	12. Woman who delivered a macrosomic baby(>4 kg)
3. High risk ethnic groups—Africans, Carribeans, Asians	13. Have other clinical conditions associated with insulin resistance
4. Family history(first-degree relatives (increase risk by 2–4 fold	14. Hypertension
5. High waist circumference(>92 cm, >80 cm)	15. Recurrent infections
6. Sedentary lifestyle	16. It also helps determine if there is other condition that affects blood glucose levels (e.g., Cushing’s syndrome, celiac disease, cystic fibrosis, acromegaly, pheochromocytoma, hemochromatosis, or Wilson’s disease).
7. History of gestational diabetes mellitus	
8. Previous evidence of IGT or IFG	
9. Dyslipidaemia(decrease HDL and increase TGs)	
10. Patient with Cardiovascular disease	

**Table 4.**  
*Indications for OGTT.*

education and preparation. Interacting with patient is important in improving reproducibility of test for the following reasons:

- a. Enable the caregiver know about the patient—classify patient according to the three categories of tests mentioned earlier
- b. Educate patient about why he/she is coming for the tests, and emphasize on what to avoid during pre-test period, and make patient to understand his/her role in obtaining good result
- c. Know types of medications patient is on and withdraw those possible and record those which cannot be withdrawn
- d. Emphasize the importance of patient's compliance and the result outcome
- e. This interaction will prepare patient's mind and will alleviate fears and stress

## **6. Instructions to patient before the procedure: improving reproducibility**

The OGTT results can be affected by carbohydrate intake and duration of fasting preceding the test, time of day for the test to be performed or activity during the test, sample collection, and medications. Instructions are as follows:

1. Patient must be on meal containing >150 g carbohydrate (approximately ten 40 g slices of bread per day) in the last three days before the test, and in the night before the test should take 30-50 g of carbohydrate containing meal
2. No strenuous exercise three days prior to test, but normal work is allowed. Patient should not rush when coming for the test (avoid stress). Need to rest before for minimum of 15 minutes before conducting test
3. No alcohol or Caffeine use 48 hrs before the test and during the test
4. Overnight fast (8-14 hr) water is allow—for patients convenience
5. Time for the test (morning hour is preferred, convenience of overnight fast, and fluctuation in FPG-higher in the morning and lower in the evening)
6. Maximum 75 g, anhydrous (82 g monohydrate) glucose dissolved in 250–300 ml of water
7. Glucose solution ingestion within the shortest possible time—usually within 5 minutes. Intolerance for sweet taste—patient may come with lemon juice, sometimes lucozide (375 ml) can be used instead.
8. Others are Glucola (224 ml) equivalent of 75 g anhydrous glucose. Polycal liquid (previously called Fortical) is used as the glucose load. 61.4 g maltodextrin/100 ml. Oral glucose solutions come in 10 US fluid ounces



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<div><div>a. Once patient arrived, confirm compliance with preparations, with emphasis on duration of fasting</div><div>b. You may wish to put in place an indwelling drip for sampling to avoid the stress of repeated needle pricking during sampling</div><div>c. Ensure patient is comfortable before starting the procedure</div><div>d. Take sample for fasting and any other investigations intended, before ingestion of glucose solution</div><div>e. Constitute the glucose solution—75 g(anhydrous) and 82 g(monohydrous)—10% more of anhydrous glucose, in 250–300 ml</div><div>f. Ask the patient to take the solution within 5 minutes</div><div>g. Time 0 minute of the test is when patient start taking the glucose solution and not when fasting sample is taken</div><div>h. Take samples at 30 minutes interval for 2 hr.(3, 5 hrs) or at 2 hr. only</div><div>i. Same type of sample must be taken throughout the procedure(, venous or capillary)</div><div>j. No smoking, caffeine, alcohol or any exercise during the waiting period</div><div>k. Monitor patient especially when approaches convenience—patient may vomit</div><div>l. Should the patient sit, lie, stand, walk, talk, etc.(seating is preferred—minimal activity)</div><div>m. Only minimal activity is allow but ensue that patient remain comfortable throughout the period of the test</div><div>n. Label samples appropriately, place sample ice-water slurry and ensure separation within 30 min of sampling</div></div>
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**Table 5.**  
*Conduct of OGTT in a non-pregnant adult.*

(296 ml) bottles containing 50, 75, or 100 g of glucose (5, 7.5, and 10 g per fluid ounce)

9.If patient is under unavoidable stress, the test should be postponed

10.Patient should be aware of being seated in waiting area for a minimum of 2 hrs for the test

11.Failure to comply with all instructions will invalidate result

Ensure that all staff involved in undertaking any elements of the test have been provided with suitable training and are assessed to be competent (**Table 5**).

## 7. Interpreting OGTT result: improving reproducibility

### 7.1 Considerations when interpreting OGTT result

When interpreting the result remember that OGTT has variable reproducibility and care should be taken not to over-interpret the results. Use only one criterion, eg WHO criteria, to indicate a diagnosis of IFG, IGT or diabetes. In most cases the results of fasting and 2-hr post-glucose load are enough. Always look for help from local diabetes serves in uncertainty. Refer cases you can not evaluate to endocrinologist for further for assessment. Usually there are no causes of false-positive result when processes are strictly followed. These arts will improve the reproducibility.

### 7.2 While interpreting OGTT result you will not get information concerning

a. Patient preparation for and how the glucose was administrated.



- b. The result shows assessment of glucose tolerance at the time of the test only and cannot provide any other information.
- c. Results give only a qualitative idea of the average 24-hr blood glucose
- d. Nor will result predict response to hypoglycaemic therapy or the current or future risk of diabetes complications

Therefore result will be better interpreted with the cognition of the above in mind.

### **7.3 Result interpretation**

- a. Normal response has the following characteristics:

- 1. Initial fasting glucose within normal limits
- 2. The highest value does not exceed the renal threshold (160-180 mg/dl (8.8-10 mmol/L))
- 3. The fasting level is again reached by 2–2.30 hours
- 4. No glucose or ketone bodies are detected in any urine specimen

- b. Response of diabetic patient

- 1. Fasting blood glucose may raise above normal usually in the impaired range
- 2. The peak is reached between 1 and 1.30 hours
- 3. Glucosuria is usually present because the highest value exceeds the renal threshold
- 4. Plasma glucose does not return to fasting level within 2.30 hours, the most characteristic feature of DM response

- c. LAG curve for oxyhyperglycaemia

- 1. Normal Fasting glucose level
- 2. Plasma glucose rises rapidly within 30 minutes to 1-hr post glucose ingestion exceeds renal threshold with corresponding glucosuria
- 3. Return to normal quickly and completely
- 4. This is usually noted in Hyperthyroidism, post gastroenterostomy, during pregnancy, early diabetes

- d. Response for renal glycosuria

- 1. Glucose appears in the urine at normal plasma glucose much below renal threshold

- 2. Usually no glucosuria during fasting but mainly post-prandial
- 3. It may be physiological, in pregnancy or in renal disease or early diabetes
- e. A flat glucose tolerance curve can be a normal finding and is as a result of rapid metabolism and not of either deficient absorption or slow gastric emptying.

Under certain pathological conditions such as hyper- and hypothyroidism changes in the gastric emptying rate may significantly alter the shape of the glucose tolerance curves [79]. Rapid gastric emptying associated with duodenal ulcer and partial gastrectomy where plasma glucose rises rapidly within 30 minutes of glucose ingestion stimulating hyperinsulinaemia and resultant reactive hypoglycaemia though measurement of serum insulin levels does not reveal evidence of such direct relationship.

In a healthy young adult with increase physiologic activities, there is associated rapid metabolism and when venous rather than capillary blood is analyzed, a flat curve can be a normal findings and not of either deficient absorption or slow gastric emptying. Hypoglycaemia in a fasting subject is normally prevented by hepatic gluconeogenesis. This stopped after glucose ingestion when blood glucose rises, and begun when plasma glucose is falling preventing fasting hypoglycaemia Reactive hypoglycaemia in either normal healthy young adult, patient with peptic ulcer or partial gastrectomy might, therefore, be due to the failure of the liver to resume glucose production sufficiently and rapidly. The normal exponential pattern of gastric emptying results in a very gradual decline of the rate at which glucose enters the intestine and this should provide ideal conditions for the liver gradually to resume glucose production. The absorption of glucose by the small intestine is highly efficient. After ingestion of a concentrated solution, a combination of slow gastric emptying, dilution within the duodenum, and active peristalsis ensure that within the jejunum the glucose solution no longer remains hypertonic. The small intestine is efficient in glucose absorption.

Every dynamic test requiring appropriate patient preparation and procedure for the conduct of the test will not be without contraindication if result is to be reliable. Such contraindications for conduct of OGTT are shown in **Table 6**. The primary objective is to demonstrate presence of dysglycaemia in a condition that has long latent period, except when monitoring success of treatment in secondary causes of hyperglycaemia. Subject must be conscious and alert to obey order (in both preparation and conduct of the test), in a no stressful condition, physically or otherwise. Patient should be able to take the stated amount or an equivalent and under influence of no other condition except what is being investigated for.

a. Diagnosed diabetes mellitus	h. Vomiting during the procedure
b. Suspected Type 1 DM	i Patient who could not consumed the glucose solution
c. Unconscious patient	j. Patient who developed moderate to severe hypoglycaemia during the test
d. Patient who can not obey instructions	k. Do not perform the test on patients with uncontrolled thyroid dysfunction, under physical stress, eg post surgery, trauma, infection or extreme psychological stress or in patient with hypokalaemic periodic paralysis
e. Refusal to follow instructions	
f. Not for diabetes follow-up except during treatment of secondary diabetes; eg acromegaly, glucagonoma, Cushing's syndrome, Pheochromocytoma	
g. Hospitalized, acutely ill or immobile patients	

**Table 6.**  
*Conditions under which OGTT should not be conducted or when procedure should be stopped.*

## 7.4 Testing of children for type 2 diabetes mellitus

Until recently, type 1 diabetes was the most frequent form of diabetes among young people [80]. Recently however, there are increasing reports of T2DM, previously a disorder of middle-aged or elderly persons among children and adolescents. In the 1990s, various reports indicated that the incidence of childhood type 2 diabetes was increasing and this trend continues at present. The ADA and the American Academic of Paediatrics approved screening for T2DM in children because T2DM can be asymptomatic at diagnosis and requires tight glycaemic control to delay the onset of chronic vascular complications. Several studies have shown an increased risk of microvascular complications among young adolescents with T2DM compared to those with T1DM. Therefore, screening for IGT and T2DM in children at risk of glucose intolerance is necessary.

### 7.4.1 Criteria/indications

- a. Overweight (BMI  $\geq$  85th percentile for age and sex, weight for height  $\geq$  85th percentile, or weight  $>120\%$  of ideal for height)
  1. Plus any two of the following risk factors
    2. Family history of Type 2 DM, 1<sup>o</sup> or 2<sup>o</sup>
    3. Native American, black, Asian, Latino
- b. Signs of insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia)
- c. Age of initiation: 10 years or onset of puberty
- d. Frequency: every two years
- e. Test: FPG preferred

The dose of glucose is weight dependent-1.75 g/kg body weight. The maximum load is 75 g. Lucozade may be given instead which is more palatable. Formulation 73 kcal carbohydrate/100 ml, gives 75 g glucose in 419 ml Maximum dose is 75 g. Apply ametop gel 45 minutes prior to cannulations to ensure the area is numbed. Utilize a member of the play team to prepare the child for the procedure and provide distractive techniques throughout. Give full explanations to the child and family about the procedure and answer any questions they may ask.

## 8. OGTT in gestation diabetes mellitus, an undeniably the only test for dysglycaemia of GDM

### 8.1 Gestational Diabetes Mellitus (GDM)

Normal pregnancy is characterized by approximately 50% decrease in insulin-mediated glucose disposal in humans and a 200–250% increase in insulin secretion to maintain euglycaemia in the mother [81]. Women with adequate insulin secreting capacity overcome this insulin resistance of pregnancy by secreting more endogenous insulin to maintain normal blood glucose. In a study involving

non-GDM pregnancies, plasma glucose levels during late pregnancy (mean  $\pm$  1 SD) were noted to be fasting  $3.9 \pm 0.4$  mmol/L, 1 hour postprandial  $6.1 \pm 0.7$  mmol/L, and 2 hours postprandial  $5.5 \pm 0.6$  mmol/L with a mean glucose of  $4.9 \pm 0.6$  mmol/L [82]. The HAPO study reported a mean fasting glucose of  $4.5 \pm 0.4$  mmol/L, derived from 23316 pregnant women [38]. But women with diabetes or those who have tendency to develop GDM, endogenous insulin secretion is inadequate to compensate for the insulin resistance (IR), hence their hyperglycaemia worsen or they development hyperglycaemia.

Numerous factors such as placental hormones, obesity, inactivity, an unhealthy diet, genetic and epigenetic contributions influence IR in pregnancy, but the causal mechanisms are complex and still not completely elucidated [83]. Placental derived hormones are believed to be a major factor in reprogramming maternal physiology to achieve an I-R state. Human placental lactogen (hPL) and human placental growth hormone (hPGH) are the major player in pregnancy induced IR [84]. Prolactin, progesterone, estradiol and cortisol are increased during pregnancy and may contribute to the development of IR in pregnancy [85]. Recently, studies have implicated adiponectin from adipocytes and secreted factors, such as TNF- $\alpha$ , leptin, IL-6, resistin in mediating IR of pregnancy [86]. Most women who develop GDM have increased IR caused by alteration in insulin signaling pathway, abnormal subcellular localization of GLUT4 transporters, increased expression of the membrane glycoprotein PC-1 or reduced insulin-mediated glucose transport. GDM is usually diagnosed after 20 weeks' gestation when placental hormones are increase substantially as the placental size increases.

In 2014, the WHO has defined hyperglycaemia in pregnancy (HIP) as diabetes first detected at any time during pregnancy, along with pre-existing diabetes and is further sub-classified as diabetes in pregnancy (DIP) and gestational diabetes mellitus (GDM) [87]. Nowadays type 2 diabetes is frequently found in young women due to ongoing epidemics of obesity therefore the number of undiagnosed (before pregnancy) is increasing. Screening for GDM earlier than 24-28 weeks in identifying these young women and address perinatal risks that may be particular to their greater degree of hyperglycaemia is becoming more important because of the following [87]:

1. Rise chances of congenital malformations in offsprings
2. Risk of diabetes complications requiring treatment during early part pregnancy
3. Early treatment Prompt or frequent follow-up to maintain normoglycaemia
4. Post-pregnancy screening ensuring confirmation and appropriate treatment of diabetes after pregnancy

How then do we identify these women? Early glucose testing is important. Usually in early part of pregnancy (e.g. first trimester and first half of second trimester) fasting and postprandial glucose concentrations are normally lower than in normal due to less effect of placental hormone and decreased appetite, compared to non-diabetes women. Elevated fasting or postprandial plasma glucose levels at this time in pregnancy may reflect diabetes antedating pregnancy. In this regards there was a uniform agreement during IADPSG Pasadena meeting that this assessment should be made during the initial visit for prenatal care. However, there is variability in time of enrollment for prenatal care beyond the control of health care providers. Accordingly, no limit can be place on the timing of initial assessment for



detection of overt diabetes in pregnancy. It was advised that selective, stepwise screening particularly in the low- and mid-income countries is more cost effective. This entail: (a) Categorizing all women at first antenatal visit into low, moderate and high risk of GDM; (b) Those in moderate to high risk groups should have glucose challenge test with 50 g anhydrous glucose diluted in 150 ml of water to drink and venous sample is taken at 1-hr. If result is 7.8 (7.2) mmol/L, at first visit, proceed to diagnostic OGTT. If result is negative repeat glucose challenge test at 24–28 weeks of gestation; (c) Those in low risk group should be screening only at 24–28 weeks of gestation. However, if enrollment is at 24 weeks gestation or later and overt diabetes is not found, the initial test should be either 50 g glucose challenge first or the 75-g OGTT. Although IAFPSG Consensus Panel members favored use of A1c at first visit, this is not feasible in most low- and mid-income countries. It was also recommended that an FPG value in early pregnancy  $\geq 5.1$  mmol/L (92 mg/dl) also be classified as GDM.

Determining prevalence of GDM is difficult due to inconsistencies in screening methods. Because the IADPSG's is stricter when applied by IDF about 14% of 18 million live births were affected by gestational diabetes mellitus, where South-East Asia had the highest prevalence of GDM at 24.2% and the lowest was in Africa at 10.5% [88]. Almost 90% of cases of hyperglycaemia in pregnancy occurred in low- and middle-income countries, where access to maternal healthcare is limited. In Nigeria, the prevalence of HIP is projected to be 13.9%, and age-adjusted prevalence of 37.5% (crude 41.0%) in the United Arab Emirates is note [89]. The incidence of GDM has increased over the past decades in parallel with the increase in rates of obesity and type 2 diabetes mellitus, and this trend is expected to continue. GDM affects 7% of all pregnancies worldwide, 1.1% to 14.3% in USA, 3.8% to 6.5% in Canada, 6–9% in India. It is diagnosed at 16.3% in  $\leq 16$  weeks of gestation, 22.4% between 17 and 23 weeks and 61.3% after 23 weeks of gestation [90]. It occurs more frequently among African Americans, Hispanic/Latino Americans, and American Indians. It is also more common among obese women and women with a family history of diabetes. After delivery, GDM will follow 1 of 3 clinical courses [91, 92]:

- a. Approximately 10% continue to have markedly abnormal glucose metabolism and fulfill criteria for diabetes in the nonpregnant adult these patients are reclassified as having diabetes (Hyperglycaemia in pregnancy).
- b. Approximately 5–10% of patients continue to exhibit abnormal glucose metabolism that is below diabetic levels. These patients are reclassified as having IFG or IGT, as appropriate.
- c. The remainder exhibit normal glucose metabolism.

GDM has about 20–50% chance of developing type 2 diabetes in about 5–10 years even when there is lack of signs and symptoms of diabetes. The enormity defers among different ethnic groups, ranging from 9% in Caucasians, 11.9% in Latinos, and 25% in women of Mediterranean or east-Asian descent [93]. When GDM women were followed for a longer period, higher incidence of type 2 diabetes after index pregnancies was noted in 40% while there are evidence rates as high as 70% in Canadian Aboriginal women [93].

## **8.2 Should we then screen for GDM**

Screening and diagnosis of GDM and treating it effectively not only prevent adverse maternal and perinatal outcome but also future diabetes in both mother



and child. The goal of screening therefore is to reduce maternal and fetal complications such as preeclampsia, caesarean delivery, congenital malformations, macrosomia, shoulder dystocia, nerve palsy, bone fracture, hyperbilirubinaemia and infant death, or later childhood/adolescent overweight as demonstrated in some studies. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) [94], showed a 4% reduction in the composite outcome of severe perinatal complications (death, shoulder dystocia, bone fracture, nerve palsy) among women randomized to routine care compared with 1% among the intervention group, while in the National Institute of Child Health and Human Development (NICHD) study, though there was no reduction in the composite primary outcome (perinatal mortality, birth trauma and neonatal hypoglycaemia, hyperbilirubinaemia, or hyperinsulinaemia), there was reductions in fetal overgrowth, shoulder dystocia, caesarean section delivery and pre-eclampsia. During pregnancy, gestational diabetes requires treatment to normalize maternal blood glucose levels to avoid complications in both the infant and the mother. Untreated hyperglycaemia in pregnancy may result into either or all of the following complications in **Table 7**.

About 10–25% of infants born of GDM pregnancies are macrosomic; maternal euglycaemia in labour reduces the risk of hypoglycaemia, hypocalcaemia, hyperbilirubinaemia and polycythemia in the baby. In addition, the maternal metabolic milieu was identified as a key determinant for the susceptibility to obesity, metabolic syndrome and T2DM in the offspring, a phenomenon often described as ‘fetal programming’. A study showed that infant of GDM were followed biennially from the age of 5 years using 75 g 2-hr OGTT among the Pima Indians in Arizona, USA, and Diabetes developed in the next generation in 6.9% and 30.1% of breast-fed offspring of non-diabetic and diabetic women, respectively and in 11.9% and 43.6% of bottle-fed offspring, respectively. Shoulder dystocia (SD) occurs in 1–2% of pregnancies, with majority of cases occurring in non-macrosomic fetuses, however, it increased for all birth weights, with a three-fold increase when birth weight is >4000 g. Brachial plexus injury (BPI) occurs in 0.06%–0.26% of normal deliveries but occurs in 16–23% of births complicated by shoulder dystocia. GDM is an independent risk factor for BPI with a relative risk of 1.9–3.19 but in only 6–10% of BPI is maternal GDM documented. It can be inferred therefore that the incidence of adverse perinatal outcomes increases as glucose intolerance increases, that identification of women with hyperglycaemia in pregnancy has clinical significance. As hyperglycaemia in pregnancy is an asymptomatic condition, diagnosis is dependent on some form of screening.

a. Placenta abruption	a. Respiratory distress in the baby, and associated feeding problems
b. Premature delivery	b. Pregnancy induced hypertension, Pre-eclampsia and eclampsia
c. Shoulder dystocia and Brachial plexus injury	c. The risk of developing diabetes later in life or in a future pregnancy is increased
d. Macrosomic baby (weight ≥ 4 kg) or weight of >90th centile for gestational (according to ethnicity)	d. Haemorrhage and preterm delivery
e. Baby is prone to hypoglycaemia	e. Sevenfold higher risk of the mother developing T2DM after pregnancy
f. Hyperbilirubinaemia	f. Increase chances of death in both mother and the baby
g. Increase tendency of assisted delivery, Caesarean section, or induction of labour	

**Table 7.**  
*Complications of GDM if it is not diagnosed or properly managed [95].*

8.3 What is the optimal method of screening for GDM?

- a. The optimal method of screening for GDM depends on the location, the strength of the health facility, the principle of practicing Physician and affordability of the patients. Screening is therefore either universal based or risk factor based [96].
- b. In order to reduce the burden of screening on women and the health care system, the concept of selective (risk factor based) screening was introduced.
- c. The goal of risk factor based screening would be to ideally identify through historical and clinical factors those patients who would benefit most from biochemical screening while allowing those at lower risk to avoid the screening processes. This is preferred particular in the low-income and mid-income nations
- d. Selective screening originally consisted of taking a personal and family history in order to identify a high-risk population in need of further directed testing. With this method, women are categorized into low-risk, moderate-risk and high-risk. Women with any of the risk factors below were advised to perform a 50 g glucose challenge test.
- e. High risk women should undergo diagnostic test as early in pregnancy as possible and that testing should be repeated at 24–28 weeks if initial results are negative
- f. Screening by risk factors alone has a sensitivity of 63% and a specificity of 56%. In other words, 37–50% of women with GDM may go undiagnosed using this approach.
- g. Hence universal screening was considered and is widely practices. Universal screening for GDM is practiced by 84% of Canadian obstetricians, 94–97% of US obstetricians; however in recent survey only 17% of physicians in the UK practiced universal screening while 11% did not screen for GDM and 72% screened in the presence of maternal risk factors.

Routine screening of women at 24–28 weeks of gestation may be recommended with 50 g glucose challenge test (GCT), using a threshold of 7.8 mmol/L (140 mg/dl), except in those who fulfill the criteria for low risk and may not need screening for GDM at all. Properties used in categorizing a woman to at low-risk are [95, 96] (Table 8).

Women at moderate risk: women who do not meet all low risk criteria but lack two or more risk factors for GDM. Average-risk patients (all patients who fall between low and high risk) should be tested at 24–28 weeks of gestation. High risk

a. Caucasian or member of other ethnic group with low prevalence of diabetes
b. Pregnancy with body mass index(BMI) $\leq 27$ kg/m <sup>2</sup>
c. No previous history of GDM or glucose intolerance or adverse pregnancy outcome associated with GDM
d. No family history of diabetes in first-degree relative
e. No history of GDM-associated adverse pregnancy outcome

Table 8.  
Low-risk group.

- a. Obesity(BMI  $\geq 30$  kg/m<sup>2</sup>)
- b. Previous macrosomic baby weighing  $\geq 4.5$  kg
- c. Previous GDM
- d. Glucosuria(1+ on two occasion or 2+ on one occasion)
- e. Family history of T2DM(first degree relative with T2DM)
- f. Ethnic family origin with a high prevalence of DM
- g. Clinical conditions associated with insulin resistance like PCOS, acanthosis nigricans
- h. History of hypertension or hypercholesterolaemia

**Table 9.**  
*Feature indicators of women at high-risk for GDM.*

criteria are: This category of women needs to be screened at first antenatal visit and repeat at 24–28 week if they were negative at early screening. Women with these features are categorized as high-risk [95, 96] (**Table 9**).

The most common method of screening is with stepwise 50 g OGTT at 24 to 28 weeks of gestation, followed by an OGTT as the diagnostic test if a certain threshold has been surpassed. The procedure for glucose challenge test (GCT), is that 50 g anhydrous glucose load dissolve in 150 ml fluid to be ingested within 5 minutes irrespective of time of the day or last meal. Blood is collected 1-hr post ingestion of glucose solution Views diverge on the optimal cutoff value for the 50 g GCT. 90% of women with GDM will be identified if 7.2 mmol/L (130 mg/dl) is used, however, as high as 20–25% of those screened will to undergo 100 g OGTT for diagnosis. Increasing the cutoff value to 7.8 mmol/L (140 mg/dl) will identify only 80% of women with GDM but decrease to 14–18% of women will do 100 g diagnostic testing [97]. A cutoff value of 7.2 mmol/L is advice in those with FPG level is  $<140$  mg/dl ( $<7.8$  mmol/L) and manifests symptoms compatible with complications of diabetes. Finally, at 24 to 28 weeks of gestation, every women should undergo 50 g challenge test and those with values between 7.2 to 7.8 mmol/L (130–140 mg/dl) should proceed to 100 g OGTT for diagnosis of GDM and sampling over 3-hrs.

As women with negative GCT do not undergo the diagnostic OGTT, it is possible that they could have undiagnosed GDM or GIGT. In a study involving 202 pregnant women with a negative GCT screening test that underwent subsequent OGTT, the only positive predictor noted is the average glucose value in those with normal and those with GDM/GIGT. Therefore, false negative GCTs cannot be readily predicted by risk factors. However, their clinical implications at delivery may be benign [98]. During pregnancy, some women have a low glucose level on the 75 g OGTT. These women tend to have more booking weight and higher rate of congenital anomaly; however their pregnancy outcome was shown not to be significantly different from those with normal screening OGTT results [99]. The performance of the GCT as a screening test depends on the cutoff values used, the criteria for diagnosis of GDM and the prevalence of GDM in the screened population. A study conducted in China where 422 gravidas [100] were screened with 50-g glucose and those with a positive results ( $\geq 135$  mg/dl (7.5 mmol/L)), underwent additional glucose testing. GDM was defined using National Diabetes Data Group (NDDG) standards for the 3-h GTT. When Carpenter and Coustan was used for comparison, any woman with elevated 50-g value and no 3-hr OGTT was performed, a fasting serum glucose  $\geq 140$  mg/dl (7.8 mmol/L) were considered evidence of gestational diabetes. One hundred twenty four (29.4%) had GDM as defined by the NDDG criteria; this increased to 161 (38%) when the diagnosis was based on Carpenter and Coustan's criteria. As expected, the prevalence of GDM increased in relation to an increasing 50-g value. All subjects with a 50-g screen  $>216$  mg/dl ( $>12.0$  mmol/L) had evidence of gestational diabetes and required insulin for glycemic control. Patients with a 50-g screen  $\geq 220$  mg/dl (12.2 mmol/L) do not require a 3-h GTT. Those with fasting serum

a. Previous pregnancy with gestational diabetes	h. A family history of diabetes (first degree relatives)
b. Previous ‘big’ baby (at or over 4.5kgs – 10lbs)	i. A previous still-birth
c. Frequent loss of pregnancy or premature delivery	j. Long usage of steroids
d. Large for gestational age	k. Women with PCOS (Polycystic ovary syndrome)
e. Positive glycosuria(1+ on 2 occasions or 2 + on one occasion)	l. Polyhydramnios
f. BMI $\geq 30$ kg/m <sup>2</sup>	m. High risk ethnic groups
g. Maternal age $\geq 40$ years old	

**Table 10.**  
*Indications for OGTT in pregnancy [101].*

glucose of  $\geq 140$  mg/dl (7.8 mmol/L) may begin diet therapy, glucose monitoring, and insulin as indicated. If the fasting serum glucose is  $< 140$  mg/dl (7.8 mmol/L), a 3-h GTT should be performed for confirmation of GDM. This approach will facilitate rapid therapeutic intervention and reduce the cost of care in this subset of patients. This findings need to be validated at different places using different ethnic groups. What should be considered an indication for screening for gestation diabetes mellitus (GDM) (**Table 10**).

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive-aged and is the most common endocrine-associated cause of infertility. Approximately 6.5% of women of reproductive age have PCOS. Women with PCOS are known to be at increased risk for IR, IGT, and type 2 diabetes mellitus though often present with normal FPG [102]. The current guideline of Androgen Excess Society is that a 2-hour OGTT be performed on all obese women with PCOS [102]. Though screening for GDM is considered compulsory in affluent countries and highly recommended in low- and middle-income countries, the administering the required amount of glucose in pregnancy is not without side effects. The recognised disadvantages are as noted in **Table 11**, ranging from mild to moderate consequences.

However, advantage almost always surpasses the disadvantages. The advantages are as shown in **Table 12**.

**8.4 Diagnosis of GDM is only done using OGTT**

The gold standard for the diagnosis of GDM is OGTT irrespective of how it is performed, using 100 g as recommended by ACOG, or 75 g, according to the ADA criteria.

In 1964, O’Sullivan and Mahan first developed the two-step method OGTT for the diagnosis of GDM [103] and this is based on the risk of maternal type 2 diabetes later in life [104]. As explained earlier, those with glucose levels meeting screening limit undergo a 100 g, 3 hours or 75 g, 2-hour diagnostic OGTT and by Carpenter and Coustan (C-C) criteria, GDM is diagnosed in women with two or more abnormal values (5.3–10.0–8.6 mmol/L at fasting, 1-hr and 3-hour (2 hour) post glucose [104]. This with some modifications was adapted by many organizations, NDDG

1. There are no serious direct risks to the GTT, however, some women reported dizziness, fainting, vomiting, due to fasting and/or the use of a high glucose drink on an empty stomach
2. Fasting for 8–12 hrs in pregnancy can be difficult
3. Soreness, bruise, swelling or infection at site of needle insertion
4. More cost burden in a patient with positive or borderline result who has be closely monitor
5. Patient may not be eligible for midwifery led care options such as homebirth or MLU
6. Induction of delivery may be recommended before date is due

**Table 11.**  
*Disadvantages of the OGTT in a pregnant woman.*



- a. The GTT is considered the most effective way to determine if you have GDM
- b. Early detection of GDM gives a better chance of monitoring glucose levels
- c. Managing glucose levels early decreases the risks to the baby
- d. Managing the glucose levels early decreases the chances of macrosomic baby and its complications
- e. Managing glucose levels decreases the risk of interventions in labour and delivery

**Table 12.**  
*Advantages of OGTT for a pregnant woman.*

[105], ADA [106], as the standard method for diagnosis of GDM for more than two decades.

In 2008, the HAPO study [39] demonstrated presence of unfavourable neonatal outcomes even in those with mild hyperglycaemia which did not meet the old criteria of GDM [107]. Based on this notion the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended a one-step 75 g OGTT testing but lowered the diagnostic cut-point of the OGTT to (5.1–10.0-8.5 mmol/L, fasting, 1-hour and 2 hours postprandial) in 2010 [108] and only one abnormal value was enough to make a diagnosis. This was adopted by ADA [109], WHO [110] and FIGO [111] by recommending a one-step 75 g glucose OGTT between 24 and 28 gestational weeks and diagnosis of GDM is made with only one abnormal value equal to or exceeding 5.1–10.0-8.5 mmol/L, due to the result of the HAPO study regarding mild hyperglycaemia and adverse clinical outcome, including LGA, primary caesarean, clinical neonatal hypoglycaemia, and C-protein cord blood [108] where a more strict strategy may help reduce the frequency of these potential complications. However, several guidelines including the ACOG [112], NIH [113] and SOGC [114] did not support the IADPSG criteria and their guidelines still recommend the two-step strategy and the C-C or NDDG criteria for the OGTT, the reasons provided are:

- a. The benefit from the treatment of mild GDM in women is not well established
- b. Additional healthcare costs will be generated by increased prevalence
- c. Caesarean delivery and intensive newborn assessment will increase
- d. Life disruptions and psychosocial burdens will be developed in a patients with GDM

Current ADA guidelines recommended selective screening of high risk women for GDM, where ACOG guideline advice universal screening and NICE guideline recommended screening all women of South Asians ethnicity. In the HAPO study risk of adverse outcomes were very low when FPG was  $\leq 4.4$  mmol/L (80 mg/dl). In Chinese women with FPG value  $\geq 5.1$  mmol/L, one can make a diagnosis of GDM (specificity 100% and, in those with value  $\leq 4.4$  mmol/L one can exclude GDM (87.8%, sensitivity). These results are similar to those reported by Agarwal, et al. in the HAPO cohort. In HAPO and two other studies, the incidence of selected adverse maternal and fetal outcomes increases along a continuum of increasing maternal hyperglycaemia, with no outcome-associated glycaemic thresholds were identified that could be used to define internationally accepted criteria for the diagnosis of GDM. In 2010, IADPSG [108] consensus panel using HAPO study primary outcomes (birthweight  $>90\%$ , primary caesarean section rate, neonatal hypoglycaemia and cord C-peptide levels  $>90\%$ ) and threshold for 75-g OGTT



reached odds ratio 1.75. These arbitrary thresholds, when applied to the HAPO cohorts, led to a GDM incidence of 17.8%. In 2013 Canadian Diabetic Association expert committee conceded the dispute and chosen sequential screening with a 50 g GCT followed by 75 g OGTT using the glucose thresholds that result in an Odds Ratio (OR) of 2.00 (fasting  $\geq 5.3$  mmol/L, 1 hour  $\geq 10.6$  mmol/L, 2 hours  $\geq 9.0$  mmol/L).

Hyperglycaemia first detected at any time during pregnancy should be classified as either:

- Diabetes mellitus in pregnancy
- Gestational diabetes mellitus

When glucose abnormalities persist postpartum in a woman with GDM, her diabetes is re-categorized as overt diabetes, especially if the diagnosis of GDM occurred before 20 weeks' gestation and glucose levels were markedly elevated in pregnancy. The 2006 WHO criteria should be used in diagnosis of Diabetes mellitus in pregnancy when one or more of the following criteria are met:

- FPG  $\geq 7.0$  mmol/L (126 mg/dl), demonstrated on two occasions
- 2hPG  $\geq 11.1$  mmol/L (200 mg/dl) following a 75 g oral glucose load
- RPG  $\geq 11.1$  mmol/L (200 mg/dl) in presence of diabetic symptoms

The diagnosis of GDM at any time during pregnancy should be based on any one of the following values:

- FPG 5.1–6.9 mmol/l (95–125 mg/dl)
- 1hPG 75 g OGTT  $\geq 10.0$  mmol/L (180 mg/dl)
- 2-hPG 75 g OGTT 8.5–11.0 mmol/L (153–199 mg/dl)

There are no established criteria for the diagnosis of diabetes based on the 1-hour post-load value. At least one of these thresholds must be equaled or exceeded to make a diagnosis of GDM.

## 9. A1c, Can it replace OGTT?

The measurement of A1c equals the assessment of hundreds (virtually thousands) of fasting glucose levels and also capture postprandial glucose peaks; therefore, it is a more and reliable measurement than FPG and/or 2-hr OGTT plasma glucose (PG) oscillates above and below the cut point of 200 mg/dl.

FPG of 6.7 mmol/L to 7.2 mmol/L (120 or 130 mg/dl) or having a 2-h PG of 10.3 mmol/L to 11.9 mmol/L (185 or 215 mg/dl) are considered similar because they define a point where physiological disturbance is apparent, however from other angles it makes a lot of difference. Therefore, an appliance evaluating chronic rather than spot hyperglycaemia is unquestionably more desirable. A1c assay is now the preferred test not only for chronic management of diabetes but also for its diagnosis. However, the cost of assay in some parts of the world rules out its typical

use. In such instances, clinicians should continue using glucose measurements for both diagnosis and monitoring of diabetes.

A1c assay may not be reliable under the underlisted conditions [115]

- a. First, some haemoglobin traits, such as HbS, HbC, HbF, and HbE, interfere with some A1c assay method. These are common among blacks
- b. Second, conditions causing changes in red cell turnover: haemolytic anaemias, chronic malaria, major blood loss, or blood transfusions,
- c. Third, A1c levels appear to increase with age [116], though this is not sufficiently clear
- d. Similarly, racial disparities in A1c, the etiology and significance are unclear [117]
- e. Finally, in rapidly evolving type 1 diabetes, no time to “catch-up” with the sudden elevations in glucose levels; diagnosis should be relied on plasma glucose in association with typical symptoms

The glycated haemoglobin (HbA1c) test has been suggested as an alternative screening test for type 2 diabetes. HbA1c overcomes many of these difficulties as fasting state is not required, analytical variability is less than 2% and gives glycaemic status over past 2–3 month. The coefficient of variation is usually 2–3% for the same day analysis, while the inter-assay variation is 4–5%. HbA1c values are relatively stable after collection, and the recent introduction of a new reference method to calibrate all HbA1c assay instruments should further improves HbA1c assay standardization.

Advantages of HbA1c assay are:

- a. better indicator of overall glyceimic exposure
- b. less variability, unaffected by outside factors like stress
- c. not a timed test, requires no fasting; more convenient
- d. Better at predicting complications

Regrettably, at variance with that report, the New Hoorn Study [118] showed that 44% of people with newly diagnosed diabetes with OGTT had A1c < 6.0% and that a stronger correlations between plasma glucose and A1c is better in subjects with known diabetes, but not in the general population. Moreover, in the Rancho Bernardo Study [119], 85% of the participants with A1c ≥6.5% were not classified as diabetes by ADA criteria and a 1/3rd of people with diabetes on OGTT had A1c

1. Assay is normalized and aligned to the DCCT/UKPDS
2. Better summary of overall glycaemic exposure and risk for long-term complications
3. It has significantly less biologic fluctuation
4. No need for fasting or timed samples
5. Relatively unaffected by acute(eg stress or illness related) perturbations in glucose levels
6. Currently used to guide management and adjust therapy

**Table 13.**  
*The beauty of A1c testing compared to blood glucose for diagnose of diabetes mellitus.*

< 6.0%. Thus, this study demonstrated that 30% of subjects who are already diabetic or pre-diabetic would have been missed if A1c had been used instead of OGTT. In conclusion, the data confirmed, in agreement with an Australian study, that an A1C  $\leq 5.5\%$  or  $\geq 7\%$  can predict the absence or presence of diabetes respectively, while intermediate values are inconclusive (**Table 13**).

A1C values just above the upper limits of normal, depend upon post-prandial glycaemias (ie 2hPG), still requiring the OGTT to be correctly interpreted. Although in certain cases A1c gives equal or almost equal sensitivity and specificity to glucose measurement, it is not available in many part of the world and it is not well enough standardised for its use to be recommended at this time particularly in low- and mid-income countries.

Finally, although ADA recommended the use of A1c, by emphasizing the importance of IFG and IGT, which cannot be diagnosed without OGTT, to disclose high-risk subjects for diabetes, obviously shows that A1c would be of minute use without OGTT and that pre-diabetes includes different entities. OGTT is the only test that can efficiently disclose obscure diabetes when FPG < 7.0 mmol/L and screen competently within the range of rather heterogeneous pre-diabetic values [120].

In conclusion an OGTT is undeniably the best test in investigation of dysglycaemia, either with the intention of testing for pre-diabetes, type 2 diabetes, or for gestational diabetes mellitus.

## Author details

Dahiru Saleh Mshelia<sup>1\*</sup>, Sani Adamu<sup>2</sup> and Rebecca Mtaku Gali<sup>3</sup>


1 Chemical Pathology, Faculty of Basic Clinical Sciences, College of Medical Sciences, University of Maiduguri, Maiduguri, Nigeria

2 Chemical Pathology, Faculty of Basic Clinical Sciences, College of Medical Sciences, Gombe State University, Gombe, Nigeria

3 Medical Laboratory Science, Faculty of Allied Health Science, College of Medical Sciences, University of Maiduguri, Maiduguri, Nigeria

\*Address all correspondence to: dsmkinging@gmail.com

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