Review Article

ORAL GLUCOSE TOLERANCE TEST: AN ESSENTIAL TOOL TO MAKE THE DIAGNOSIS OF DIABETES

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ABSTRACT

Diagnosis of diabetes defines a group at high risk for micro- and macro-vascular disease. The diagnostic criteria (table 1) were established by the NDDG and WHO in 1979-80. For individuals with symptoms of diabetes, such as excessive thirst and urination or unexplained weight loss, only elevated FPG (≥140 mg/dl) or random plasma glucose ≥200 mg/dl is required to confirm the diagnosis.Oral glucose tolerance test is used not only to diagnose diabetes, but also help to provide additional information about the body's ability to metabolize blood glucose. Higher OGTT values are likely to reflect diet, lifestyle problems and problems of insulin functioning. Information in regard to reliability of the oral glucose tolerance test is important, as some conditions (common cold), or food (caffeine), or lifestyle habits (smoking) may alter the results of the oral glucose tolerance test.

Keywords: Diabetes mellitus, oral glucose tolerance test, gestational diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a disease common in all parts of the world and recognized as one of the leading causes of death in the world[1-2]. DM is the serious endocrine disorder that affects more than 100 million people worldwide (6% of the population) and in the next 10 years it may affect about five times more people than it does now[3-4]. In India, the prevalence rate of diabetes is estimated to be 1-5%[5-6]. Approximately 10% of diabetic patient have type 1 diabetes mellitus, remainder have type 2[7].

DM is a metabolic syndrome, characterized by a loss of glucose homeostasis that result in impaired metabolism of glucose and other energy- yielding fuels such as lipids and proteins[8]. DM is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. This deficiency results in abnormal high concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves[9]. The long-term effects of DM include dysfunction and failure of various organs[10]. Hyperglycemia is an important factor in the development and progression of the complications of diabetes mellitus[11].

Definition

Diabetes mellitus is a metabolic disorder initially characterized by a loss of glucose homeostasis with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both[12].

Without enough insulin, the cells of the body cannot absorb sufficient glucose from the blood; hence blood glucose levels increase, which is termed as hyperglycemia. If the glucose level in the blood remains high over a long period of time, this can result in long-term damage to organs, such as the kidneys, liver, eyes, nerves, heart and blood vessels.

The diabetic patients usually show varied symptoms of polyurea, polydypsia and polyphagia. In severe forms, weight loss may be seen, in some cases, symptoms may be absent, and consequently hyperglycemia may remain undetected causing vascular damage, even prior to the detection of the disease. Diabetics are prone to develop secondary complications like nephropathy[13], ketoacidosis[14], neuropathy[15], retinopathy[16], atherosclerosis[17] and cardiovascular problems[18,19]. In addition, diabetics are immunocompromised and are readily susceptible to microbial infections and more so with opportunistic fungal infections[20,21].

CLASSIFICATION

In 1997, the ADA issued new diagnostic and classification criteria[1]; in 2003, modifications were made regarding the diagnosis of impaired fasting glucose (IFG)[2]. The classification of diabetes includes following four clinical classes:[22,23]

- Type 1 diabetes (results from beta-cell destruction, usually leading to absolute insulin deficiency).
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance).
- Other specific types of diabetes due to other causes, e.g., genetic defects in β cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical induced (such as in the treatment of AIDS or after organ transplantation).

● Gestational diabetes mellitus (GDM) (diagnosed during pregnancy).

Insulin-dependent diabetes mellitus (IDDM)

- Low or absent levels of circulating endogenous insulin and dependent on injected insulin to prevent ketosis and sustain life
- Onset predominantly in youth but can occur at any age
- Associated with certain HLA and GAD antigens
- Abnormal immune response and islet cell antibodies are frequently present at diagnosis
- Etiology probably only partially genetic, as only ~35% of monozygotic twins are concordant for IDDM

Non-insulin-dependent diabetes mellitus (NIDDM)

- Insulin levels may be normal, elevated, or depressed; hyperinsulinemia and insulin resistance characterize most patients; insulinopenia may develop as the disease progresses
- Not insulin-dependent or ketosis-prone under normal circumstances, but may use insulin for treatment of hyperglycemia
- Onset predominantly after age 40 years but can occur at any age
- Approximately 50% of men and 70% of women are obese
- Etiology probably strongly genetic as 60%-90% of monozygotic twins are concordant for NIDDM

Gestational diabetes (GDM)

GDM may arise from the physiological stresses of pregnancy or it may be a degree of abnormal glucose tolerance that precedes pregnancy and is discovered during the routine metabolic testing that occurs during pregnancy. Characteristics of GDM are:

- Glucose intolerance that has its onset or recognition during pregnancy
- Associated with older age, obesity, family history of diabetes
- Conveys increased risk for the woman for subsequent progression to NIDDM
- Associated with increased risk of macrosomia

Other types of diabetes

Other types of diabetes includes diabetes secondary to or associated with pancreatic disease, hormonal disease drug or chemical exposure ,insulin receptor abnormalities or certain genetic syndromes. In addition to the presence of the specific condition, hyperglycemia at a level diagnostic of diabetes is also present. Causes of hyperglycemia are known for some conditions, e.g., pancreatic disease; in other cases an etiologic relationship between diabetes and the other condition is suspected[24,25,26].

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individual do not easily fit into a single class. For example, a person with gestational diabetes may continue to be hyperglycemic after delivery and may be determined to have infact type-1 diabetes. A person with steroid-induced diabetes may be normoglycemic after stopping steroids but develops diabetes years later after the current pancreatitis[27,28].

EPIDEMIOLOGY OF DIABETES MELLITUS

The prevalence of diabetes mellitus is increasing with ageing of the population and lifestyle changes associated with rapid urbanization and westernization. The disease is found in all parts of the world and is rapidly increasing in its coverage[29,30].

Prevalence and incidence of diabetes mellitus

Globally, the prevalence of diabetes, without type distinction, was estimated to be 4% in 1995. According to WHO, it is estimated that 3% of the world's population have diabetes and the prevalence is expected to double by the year 2025 to 6.3%[31,32]. There will be a 42% increase from 51 to 72 million in the developed countries and 170% increase from 84 to 228 million, in the developing countries. Thus, by the year 2025, over 75% of all people with diabetes will be in the developing countries, as compared to 62% in 1995[33].

DIAGNOSTIC CRITERIA

Diagnosis of diabetes defines a group at high risk for micro- and macro-vascular disease. The diagnostic criteria (table 1) were established by the NDDG and WHO in 1979-80. For individuals with symptoms of diabetes, such as excessive thirst and urination or unexplained weight loss, only elevated FPG (≥140 mg/dl) or random plasma glucose ≥200 mg/dl is required to confirm the diagnosis.

The NDDG and WHO criteria for diabetes both permit a diagnosis based on the presence of the classic diabetic symptoms and random plasma glucose ≥200 mg/dl. Both also permit a diagnosis of diabetes based on FPG ≥140 mg/dl. In persons without unequivocal symptoms and in those with lower FPG, both require measurement of plasma glucose at 2 hours after a 75-g oral glucose challenge. For diagnosis of diabetes, this 2-hour value must be ≥200 mg/dl. The NDDG suggested that a mid test OGTT value ≥200 mg/dl is also required, but essentially all persons meeting the 2-hour criterion also meet this mid test requirement.

Both the NDDG and WHO criteria require a repeat determination of fasting or post-challenge plasma glucose for a definitive diagnosis of diabetes in an asymptomatic patient: that is, the diagnosis cannot be made with a single glucose result. For patients with symptoms of

diabetes, a single elevated blood glucose value is considered sufficient for confirmation of the diagnosis[16,17].

American Diabetes Association (ADA) stated that diabetes can be provisionally diagnosed with any one of the three criteria listed below. In the absence of unequivocal hyperglycemia with acute metabolic decompensation the diagnosis should be confirmed, on a subsequent day, by any one of the same three criteria (Table 1).

1. A fasting plasma glucose of >126 mg/dl (after no caloric intake for at least 8 hours)

   or,

2. A casual plasma glucose >200 mg/dl (taken at any time of day without regard to time of last meal) with classic diabetes symptoms: increased urination, increased thirst and unexplained weight loss

   or,

3. An oral glucose tolerance test (OGTT) (75 gram dose) of >200 mg/dl for the two hour sample. Oral glucose tolerance testing is not necessary if patient has a fasting plasma glucose level of >126 mg/dl.

The Committee (ADA) states that the fasting plasma glucose is the preferred test and recommends moving toward its universal use for testing and diagnosis because of its ease of administration, convenience, acceptability to patients, and lower cost in comparison to the OGTT.

Use a fasting plasma glucose (FPG) test and/or an oral glucose tolerance test (OGTT) to detect pre-diabetes and Type 2 diabetes. Both of these tests are useful in terms of their ability to detect hyperglycemia and diagnose pre-diabetes and Type 2 diabetes, but the tests are not exactly interchangeable. The FPG test does not always detect impaired glucose tolerance (IGT) and the 2-hour plasma glucose value in the OGTT does not always detect impaired fasting glucose (IFG). A "random" or "casual blood test" with results ≥ 200 mg/dL is also used to diagnose Type 2 diabetes. Although the random test is the most convenient, it is not nearly as reliable or effective as the FPG and OGTT tests[34].

Table1: Diagnosis of Pre-diabetes and Type 2 Diabetes

Test	Fasting Plasma Glucose (FPG)	Oral Glucose Tolerance Test (OGTT)	Random/Casual Plasma Glucose (with symptoms)
How performed	Blood glucose is measured after at least an 8 hour fast.	75-gram glucose load (drink) is ingested after at least an 8 hour fast; blood glucose is measured at 2 hours	Blood glucose is measured at any time regardless of eating.
Normal	< 100 mg/dL (< 5.6 mmol/L)	< 140 mg/dL (< 7.8 mmol/L)	
Pre-diabetes (IFG)	100 – 125 mg/dL (5.6 – 6.9 mmol/L)		
Pre-diabetes (IGT)		140 – 199 mg/dL (7.8 – 11.0 mmol/L)	
Diabetes Mellitus	≥ 126 mg/dL * 7.0 mmol/L *	≥ 200 mg/dL (≥ 11.1 mmol/L)	≥ 200 mg/dL * # (≥ 11.1 mmol/L) (with symptoms)
IFG: Impaired fasting glucose IGT: Impaired glucose tolerance *Must confirm test by repeating on a different day # It is not appropriate to have a person eat a meal and then draw a random glucose two hours after			

Table 2: oral glucose tolerance test in non-pregnant adult[22,35]

Non-pregnant adult tolerance	Normal	Diabetes	Impaired glucose
fasting	70-105 (70-105 if > 60 y.o)	>=140 mg/dL	<140 mg/dL
30 minute (0.5 hour)	110-170	**	**
60 minute (1 hour)	120-170	**	**
90 minute (1.5 hour)	100-140	**	**
120 minute (2 hour)	70-120	>200 mg/dL	140-200 mg/dL
** at least one of these results must be >=200 mg/dL			

ORAL GLUCOSE TOLERANCE TEST

The oral glucose tolerance test (OGTT), also referred to as the glucose tolerance test, measures the body's ability to metabolize glucose, that is the body's main source of energy or clear it out of the bloodstream. The test can be used to diagnose diabetes, gestational diabetes (diabetes during pregnancy) or prediabetes (a condition characterized by higher-than-normal blood sugar levels that can lead to type 2 diabetes).

According to the National Institutes of Health (NIH), the OGTT it is better able to diagnose high blood glucose after a glucose challenge than the fasting blood glucose test. A doctor may recommend it if he or she suspects diabetes in cases where a patient's fasting blood glucose level is normal. However, the test is more time-consuming and complicated than the fasting blood glucose test. It is one of the best diagnostic procedures though rarely used because it is tedious to the patient. It is one of the best diagnostic procedures though rarely used because it is tedious to the patient. It gives a medical practitioner a better leverage on how to deal with the disease, though the exceptions are quite demanding before one takes the test. It is expected that as a patient, you must be in normal good health, free from the common vagaries of the environment e.g. colds, malaria etc; that is, free from ill health. It is expected too, that alcohol drinking, smoking etc should be stopped for a while till all processes are over.

The oral glucose tolerance test (OGTT) is done to:

- Check pregnant women for gestational diabetes. When done for this purpose, the test is called a glucose challenge screening test, and it is usually done during the 24th to the 28th week of pregnancy. You have an increased chance of developing gestational diabetes if you:
  - Have had gestational diabetes during a previous pregnancy.
  - Have previously given birth to a baby who weighed more than 9lb.
  - Are younger than age 25 and were overweight before getting pregnant.
- Diagnose gestational diabetes if other blood glucose measurements are high.
- Screen women who have polycystic ovary syndrome (PCOS) for diabetes.
- Diagnose prediabetes and diabetes.

Factors affecting results

- Failure to maintain normal exercise and dietary habits for three days before the test, especially restricting your carbohydrate intake to less than 150 grams per day.
- Illness.
- Anxiety about needle sticks.
- Smoking or consuming caffeine before or during the test.

Advantages: It can detect very subtle disturbances in carbohydrate metabolism that are not apparent from a measurement of fasting glucose. It's valuable in pregnancy to protect the health and safety of the fetus.

Disadvantages: It may lead to an erroneous diagnosis, especially if the physician fails to take into consideration the many factors that can adversely affect test results.

Glucose tolerance tests may lead to one of the following diagnoses:

- **Normal response:** A person is said to have a normal response when the 2-hour glucose level is less than 140 mg/dl, and all values between 0 and 2 hours are less than 200 mg/dl.
- **Impaired glucose tolerance:** A person is said to have IGT when the fasting plasma glucose is less than 126 mg/dl and the 2-hour glucose level is between 140 and 199 mg/dl.
- **Diabetes:** A person has diabetes when two diagnostic tests done on different days show that the blood glucose level is high. This means either the 2 hour levels is greater than 200 mg/dl or the fasting glucose is noted as greater than 126 mg/dl.
- **Gestational diabetes:** A woman has gestational diabetes when she has any two of the following: a 100g OGTT, a fasting plasma glucose of more than 95 mg/dl, a 1-hour glucose level of more than 180 mg/dl, a 2-hour glucose level of more than 155 mg/dl, or a 3-hour glucose level of more than 140 mg/dl[22-26].

ORAL GLUCOSE TOLERANCE TEST IN NON-PREGNANT ADULT: AN OVERVIEW

The oral glucose tolerance test can be useful in diagnosing patient with diabetes, by monitoring glucose level following an oral glucose challenge (Table 2).

Test Preparation:

(1) Starting 3 days prior to test, the patient receives a diet containing 150 g of carbohydrate per day.

(2) The patient must not be stressed by illness prior or during the test.

(3) All on essential medication should be discontinued at least 3 days prior to testing many medication can impair glucose tolerance.

(4) A 10-16 hr fast is recommended.

(5) dUndue exercise before or during the test is to be avoided.

(6) No coffee or smoking is allowed once the fast has started or during the test.

Dose of glucose for test:

- 75 g orally (1.75 grams of glucose per kilogram of ideal body weight up to 75 grams)
- Oral glucose solution come in 10 US fluid ounces (296 mL) bottles containing 50,75,or 100 grams of glucose (5, 7.5 and 10g per fluid ounce)

Initial evaluation

- If the fasting glucose is < 115 mg/dL, then diabetes is excluded
- If the fasting glucose is 115-140 mg/dL, then an oral glucose tolerance test should be done
- If the fasting glucose is >140 mg/dL, then the diagnosis is supported.

The abnormalities in glucose tolerance test must be present on at least 2 occasions before the diagnosis of diabetes mellitus is made. An oral tolerance test need not be done

- if a fasting glucose is > = 140 mg/dL at least twice
- a random glucose level is > 200 mg/dL and classic symptoms (polyuria, polydipsia, ketonuria, weight loss) are found.

Drugs may cause decreased glucose tolerance: beta – adrenergic blocking agents, catecholamines, corticosteroids, diuretics, estrogen, oral contraceptives, phenothiazines, phenytoin, thyroid hormones and several others [22,35].

ORAL GLUCOSE TOLERANCE TEST IN PREGNANT ADULT FEMALE

Pregnant women should be screened for diabetes mellitus sometimes between the 26th and 28th week of gestation. Starting 3 days prior to test, the patient receives a diet containing 150 g of carbohydrate per day. The patient must not be stressed by illness prior or during the test. All on essential medication should be discontinued at least 3 days prior to testing many medication can impair glucose tolerance. A 10-16 hr fast is recommended. Undue exercise before or during the test is to be avoided. No coffee or smoking is allowed once the fast has started or during the test.

Dose of glucose for test:

- Screening test: 50 grams orally
- Diagnostic test: 100 grams orally
- Oral glucose solutions come in 10 US fluid ounces (296 mL) bottles containing 50,75,or 100 grams of glucose (5, 7.5 and 10g per fluid ounce).

Screening test: if 1 hour after the 50 gram the serum glucose is >= 150mg/dL, then the full dose test should be performed.

Gestational diabetes: at least 2 glucose values must exceed the following after the 100 gram loading dose[22,36-38](Table 3)

Table 3: oral glucose tolerance test in pregnant adult female[22, 36-38]:

Specimen	Serum	Whole blood or capillary
Fasting	105 mg/dL	90 mg/dL
1 hour	190 mg/dL	170 mg/dL
2 hour	165 mg/dL	145 mg/dL
3 hour	145 mg/dL	125 mg/dL

ORAL GLUCOSE TOLERANCE TEST IN PEDIATRIC POPULATION

The oral glucose tolerance test can be useful in the diagnosis of diabetes mellitus, by glucose levels following an oral glucose challenge (Table 4). (Note: This data reflects recommendation prior to the 1997American Diabetes Association revised criteria.)

Table 4: oral glucose tolerance test in pediatric population[22,38,39]

Pediatric Patient	diabetes	Impaired glucose tolerance
Fasting	<140 mg/dL	< 140 mg/Dl
30 minute (0.5 hour)	**	N/A
60 minute (1 hour)	**	N/A
90 minute (1.5 hour)	**	N/A
120 minute (2 hour)	>200mg/dL	140-00 mg/dL

** at least one of these results must be > 200mg/dL

Test Preparation

(1) Starting 3 days prior to test, the patient receives a diet containing 150 g of carbohydrate per day.

(2) The patient must not be stressed by illness prior or during the test.

(3) All on essential medication should be discontinued at least 3 days prior to testing many medication can impair glucose tolerance.

(4) A 10-16 hr fast is recommended.

(5) Undue exercise before or during the test is to be avoided.

Dose of glucose for test

- 1.75 gram per kilogram of ideal body weight, up to a maximum of 75 grams.
- Oral glucose solutions come in 10 US fluid ounces (296 mL) bottles containing 50,75,or 100 grams of glucose (5, 7.5 and 10g per fluid ounce).

Interpretation

- Both an elevated fasting glucose and a sustained elevated glucose during the oral tolerance test need to be present on at least 2 occasions to make the diagnosis of diabetes mellitus.
- The oral tolerance test is not needed if classic symptoms are present (polyuria, polydipsia, ketonuria, weight loss) and if a random glucose exceeds 200mg/dL[22, 38-39].

Glucose Tolerance Test, Intravenous

This test is indicated if the patient cannot tolerate a large oral carbohydrate load or if the patient has a gastrointestinal condition (disease, surgery) that could affect the rate of glucose absorption from the GI tract. The test is done only infrequently and shows a poor correlation with the oral GIT (Note: This data reflects recommendations prior to the 1997 American Diabetes Association revised criteria.)

Test Preparation

(1) Starting 3 days prior to test, the patient receives a diet containing 150 g of carbohydrate per day.

(2) The patient must not be stressed by illness prior or during the test.

(3) All on essential medication should be discontinued at least 3 days prior to testing many medication can impair glucose tolerance.

(4) A 10-16 hr fast is recommended.

(5) Undue exercise before or during the test is to be avoided.

Dose of glucose for test: 0.5 gram per kilogram, body weight up to a maximum of 35 grams, given IV as 5 g glucose per 100 mL solution within 1-2 minutes

Specimen Collection

Glucose levels are drawn fasting, and then 3, 5, 10, 20, 30, 45 and 60 minutes after the infusion is complete.

Occasionally plasma insulin levels are drawn at 2, 3 and 5 minutes after the infusion is complete.

Shortly after the infusion, transient glucose concentration up to 250 mg/dL can be seen in normal individuals, but fasting glucose levels will be achieved by 90 minutes, with sub fasting levels at 120 minutes return ti fasting levels at 180 minutes. Transient glucosuria can be seen right after the infusion since the renal threshold for glucose will be exceeded.

The rate in decrease in glucose level is then determined. Blood glucose level tends to decrease exponentially. Normal adults under 50 years of age show a mean rate of glucose disappearance of 1.5 % per minute. Normal adults over 50 years of age will show a mean rate of glucose disappearance which declines with age over 50 (about 0.09% per decade). Diabetes show a mean rate of glucose disappearance of <1% per minute.

The rate of decrease can be measured is several ways. The rate of disappearance of glucose expressed as a percent per minute of the 10 minute level (take 10 minute level as 100%, and then the subsequent levels are percentage). A semi logarithmic rate of decline of glucose from 10 to 30 minutes[38,40].

DISCUSSION

DM is the 3rd biggest disease[41] and characterized by persistent hyperglycemia and needs careful management by using drugs, diet control and mild exercise for the rest of lifetime. DM is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. This deficiency results in abnormal high concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves[42].

OGTT is better able to diagnose high blood glucose after a glucose challenge than the fasting blood glucose test. Doctor may recommend OGTT, if suspect's diabetes in cases where a patient's fasting blood glucose level is normal, but have other symptoms of diabetes or overweight. An OGTT is most commonly preferred to check for diabetes that happens during pregnancy (gestational diabetes).

Oral glucose tolerance test is used not only to diagnose diabetes, but also help to provide additional information about the body's ability to metabolize blood glucose. Higher OGTT values are likely to reflect diet, lifestyle problems and problems of insulin functioning.

Information in regard to reliability of the oral glucose tolerance test is important, as some conditions (common cold), or food (caffeine), or lifestyle habits (smoking) may alter the results of the oral glucose tolerance test

Though not routinely used anymore, the oral glucose tolerance test (OGTT) is the gold standard for making the diagnosis of type 2 diabetes. It is still commonly used for diagnosing gestational diabetes[22-24].

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