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CHANGING TRENDS IN DIAGNOSTIC CRITERIA OF DIABETES MELLITUS: AN OVERVIEW

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ABSTRACT

Over the years, the matter of classification and diagnostic criteria of Diabetes mellitus have lacked consensus among health care professionals. Healthcare providers have got their own perceptions based on the knowledge acquired during their study period, training and practical exposure. However, with the increasing knowledge in the field of etiopathogenesis and the treatment of Diabetes; it is deemed essential in the healthcare community to remain comprehensively acquainted with the new developments and changing trends in this field. Since the diagnostic criteria are changing from time to time, it is imperative to update the knowledge of these trends.

KEY WORDS: **Diabetes mellitus, diagnostic criteria, classification, changing trends**

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.[1] With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality in the foreseeable future.[1]

BRIEF HISTORY

In 1979, for the first time the National Diabetes Data Group (NDDG) produced a consensus document standardising the nomenclature and definitions for Diabetes mellitus.[2] Before this, there had always been an enormous variation and chaotic situation with lack of consensus among health care professionals regarding the definition, nomenclature and diagnostic criteria of Diabetes mellitus. This was further endorsed by World Health Organisation (WHO) and the first widely accepted classification of Diabetes mellitus was published by it in 1980[3] and in the modified form in 1985.[4] But with the growth of knowledge regarding the etiology and pathogenesis of diabetes; many individuals, groups and committees in the Diabetes community had felt the need for a revision of its nomenclature, diagnostic criteria and classification which should reflect thecurrentongoingknowledge.[2]Aninternational Expert committee, working under the sponsorship of American Diabetes Association (ADA) was established in 1995 to review the scientific literature since 1979 and to decide if changes in classification and diagnosis of Diabetes mellitus were warranted. In June 1997, an international expert committee released a report with new recommendations for the classification and diagnosis of diabetes mellitus. These new recommendations were the result of more than two years of collaboration among experts from the American Diabetes Association and the World Health Organization (WHO). The use of classification systems and standardized diagnostic criteria facilitated a common language among patients, physicians, other health care professionals and scientists. Since then more information relevant to the diagnosis of Diabetes mellitus had become available and in 2003, ADA reviewed its diagnostic criteria. This was followed by WHO in 2005 which presented the report in 2006. ADA since then had been publishing its position statement and committee report every year after reviewing works done by various individuals and groups along with their suggestions from across the world in order to produce uniformity and to enlighten changes, if any, towards the classification, screening and diagnosis of DM .In the present article, we shall outline the important changes and highlight the developments in classification, diagnostic criteria and screening of Diabetes mellitus chronologically.

CHANGING TRENDS IN THE CLASSIFICATION OF DIABETES MELLITUS

In 1985, according to WHO the classification of Diabetes mellitus was as follows (table 1)

Table 1
Classification of Diabetes mellitus (WHO 1985)[4]

A.	Clinical classes:
1.	Diabetes mellitus (DM)
➢	Insulin dependent diabetes mellitus (IDDM)
➢	Non- insulin dependent diabetes mellitus (NIDDM)
a)	Non-obese b) Obese
➢	Malnutrition related diabetes mellitus (MRDM)
➢	Other types of diabetes associated with certain conditions and syndromes.
2.	Impaired glucose tolerance (IGT)
➢	Non – obese
➢	Obese
➢	Associated with certain conditions and syndromes
3.	Gestational diabetes mellitus (GDM)
B.	Statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)

American diabetes association (ADA) in 1997 proposed following changes towards NDDG/WHO classification scheme and diagnostic criteria:[5]

1) The terms insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus and their acronyms, IDDM and NIDDM, were eliminated.
2) The terms type 1 and type 2 diabetes were retained, with Arabic numerals being used rather than roman numerals. The class, or form, named type 1 diabetes encompassed the vast majority of cases that were primarily due to pancreatic islet (β-cell) destruction and were prone to ketoacidosis. Most type1 diabetes was characterized by the presence of islet cell auto antibodies as well as GAD, IA-2, IA-20 or insulin auto antibodies. However in some subjects, where there had been no evidence of autoimmunity; these cases were classified as type 1 idiopathic.[6,7,8,27]
3) The class, or form, named type 2 diabetes included the most prevalent form of diabetes, which resulted from insulin resistance with an insulin secretory defect.
4) The class malnutrition-related diabetes mellitus was eliminated.
5) The stage impaired glucose tolerance (IGT) had been retained. The analogous intermediate stage of fasting glucose was named impaired fasting glucose (IFG).
6) The class, Gestational diabetes mellitus (GDM) was retained.
7) Diabetes mellitus was now classified into four major types based on etiology rather than treatment:

I. Type 1 diabetes (β-cell destruction: immune mediated or idiopathic)
II. Type 2 diabetes (predominantly insulin resistance variety)
III. Other specific types(including genetic defects in β-cell function and insulin action, endocrinopathies, drug or chemical induced diabetes)
IV. Gestational diabetes mellitus

Since then there had been no change in the classification system and it is still being accepted universally.

CHANGING TRENDS IN THE DIAGNOSTIC CRITERIA OF DIABETES MELLITUS:

As per WHO (1985):[4]

Diagnosis of diabetes mellitus was based on the symptoms suggestive of the diabetes such as increased thirst and urine volume, unexplained weight loss and plasma glucose value as follows

Random plasma glucose concentration ≥200mg/dl

or

Fasting plasma glucose ≥126mg/dl

or

Blood glucose value, 2hrs. after 75g of glucose load in an OGTT ≥200mg/dL[4](In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. However OGTT was not recommended for routine clinical use)This was followed universally with no change until ADA in 2009, after an extensive review of both established and emerging epidemiological evidences, recommended the use of the HbA_{1C} to diagnose diabetes (which earlier was only a prognostic criteria), with a threshold of ≥6.5%. The diagnostic test should be performed using a method that was certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay.[9]

So HbA_{1C} came in the diagnostic criteria and the revised diagnostic criteria according to ADA 2010 which is being followed till date for diabetes mellitus is shown in table 2.[10]

Table 2

Recent diagnostic criteria of diabetes mellitus[10]

HbA_{1C} ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
Or
FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h.
Or
2-h plasma glucose ≥200 mg/dl during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
Or
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl.

IMPAIRED GLUCOSE TOLERANCE

- Subjects, whose blood glucose concentrations could not meet the criteria of diagnosis of diabetes and did not fall in the normal range either had always been a subject of debate and had been addressed differently; when in 1985 for the first time WHO totally replaced the previously used terms i.e. borderline diabetes, pre-diabetes and chemical diabetes by Impaired glucose tolerance(IGT)**.**[2]

- ***This was characterised by***

- ***The categories of FPG values were as follows*** fasting plasma glucose value <140mg/dl and
- plasma glucose value in a 2 Hrs post 75g of glucose load sample in the range of 140-200mg/dl. Still IGT continued to lack consensus among healthcare professionals and remained a subject of research in terms of mechanisms and prognostic implications.

- In 1997**,** ADA recognised this group as an intermediate group with following blood glucose levels:[5]

- FPG <110 mg/dl→ normal fasting glucose
- FPG >110 to <126 mg/dl→ IFG (impaired fasting glucose)
- FPG ≥126 mg/dl→ provisional diagnosis of diabetes

The corresponding categories when the OGTT was used

- 2-h post glucose load (2hPG) <140mg/dl→ normal glucose tolerance
- 2hPG >140 to <200 mg/dl→(impaired glucose tolerance) IGT
- 2hPG >200 mg/dl→provisional diagnosis of diabetes

Since the 2-h OGTT cut off of 140mg/dl would identify more people as having impaired glucose homeostasis than would the fasting cut off of 110 mg/dl, it was essential that investigators should always report which test was used.

- In 2004, ADA in its position statement for the first time lowered the lower limit of impaired fasting glucose from 110mg/dl to 100mg/dl.[11] However it must be noted that WHO and some other organisations lacked consensus with ADA.
- In 2009, IFG and IGT were officially termed "pre-diabetes" by ADA and it was further mentioned that both the categories of pre-diabetes were risk factors for future diabetes and for cardiovascular disease.[12]
- In 2010, ADA, after affirming the use of HbA_{1C} in the diagnostic criteria, further extended its inclusion in the criteria of increased risk for acquiring diabetes in future. So the most recent

criteria for pre-diabetes are as follows:[10]

- ✓ FPG >100 to <126mg/dl→IFG.
- ✓ *2hPG in a 75g OGTT >140 to <200mg/dl→IGT.*
- ✓ HbA_{1C} 5.7-6.5%

Compared to the fasting glucose cut point of 100 mg/dl, an HbA_{1C} cut point of 5.7% is less sensitive but more specific and has a higher positive predictive value to identify people at risk for later development of diabetes.[10]

DEVELOPMENTS IN THE DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS (GDM)

In the past, the term GDM was applied only to women in whom glucose intolerance was first detected during pregnancy. Reclassification was required post- partum. However WHO in 1985 recommended that the diagnostic procedures and criteria for pregnant women should be the same as those proposed for adults. Still there was need for international standardisation of diagnostic criteria for gestational diabetes that could form the basis for prospective studies of the health of mothers and their infants.[13]ADA in 1997 and the American College Of Obstetricians and Gynaecologists (ACOG) finally reached a consensus for diagnosis of GDM.[14,15,16] At that time most American obstetricians used a screening test consisting of a 50-g oral glucose load followed by a plasma glucose determination 1 h later.[14] This test was performed (unless otherwise indicated) between 24 and 28 weeks of gestation, and the patient need not be fasting. A value of >140 mg/dl 1 h after the 50-g load indicated the need for a full diagnostic, 100-g, 3-h OGTT performed in the fasting state. This two-step process—a 50-g screening test and, if positive, a 100-g diagnostic test—was the testing scheme

.**Table 3**

Screening and diagnosis scheme for GDM (ADA 1997)[5]

Plasma glucose	50-g screening test	100-g OGTT
Fasting	-	105 mg/dl
1-h	140 mg/dl	190 mg/dl
2-h	-	165mg/dl
3-h	-	145mg/dl

The diagnosis of GDM required any two of the four plasma glucose values obtained during the test to meet or exceed the value (table 3).

Screening for GDM might not be necessary in pregnant women who met all of the following criteria

<25 years of age, normal body weight, no first degree relative with diabetes, and not Hispanic, Native American, Asian-, or African-American.[5] ADA expert committee in 2003 revised the previous recommendations and criteria for GDM and outlined it as follows:[17]

- ✓ Risk assessment for GDM should be undertaken at the first prenatal visit.

- ✓ Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing as soon as feasible.
- ✓ If they were found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation.
- ✓ Women of average risk should have testing undertaken at 24–28 weeks of gestation.[18,19,20]
- ✓ A fasting plasma glucose level >126 mg/dl or casual plasma glucose >200 mg/dl met the threshold for the diagnosis of diabetes, if confirmed on a subsequent day, and precludes the need for any glucose challenge.
- ✓ In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches:

One-step approach

Perform a diagnostic OGTT without prior screening. This was especially beneficial in high risk patients.

Two-step approach

Perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. With either approach, the diagnosis of GDM was based on an OGTT. Diagnosis could also be made using a 75-g glucose load, however this test was not as well validated as the 100-g OGTT.[21]

Table 4

Diagnosis of GDM with a 100-g or 75-g glucose load[21]

	mg/dl	mmol/l
100 g glucose load		
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6
3-h	140	7.8
75 g glucose load		
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. Although numerous national and international medical organisations, along with expert panels and working groups had issued specific guidelines with recommendations for screening and diagnosing GDM, Still a universal recommendation for the ideal approach for screening and diagnosis of GDM remained elusive. In 2011, ADA affirmed the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG),[22] based on the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO)[23] study. Its current universal screening test is the 75 g OGTT, with measurement of plasma glucose over 2 hrs. The test is performed at 24-28 weeks of gestation, after an overnight fast of at least 8 hrs. The diagnosis of GDM is made when one of the following plasma glucose values is met:

Fasting ≥ 92 mg/dl
1 hr. ≥180 mg/dl
2 hr. ≥153 mg/dl

TRENDS IN THE SCREENING FOR DIABETES IN ASYMPTOMATIC, UNDIAGNOSED INDIVIDUALS

In the past, population screening for diabetes was often poorly organized and used variable diagnostic criteria and standards for follow-up and patient care. The commonest approach to diabetes screening was a preliminary, semi-quantitative test for glucose in a urine sample, followed by an oral glucose tolerance test for those found to have glycosuria. Target groups included those at a high risk of glucose intolerance e.g. the obese and those with close relatives having diabetes, and those in whom even mild glucose intolerance might be a risk factor e.g. in pregnant women and patients with premature atherosclerosis.[24] In 1997, ADA, for the first time defined the need for and the group in which there was a risk for the development of diabetes and laid down clearly the criteria for testing in asymptomatic, undiagnosed individuals as given below:

Table 5
Criteria for testing for diabetes in asymptomatic, undiagnosed individuals[5]

1)	Testing for diabetes should be considered in all individuals at age 45 years and above and, if normal, it should be repeated at 3-year intervals.
2)	Testing should be considered at a younger age or be carried out more frequently in individuals who:
a)	are obese (≥120% desirable body weight or a BMI ≥27 kg/m^2)
b)	have a first-degree relative with diabetes
c)	are members of a high-risk ethnic population (e.g., African-American, Hispanic, Native American)
d)	have delivered a baby weighing >9 lb or have been diagnosed with GDM
e)	are hypertensive (blood pressure≥140/90)
f)	have an HDL cholesterol level ≤35 mg/dl and/or a triglyceride level ≥250 mg/dl
g)	on previous testing, had IGT or IFG
The OGTT or FPG test may be used to diagnose diabetes; however, in clinical settings the FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost.	

In 2003, ADA revised these criteria and included following candidates also, apart from those mentioned in table 5 in testing for diabetes in asymptomatic, undiagnosed persons who might develop diabetes in future:[17]

- ✓ BMI≥25kg/m^2 (earlier it was recommended in individuals with BMI≥27kg/m^2).
- ✓ Those who are physically inactive.
- ✓ Have polycystic ovarian syndrome (PCOS).
- ✓ Have a history of vascular disease i.e. young myocardial infarction and young stroke.
- ✓ Have history of recurrent UTI, recurrent pneumonia, TB, early cataract or frequent changes of glasses.

In 2009, ADA for the first time in their position statement mentioned that incidence of type 2 diabetes in children and adolescents had dramatically increased in the last decade. So they formed criteria for testing for type 2 diabetes in asymptomatic children who might be at risk.[25]

Table 6
Testing for type 2 diabetes in asymptomatic children

Criteria:
Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors:
✓ Family history of type 2 diabetes in first or second-degree relative
✓ Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
✓ Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small-for-gestational age birth weight)
✓ Maternal history of diabetes or GDM during the child's gestation.
Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age.
Frequency: every 3 years
Test: FPG preferred

CONCLUSION

After reviewing the landmark developments and changing trends in the diagnosis of DM over the years it is concluded that with the growth of knowledge and research, there is always a potential towards the changing concepts and recommendations to which health care professionals need to stay abreast. *So the current recommendations as per ADA standards of medical care 2012 for the diagnosis of DM are given in table 7* [26] *and an overall summary of changing trends over the years is depicted in table 8.*

Table 7
Diagnosis of Diabetes mellitus [26]

STAGE	For all the below tests, in the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.			
	HbA_{1c}NGSP certified & standardised assay	Fasting plasma glucose (FPG)	Random plasma glucose	Oral glucose tolerance test (OGTT) 75 g
Diabetes	HbA_{1c} ≥6.5%	FPG≥126mg/dl	Random plasma glucose ≥200 mg/dl plus symptoms	Two-hour plasma glucose (2hPG) ≥200 mg/dl
Increased risk of diabetes	HbA_{1c} 5.7-6.4%	Impaired fasting Glucose (IFG)= FPG 100-125mg/dl		Impaired glucose tolerance (IGT)= 2hPG 140-199 mg/dl
Normal	HbA_{1c} <5.7%	FPG<100mg/dl		2hPG<140mg/dl

Table 8
Summary of WHO and ADA criteria for the diagnosis of diabetes reflecting the changing trends over the years

	WHO 1985	ADA 1997	ADA 2004	ADA 2009	ADA 2010	ADA 2012
1. Classification	• DM ✓ IDDM ✓ NIDDM ✓ MRDM ✓ Other types • IGT • GDM	• DM ✓ Type 1 ✓ Type 2 ✓ Other specific types ✓ GDM	No change	No change	No change	No change
2. Diagnostic criteria	Random plasma glucose(RBS)≥200mg/dl **or** Fasting plasma glucose(FPG)≥126mg/dl **or** Blood glucose 2hrs. after 75 g of glucose load in an OGTT≥200 mg/dl. Along with symptoms suggestive of DM	RBS ≥200mg/dl **Or** FPG ≥126mg/dl **Or** 2hPG≥200mg/dl Single testing not diagnostic; should be confirmed by repeat testing.	No change	No change	HbA1c≥6.5% **Or** FPG≥126 mg/dl **Or** 2hPG≥200mg/dl **Or** Classic symptoms of hyperglycemia with ≥200 mg/dl	No change
	WHO 1985	**ADA 1997**	**ADA 2004**	**ADA 2009**	**ADA 2010**	**ADA 2012**
3. Impaired glucose tolerance	FPG <140mg/dl. 2hPG value 140-200mg/dl. Terms borderline diabetes, pre-diabetes and chemical diabetes that had been used earlier had been totally replaced by **impaired glucose tolerance (IGT).** IGT continued to lack consensus among healthcare professionals in terms of mechanisms and prognostic implications.	In 1997 according to ADA this group of subjects was named **intermediate group** which included: 1).**IFG** (**impaired fasting glucose**): FPG 110-125 mg/dl. 2).**IGT (impaired glucose tolerance)**: 2hPG 140-199mg/dl.	Lower limit of impaired fasting glucose was lowered from 110 to 100 mg/dl. However WHO lacked consensus here with ADA.	**IFG and IGT** were officially termed as **pre-diabetes**	Apart from IFG and IGT, a third criteria for the category carrying increased risk was HbA1c in the range of 5.7-6.4%.	Recent criteria for pre-diabetes: **IFG**: fasting plasma glucose 100-125mg/dl **IGT**: 2hPG in a 75 g OGTT 140-199mg/dl. HbA_{1c}:5.7-6.5%
	WHO 1985	**ADA 1997**	**ADA 2004**	**ADA 2009**	**ADA 2010**	**ADA 2012**
4. GDM	Criteria for gestational diabetes not mentioned. Criteria for pregnant women were same as those for adults.	**<u>Two step approach:</u>** 1). Screening with 50g oral glucose challenge test (GCT) at 24-28 weeks of gestation. 2). 100-g, 3-h OGTT performed if value in GCT >140mg/dL.	Risk assessment should be undertaken at first antenatal visit and glucose testing done in high risk females. Retested in 24-28 weeks if normal in initial testing. High risk patients: **one or two step approach** i.e. with or without 50 g GCT.	No change	No change	Screen for GDM at 24-28 weeks of gestation in all pregnant women. Perform a 75-g OGTT with plasma glucose measurement at : fasting and at 1h and 2h.

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