WHO Classification and Diagnosis of Diabetes mellitus: Historical overview

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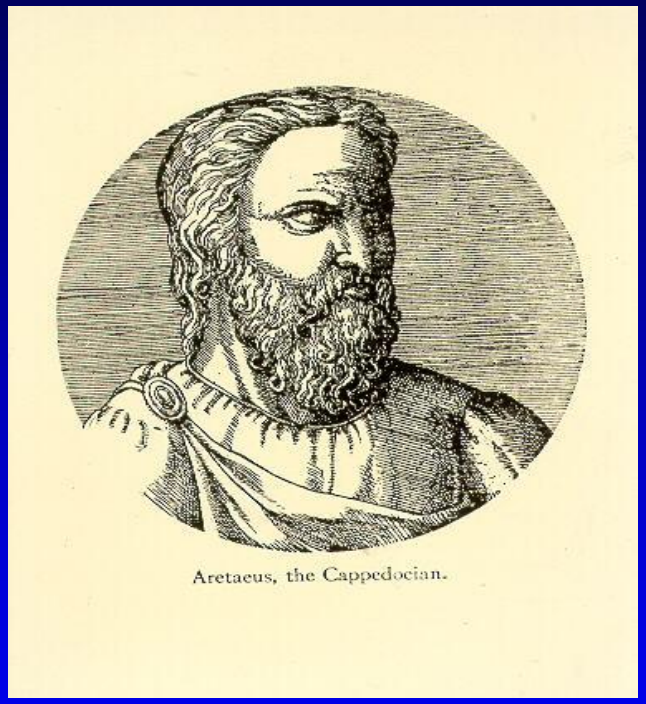
History of Diabetes Mellitus

Diabetes is described in 1550 BC in an Egyptian medical text, the Ebers Papyrus, as a condition of passing too much urine.

The papyrus is discovered in 1862 by the German Egyptologist, George Ebers.

The Ebers papyrus

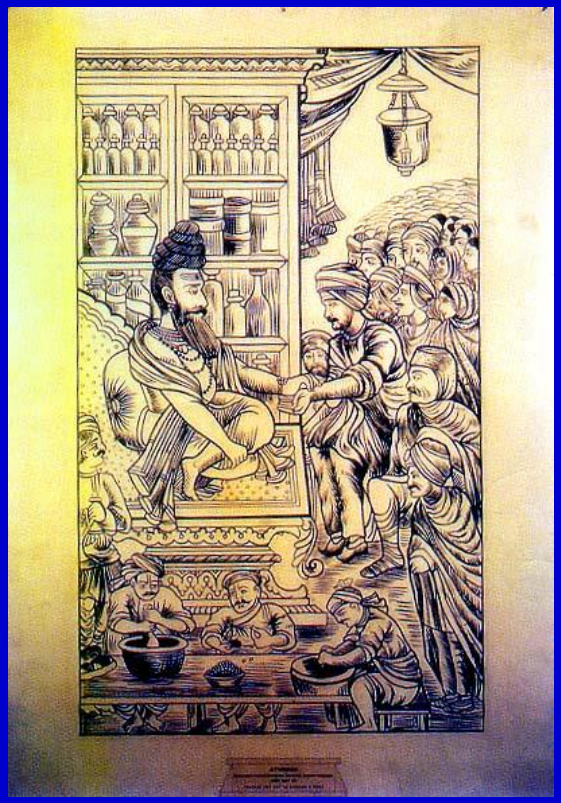
In the first century AD, Aretaeus uses the term ‘diabetes’ meaning “a siphon” in Greek to describe the disease as “melting down of flesh and limbs into urine”.



Aretaeus

During the 5th and 6th century AD the sweet, honey-like taste of urine in polyuric patients, that attracted ants and other insects, is reported by Indian physicians such as Sushruta.

These descriptions mention two forms of diabetes, one in older, fatter people and the other in thin people who do not survive for long.



Sushruta

World J Diabetes 2016 January 10; 7(1): 1-7

The sweetness of diabetic urine was re-discovered in Europe in the 17th century by the English physician, Thomas Willis (1621-1675). He remarks that, although the disease was rare in ancient times, its frequency is increasing.

'Mellitus', the latin word for honey is added (as opposed to insipidus) --leading to urine tasting as means of diagnosis.

Thomas Willis

World J Diabetes 2016 January 10; 7(1): 1-7

What is Diabetes Mellitus?

- A disease or the upper end of a continuous distribution of glycaemia? cf. cholesterol levels-hypercholesterolaemia
  - Symptoms-polyuria, polydipsia etc
  - Complications--specific or non-specific
  - A discrete entity?

- Are there certain levels of glycaemia that are associated with or predict complications?

What is Diabetes Mellitus?

2.1 Definition

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

World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, World Health Org., 1999.

What is Diabetes Mellitus?

Definition

The term diabetes mellitus describes a group of metabolic disorders (of multiple aetiology) with defects in insulin secretion, insulin action, or both and disturbances of carbohydrate, fat and protein metabolism, that are characterized and identified by the presence of chronic persistent hyperglycaemia,.

Landmark reports on classification and diagnosis of diabetes

1965 WHO Report of Expert Committee on Diabetes mellitus

1979 National Diabetes Data Group Classification and criteria for diagnosis *and*
1980 WHO Study Group Report

1985 WHO Classification and criteria for diagnosis

1997 AmericanDiabetes Association (ADA) Expert Committee *and*
1998/9 WHO Report on Definition, Diagnosis and Classification of Diabetes mellitus and i
Complications

2003 ADA Expert Committee

2006 WHO / IDF Technical Advisory Group-Definition and diagnosis of diabetes mellitus ar
interermediate hyperglycaemia

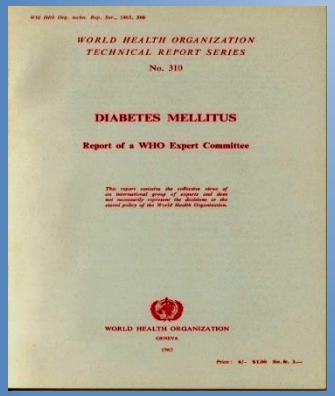
2009 International Expert Committee-role of HbA1c assay in diagnosis of diabetes mellitus

2010 American Diabetes Association-Diagnosis and Classsification of Diabetes Mellitus

2011 WHO: Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

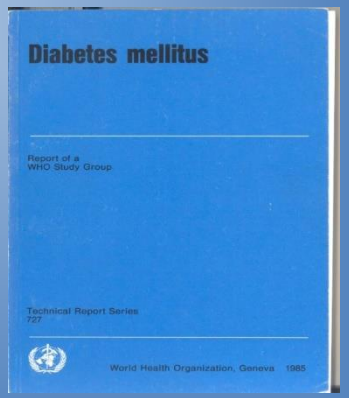
WHO Definitions, Diagnosis and Classifications of Diabetes Mellitus

1965

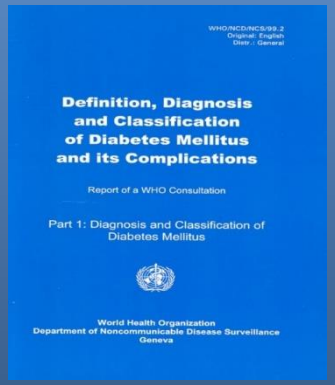


1980

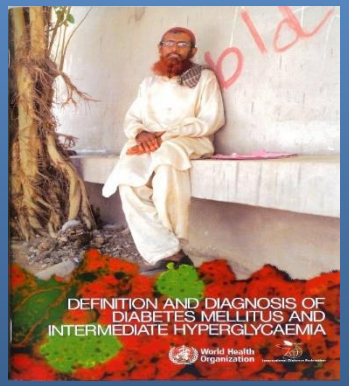
1985



1999



2006



1965 WHO Report

Definitions:
Potential
Latent
Asymptomatic (sometimes called Sub-clinical or Chemical)
Clinical
Classification:
Infantile or childhood (onset 0-14 years)
Young (onset 15-24 years)
Adult (onset 25-64 years)
Elderly (onset 65 years and over)

Alternative classifications:
Juvenile-type
Brittle
Insulin-resistant
Gestational
Pancreatic
Endocrine
Iactrogenic

1965 WHO Report

Diagnosis:

Fasting true blood sugar > 130 mg/dl or OGTT

Either 50g 0r 100g 0ral glucose tolerance test

RECOMMENDED LEVELS OF TRUE BLOOD-SUGAR TWO HOURS AFTER GLUCOSE LOADING

Blood	Normal	Diabetic
Venous	Less than 110 mg per 100 ml blood	130 mg and over per 100 ml blood
Capillary	Less than 120 mg per 100 ml blood	140 mg and over per 100 ml blood

1979-80 NDDG/WHO classification and criteria

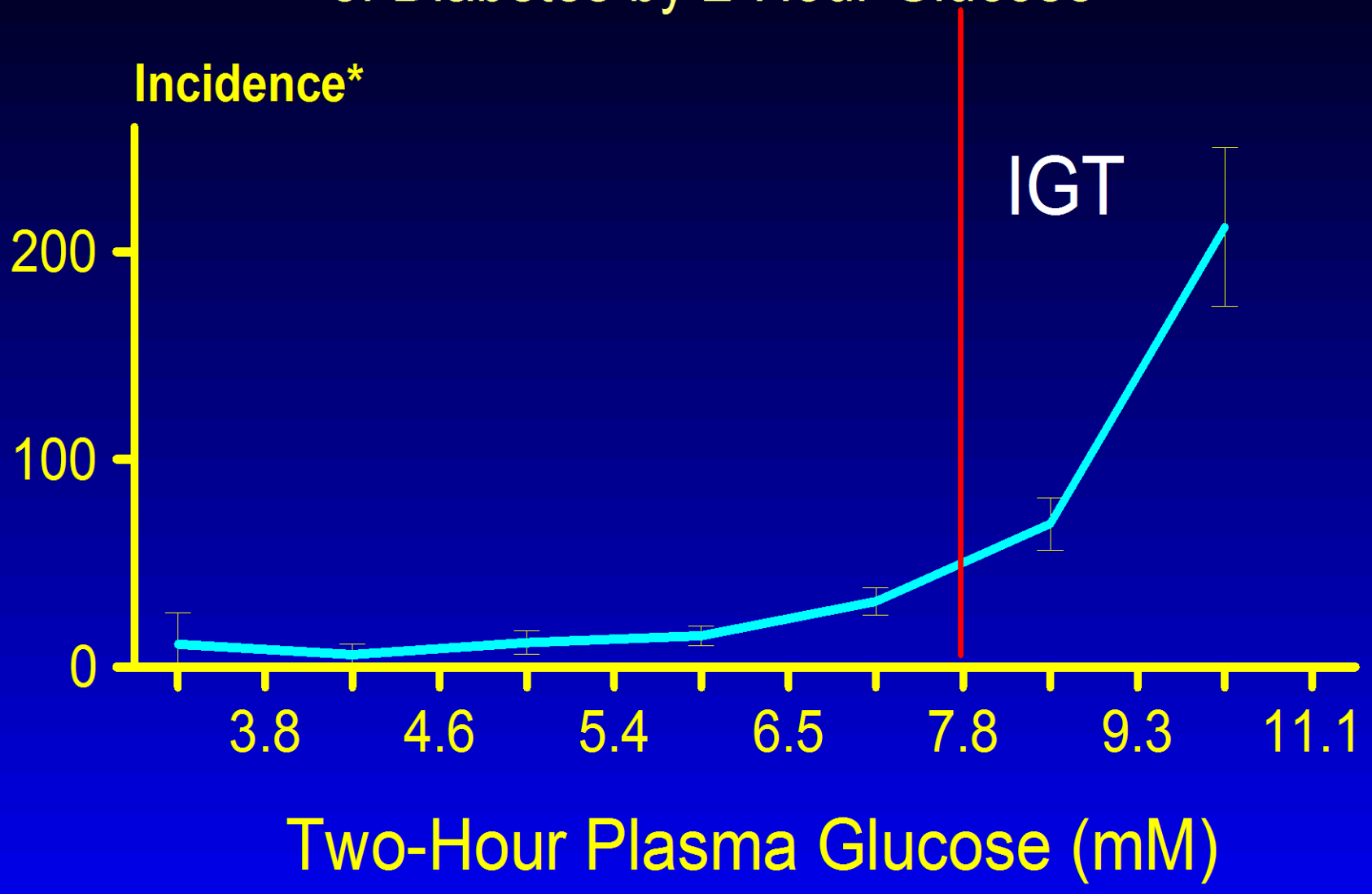
- Clear evidence of differences in IDDM and NIDDM
  - Clinical presentation
  - Islet cell antibodies
  - HLA types
  - Insulin and C-peptide levels
- Evidence of relationship of microvascular complications to levels of glycaemia
- Evidence of bi-modality in glucose distributions
- Use of 75g glucose for OGTT

1980 WHO classification of diabetes mellitus and other categories of glucose intolerance

- Diabetes mellitus
  - Insulin dependent type-Type 1
  - Non-insulin-dependent type-Type 2
  - Other types associated with pancreatic disease, diseases of hormonal aetiology, drug or chemically induced, insulin receptor abnormalities, certain genetic syndromes, miscellaneous

  - Impaired glucose tolerance
  - Gestational diabetes
  - Statistical risk classes
    - Previous abnormality of glucose tolerance
    - Potential abnormality of glucose tolerance

Age-sex-adjusted Incidence (95% C.I.) of Diabetes by 2-Hour Glucose



* New cases / 1000 person-years

1997 ADA and 1999 WHO Classification and Diagnostic criteria

1997 ADA AND 1999 WHO recommendations

- Aetiological classification urged whenever possible
- Many cases of diabetes remain undiagnosed as OGTT is not used for screeni
  but physicians rely on fasting glucose levels to screen for diabetes
- Setting an appropriate fasting glucose criterion for diagnosis of diabetes
  will lead to identification of many cases that would otherwise remain undiagnos
- FPG of 126mg/dl (7mmol/l) or over chosen as 'equivalent' to 2h PG of 200mg/
  (11.1mmol/l)
- If FPG is used for diagnosis of diabetes, what FPG levels would correspond to IGT
  i.e. 2h PG levels of 7.8-11.0 mmol/l (140-199mg/dl)?
  FPG of 6.1-6.9 mmol/l (110-125 mg/dl) chosen as 'equivalent'

1997 ADA and 1999 WHO Classification and Diagnostic criteria

- Aetiological classification adopted
  -reflects increasing knowledge of causes of diabetes
- Clinical Staging introduced
  -reflects that degree of glycaemia may vary considerably even though the disease process is present throughout
- Fasting plasma glucose (FPG) for diagnosis of Diabetes mellitus lowered to 7.0 mmol/l (126mg/dl) and above
- Category of IFG introduced
  (FPG 6.1-6.9mmol/l;110-125mg/dl)

Aetiological Types of Diabetes mellitus

- Type 1
  - Autoimmune
  - Idiopathic
- Type 2
- Other specific types
- Gestational diabetes

Other specific types

- Genetic defects of beta-cell function e.g. MODY 1-3
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug or chemically induced diabetes
- Infections e.g. congenital rubella
- Other genetic syndromes sometimes associated with DM

Major changes in diagnostic criteria made in 1997 ADA and 1999 WHO reports

- Fasting plasma glucose for diagnosis of diabetes lowered to 7.0 mmol/L and above (from 7.8 mmol/L) (corresponds better to 2h value of 11.1 mmol/L)
- Category of Impaired fasting glycaemia (IFG--FPG of 6.1 to <7.0 mmol/L) created (intended to correspond to 2h value 7.8-11.0 mmol/L)
- FPG less than 6.1mmol/L defined as 'normoglycaemia' (ADA)

1999 WHO Criteria for Diabetes, Impaired Fasting Glycaemia (IFG) and Impaired Glucose Tolerance (IGT)

		2h Plasma Glucose (mmol/l)		
		<7.8	7.8-11.0	≥11.1
Fasting Plasma Glucose (mmol/l)	≥7.0	Diabetes		
	6.1-6.9	IFG	IGT	
	≤6.0			

Changes in diagnostic criteria (ADA 2003)

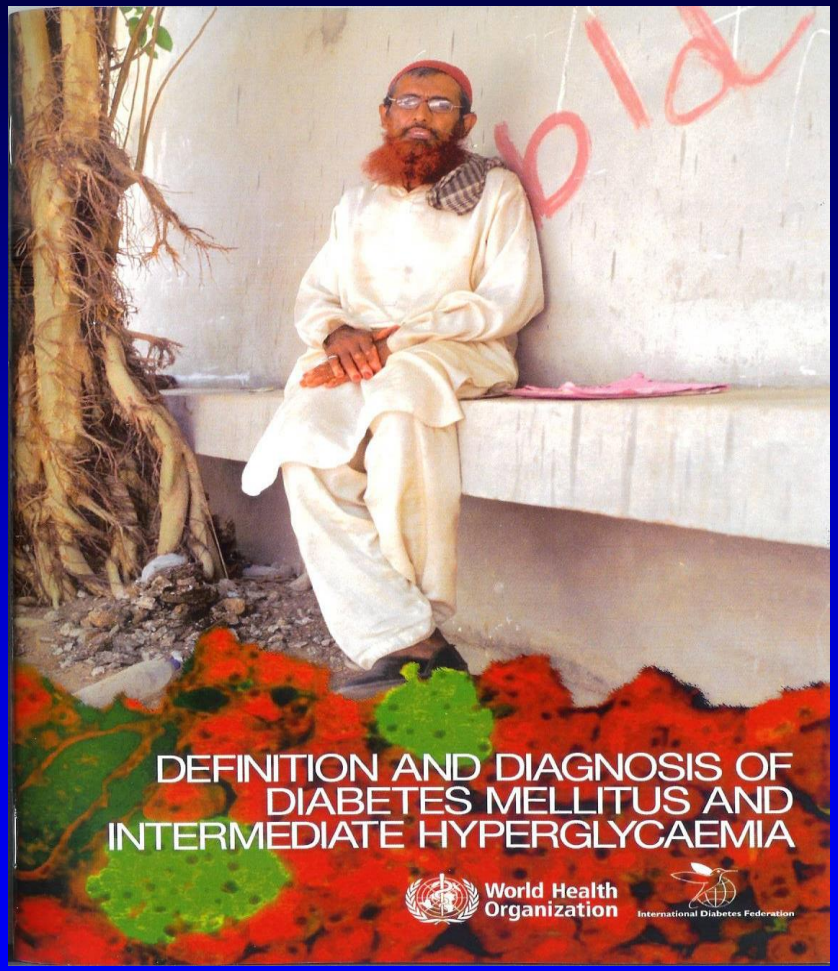
- ADA
  - Category of Impaired fasting glycaemia redefined as FPG 5.6 to <7.0 mmol/l
  - FPG Equal or less than 5.5 mmol/l defined as 'normoglycaemia' (ADA)
- WHO
  - Retained IFG as FPG 6.1 to < 7.0 mmol/l

2003 ADA Classification of glucose tolerance states

		2h Plasma Glucose (mg/dl)		
		<140	140-199	≥200
Fasting Plasma Glucose (mg/dl)	≥126	Diabetes		
	100-125	IFG	IFG + IGT	
	<100	NGT	IGT	

Expert Committee on the Diagnosis and Classifi es
Mellitus: follow-up report on the diagnosis of diabetes mellitus.
Diabetes Care 26: 3160–3167, 2003

WHO report 2006



2006 WHO Criteria for Diabetes and Intermediate Hyperglycaemia (IFG & IGT)

		2h Plasma Glucose (mmol/l)		
		<7.8	7.8-11.0	≥11.1
Fasting Plasma Glucose (mmol/l)	≥7.0	Diabetes		
	6.1-6.9	IFG	IGT	
	≤6.0	Normo-glycaemia		

Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF consultation. WHO Geneva, 2006

Should HbA1c be used for diagnosis of diabetes and other forms of hyperglycemia?

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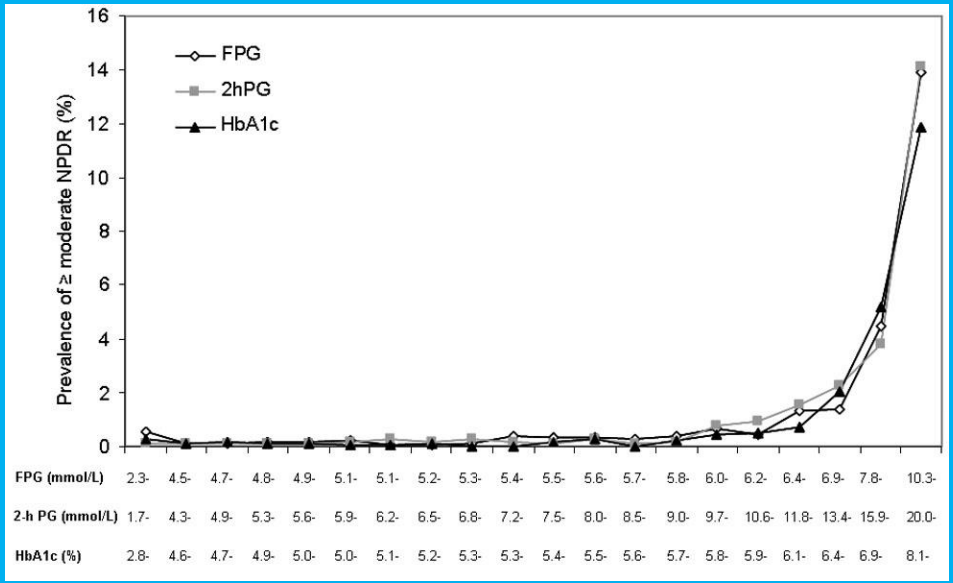
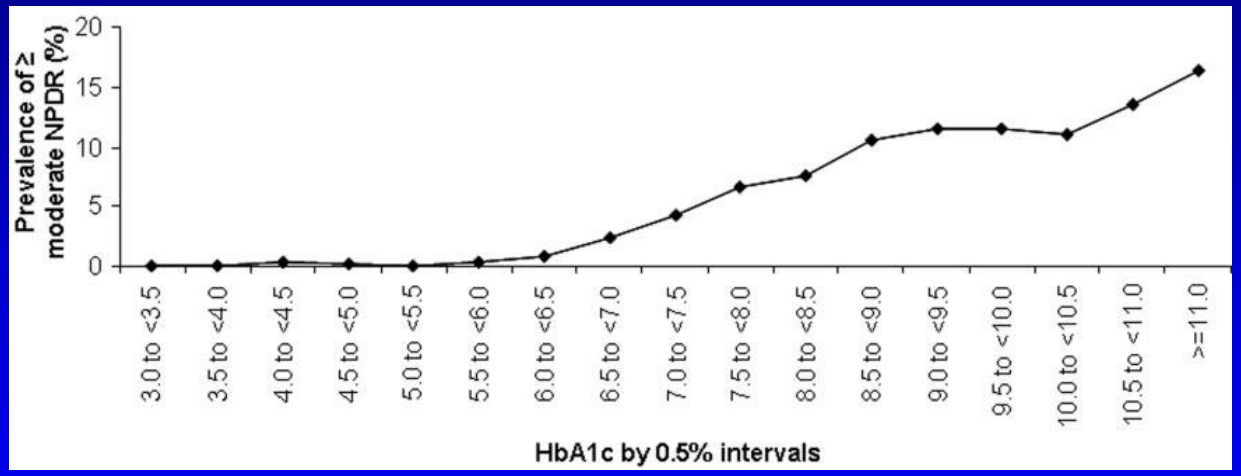


From Colagiuri S et al, Diabetes Care January 2011 34:145-150

Prevalence of diabetic retinopathy by 0.5% intervals of HbA1c in >20,000 persons aged 20–79 years



From Colagiuri S et al, Diabetes Care January 2011 34:145-150

Recommendation of the International Expert Committee on the role of A1c assay (Part 1)

For the diagnosis of diabetes:

- A1C assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.

- A1C assay has several advantages over laboratory measures of glucose

- Diabetes should be diagnosed when A1C is ≥6.5%. Diagnosis should be confirmed with a repeat A1C test. Confirmation is not required in symptomatic subjects with plasma glucose levels ≥200 mg/dl (11.1 mmol/l)

- If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.

2011 WHO: Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

http://www.who.int/diabetes/publications/report-hba1c_2011.pdf

2011 WHO: Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

Recommendation

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes.

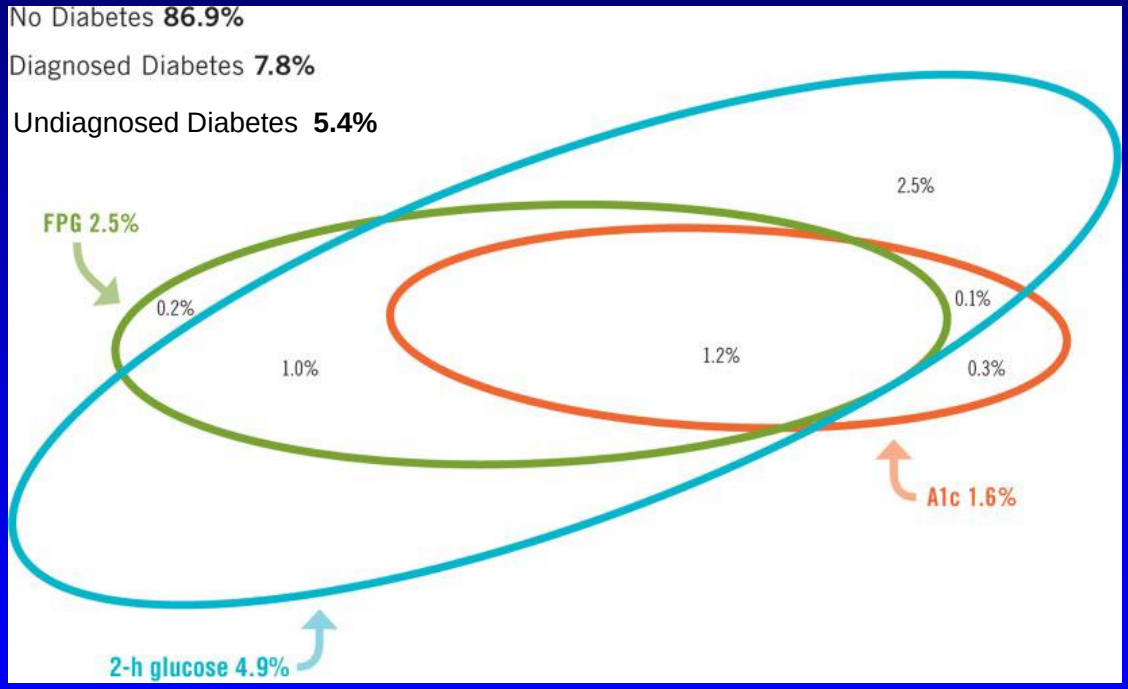
A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

http://www.who.int/diabetes/publications/report-hba1c_2011.pdf

Current (2016) WHO Criteria for Diabetes and Intermediate Hyperglycaemia (IFG & IGT)

		2h Plasma Glucose (mmol/L)		
		<7.8	7.8-11.0	≥11.1
Fasting Plasma Glucose (mmol/L)	≥7.0	Diabetes		
	6.1-6.9	IFG	IGT	
	≤6.0	Normo-glycaemia		
HbA1c	≥ 6.5%			

Undiagnosed diabetes in the U.S. population aged 20-74 years by three diagnostic criteria—NHANES 2005–2006 (n2,017). Diagnostic criteria for diabetes: HbA1c ≥6.5%, FPG ≥7.0 mmol/1, and 2-h glucose ≥11.1 mmol/1.



Cowie et al. DIABETES CARE, 33: 562-568, 2010

2019 WHO Classification

Types of diabetes

Type 1 diabetes	Other specific types
Type 2 diabetes	**Monogenic diabetes** - **Monogenic defects of β-cell function** **- Monogenic defects in insulin action**
Hybrid forms of diabetes	**Diseases of the exocrine pancreas**
Slowly evolving immune-mediated diabetes of adults (formerly LADA)	**Endocrine Disorders**
Ketosis prone type 2 diabetes	**Drug- or chemical-induced**
	Infections
	Hyperglyacemia during pregnancy **Diabetes mellitus in pregnancy** **Gestational diabetes mellitus**

CLASSIFICATION OF DIABETES MELLITUS. WHO 2019.

Other specific types of diabetes (1)
Monogenic diabetes

Monogenic defects of β-cell function

GCK MODY

HNF1A MODY

HNF4A MODY

HNF1B RCAD

mtDNA 3243 MIDD

KCNJ11 PNDM

KCNJ11 DEN

6q24 TNDM

ABCC8 MODY

INS PNDM

WFS1 Wolfram syndrome

FOXP3 IPEX syndrome

EIF2AK3 Wolcott–Rallison syndrome

Abbreviations: MODY = maturity-onset diabetes of the young;

RCAD = renal cysts and diabetes;

MIDD = maternally inherited diabetes and deafness;

PNDM = permanent neonatal diabetes;

TNDM = transient neonatal diabetes;

DEND = developmental delay epilepsy and neonatal diabetes

Monogenic defects in insulin action

INSR Type A insulin resistance

INSR Leprechaunism

INSR Rabson-Mendenhall syndrome

LMNA FPLD

PPARG FPLD

AGPAT2 CGL

BSCL2 CGL

Abbreviations: FPLD = familial partial lipodystrophy; CGL = congenital generalized lipodystrophy

Other genetic syndromes sometimes associated with diabetes

Down syndrome
Friedreich's ataxia
Huntington's chorea
Klinefelter's syndrome
Lawrence–Moon–Biedel syndrome
Myotonic dystrophy
Porphyria
Prader–Willi syndrome
Turner's syndrome
Others

Other specific types of diabetes (2)

Diseases of the exocrine pancreas

- **Fibrocalculous pancreatopathy**
- **Pancreatitis**
- **Trauma/pancreatectomy**
- **Neoplasia**
- **Cystic Fibrosis**
- **Haemochromatosis**

Endocrine disorders

- **Cushing's syndrome**
- **Acromegaly**
- **Phaeochromocytoma**
- **Glucagonoma**
- **Hyperthyroidism**
- **Somatostatinoma**

CLASSIFICATION OF DIABETES MELLITUS.
WHO 2019.

Other specific types of diabetes (3)

Infections

Congenital rubella

Cytomegalovirus

Others

Uncommon forms of immune-mediated diabetes

Insulin autoimmune syndrome

Anti-insulin receptor antibodies

“Stiff man” syndrome

Drugs or chemicals that can induce diabetes

Glucocorticoids

Thyroid hormone

Thiazides

Alpha-adrenergic agonists

Beta-adrenergic agonists

Dilantin

Pentamidine

Nicotinic acid

Pyrinuron

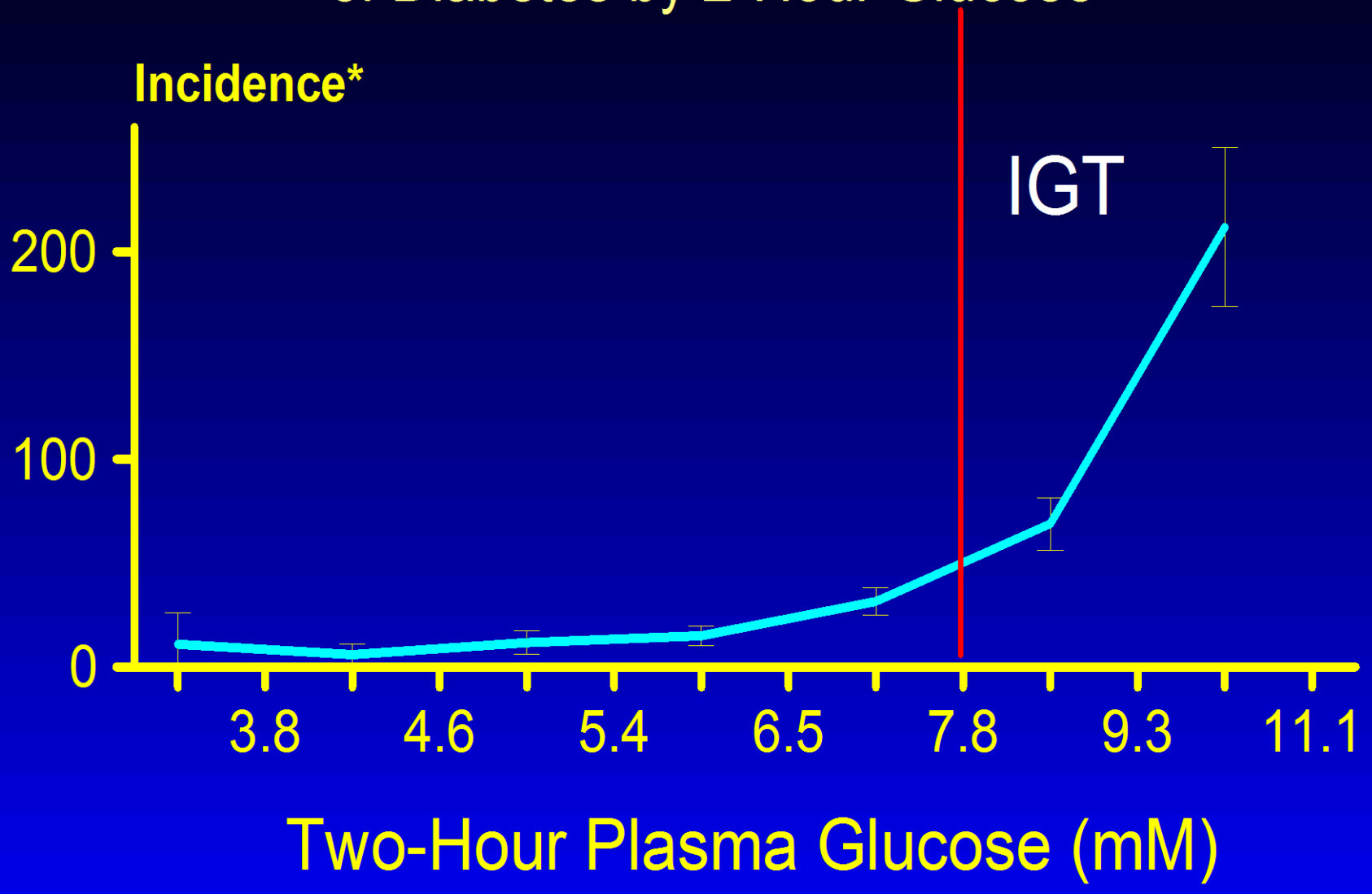
Interferon-alpha

CLASSIFICATION OF DIABETES MELLITUS. WHO 2019.

“Prediabetes” and Intermediate Hyperglycaemia

- What is “Prediabetes”?

Age-sex-adjusted Incidence (95% C.I.) of Diabetes by 2-Hour Glucose



* New cases / 1000 person-years

2010 American Diabetes Association: Diagnosis and Classification of Diabetes Mellitus (Diabetes Care 33:S62-69 (January) 2010

Categories of Inceased Risk for Diabetes

FPG	100-125 mg/dl (5.6-6.9 mmol/l)
2-h PG	140-199 mg/dl (7.8-11.0 mmol/l) in 75g OGTT
A1C	5.7-6.4%

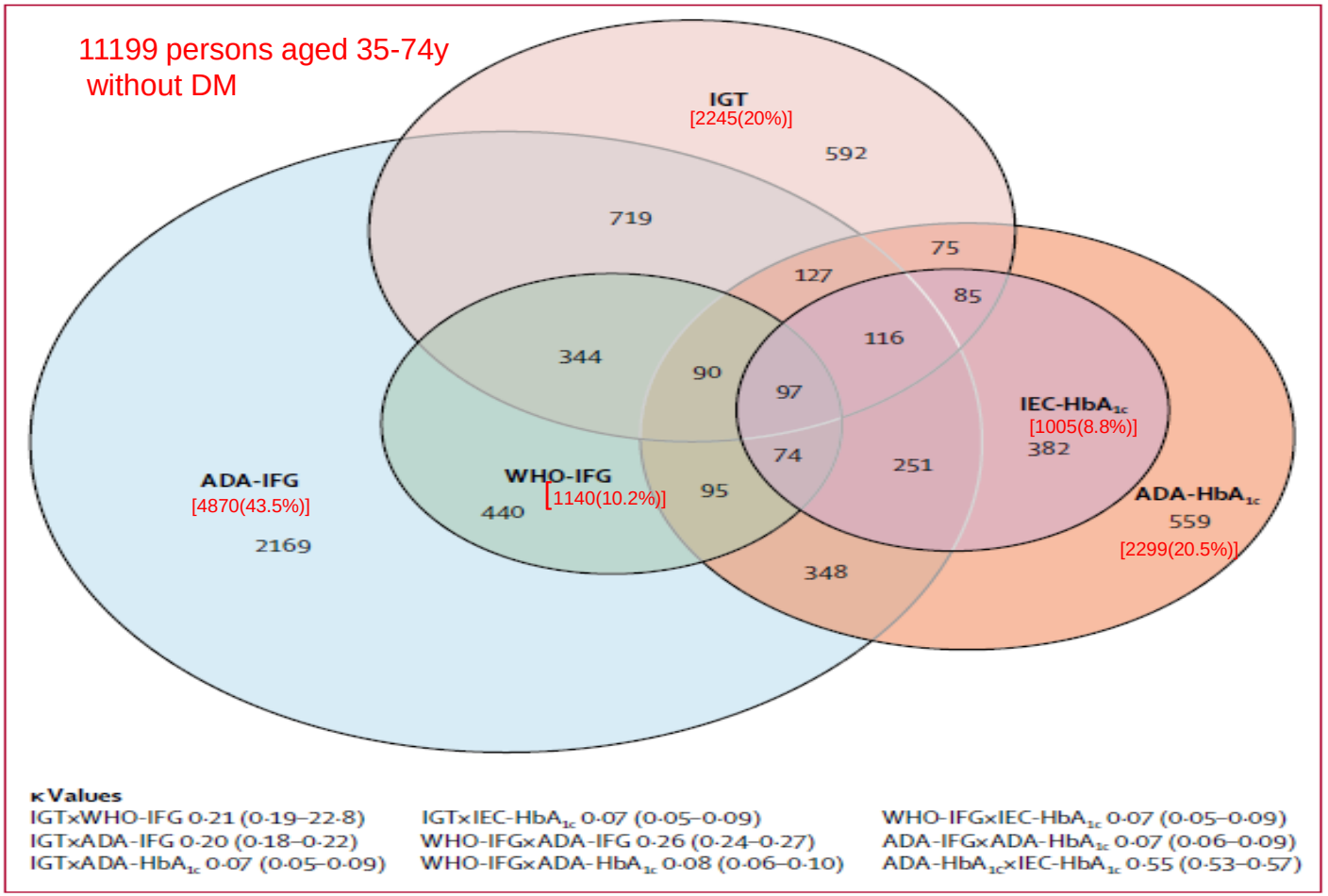


Figure 2: **Venn diagram of the 6563 patients with intermediate hyperglycaemia identified at baseline**
ADA=American Diabetes Association. IEC=International Expert Committee. IGT=impaired glucose tolerance. IFG=impaired fasting glucose. WHO-IFG=IFG based on WHO criteria. ADA-IFG=IFG based on ADA criteria. ADA-HbA_{1c}=high HbA_{1c} according to the ADA. IEC-HbA_{1c}=high HbA_{1c} according to the IEC definition.

10-year incidence of Diabetes by baseline Fasting Plasma Glucose: Ely study

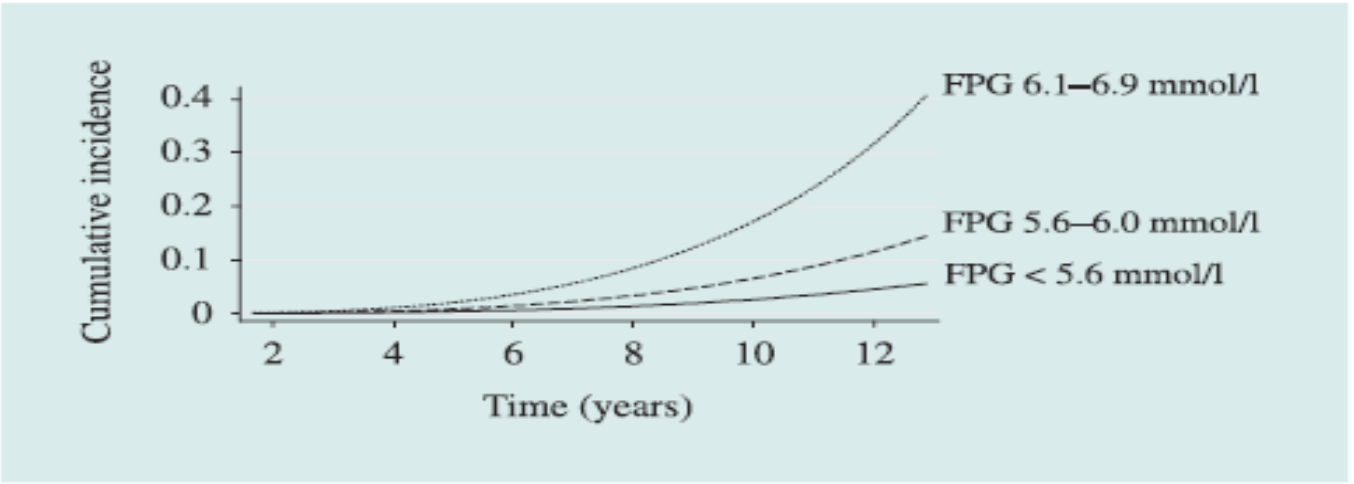


FIGURE 2 Age- and sex-adjusted cumulative hazard of incident diabetes by baseline fasting glucose status among those non-diabetic at baseline (FPG < 7.0, 2-h glucose < 11.1 mmol/l). ——, NFG; – – – –, IFG-lower; - - - -, IFG-original.

Forouhi NG et al. Diabet Med. 2007: 24; 200-7

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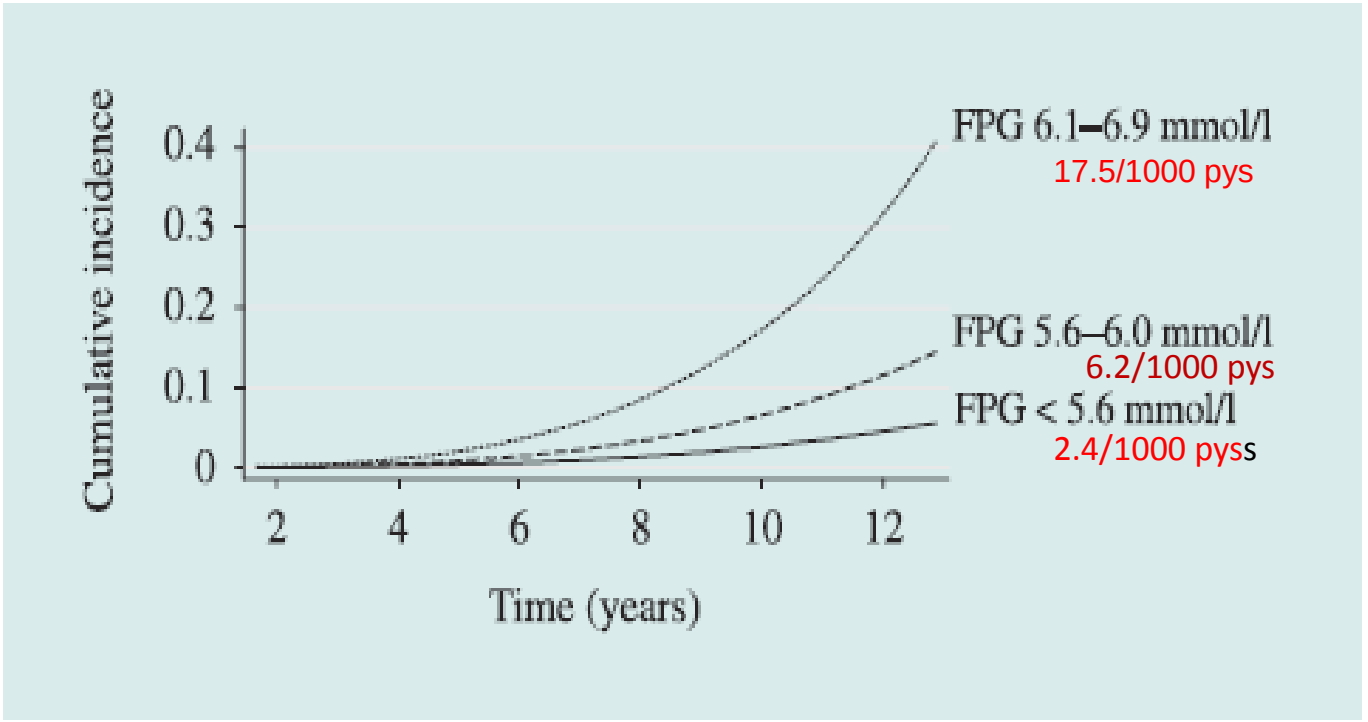

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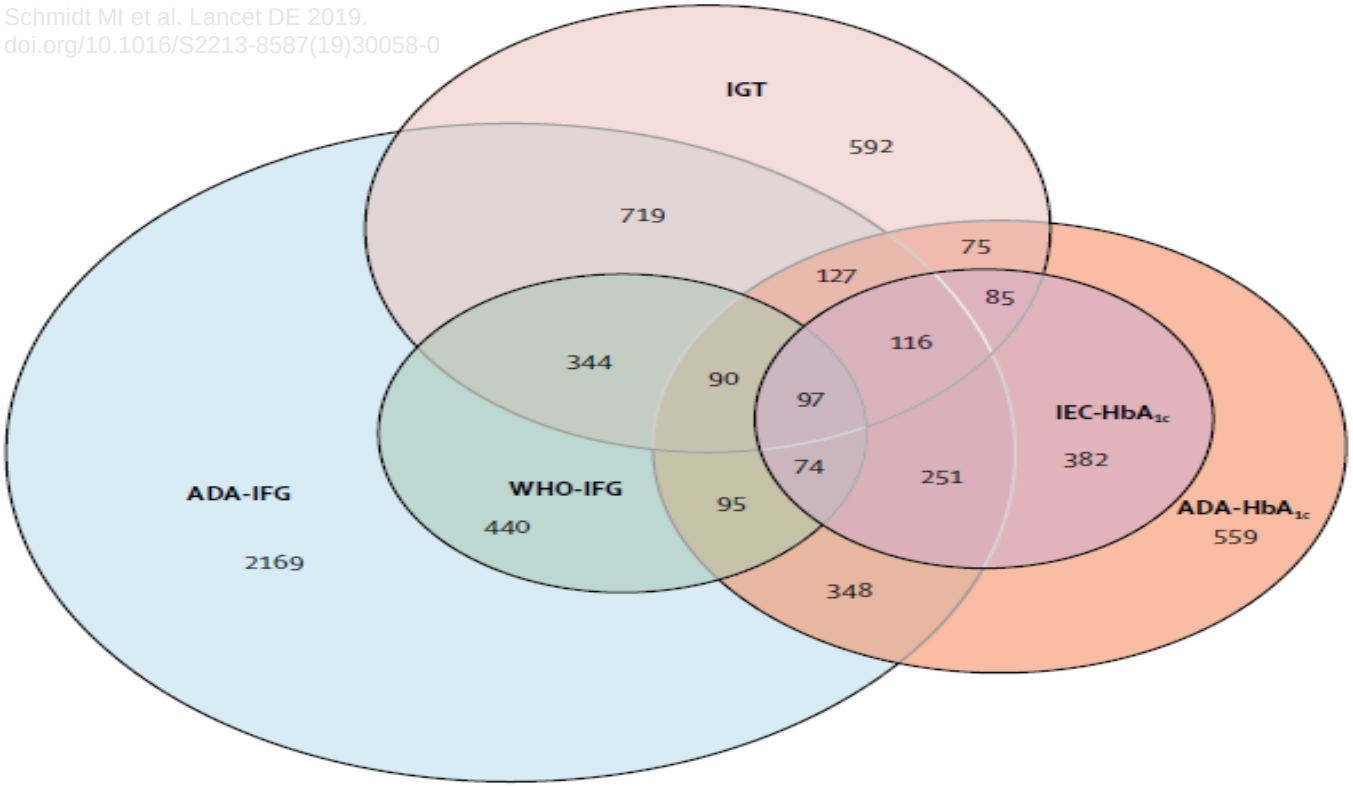

κ Values

IGT×WHO-IFG 0·21 (0·19–22·8)
IGT×ADA-IFG 0·20 (0·18–0·22)
IGT×ADA-HbA$_{1c}$ 0·07 (0·05–0·09)
IGT×IEC-HbA$_{1c}$ 0·07 (0·05–0·09)
WHO-IFG×ADA-IFG 0·26 (0·24–0·27)
WHO-IFG×ADA-HbA$_{1c}$ 0·08 (0·06–0·10)
WHO-IFG×IEC-HbA$_{1c}$ 0·07 (0·05–0·09)
ADA-IFG×ADA-HbA$_{1c}$ 0·07 (0·06–0·09)
ADA-HbA$_{1c}$×IEC-HbA$_{1c}$ 0·55 (0·53–0·57)

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2010 American Diabetes Association: Diagnosis and Classification of Diabetes Mellitus (Diabetes Care 33:S62-69 (January) 2010

- **Criteria for the diagnosis of diabetes**
- A1C ≥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 (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h. OR
- 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) 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
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

Prevalence of Retinopathy by deciles of FPG, 2hPG and HbA1c in:

A) Pima Indians
B) Egyptians
C) 40-74 year old NHANES participants

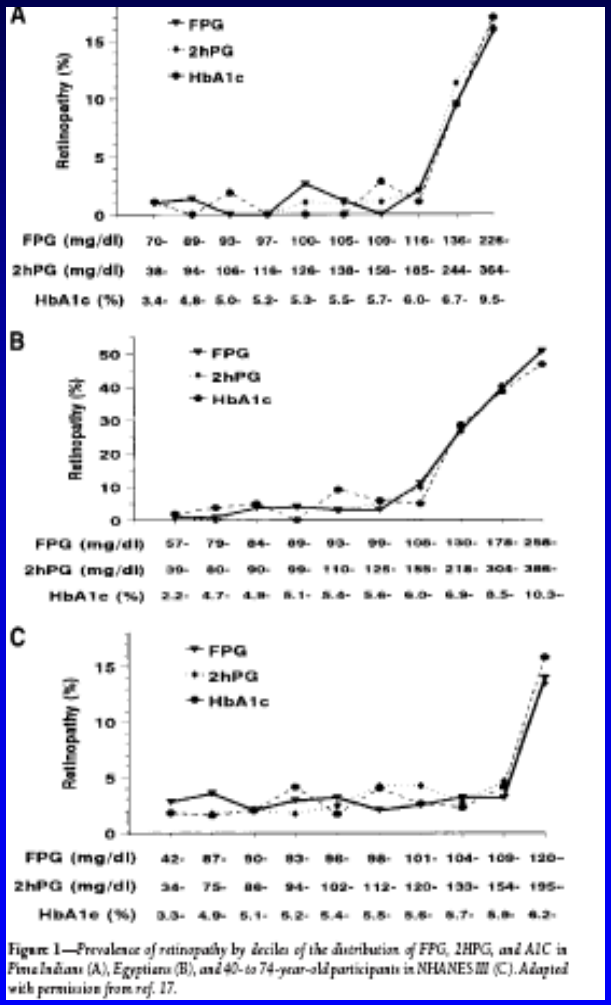

Figure 1—*Prevalence of retinopathy by deciles of the distribution of FPG, 2HPG, and A1C in Pima Indians (A), Egyptians (B), and 40- to 74-year-old participants in NHANES III (C). Adapted with permission from ref. 17.*

International Expert Committee Report on the Role of the A1c Assay in the Diagnosis of Diabetes. Diabetes Care 32:1327-1334, 2009

2016 WHO Classification of Diabetes

- Type 1
- Autoimmune
- Idiopathic
- Type 2
- Other specific types
  - Genetic defects of beta-cell function e.g. MODY 1-3
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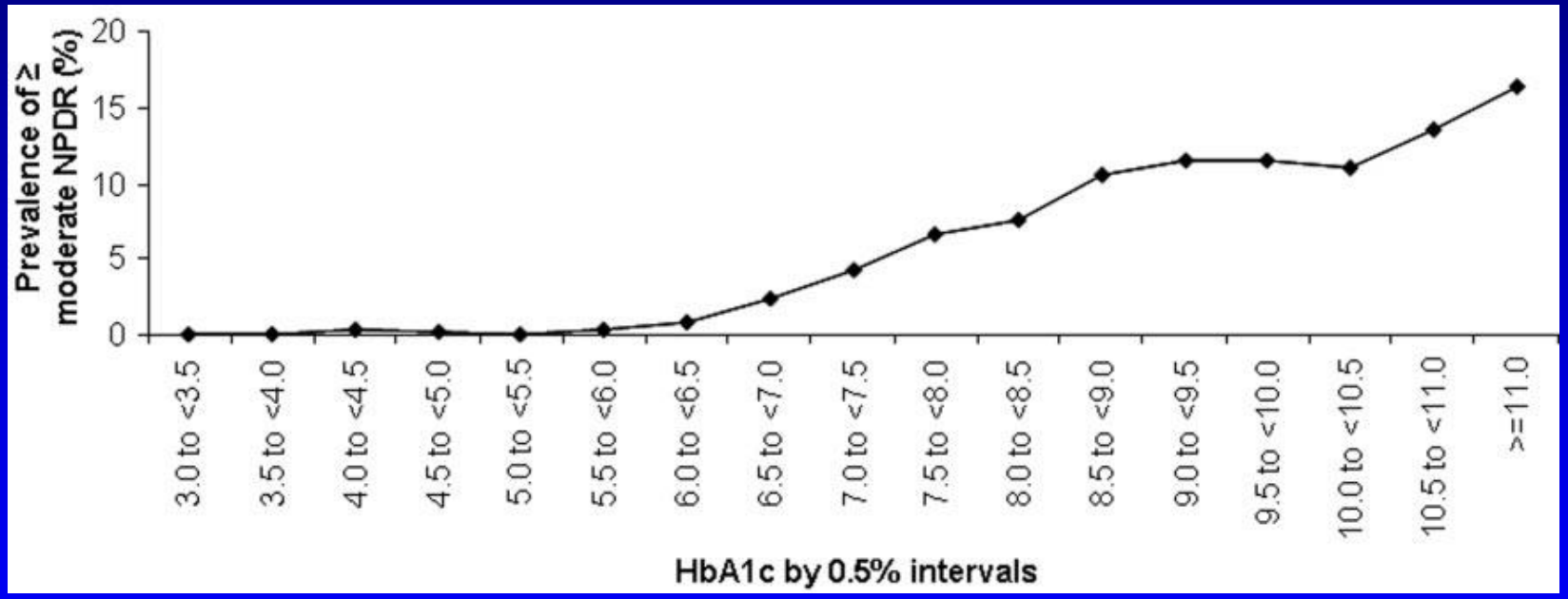
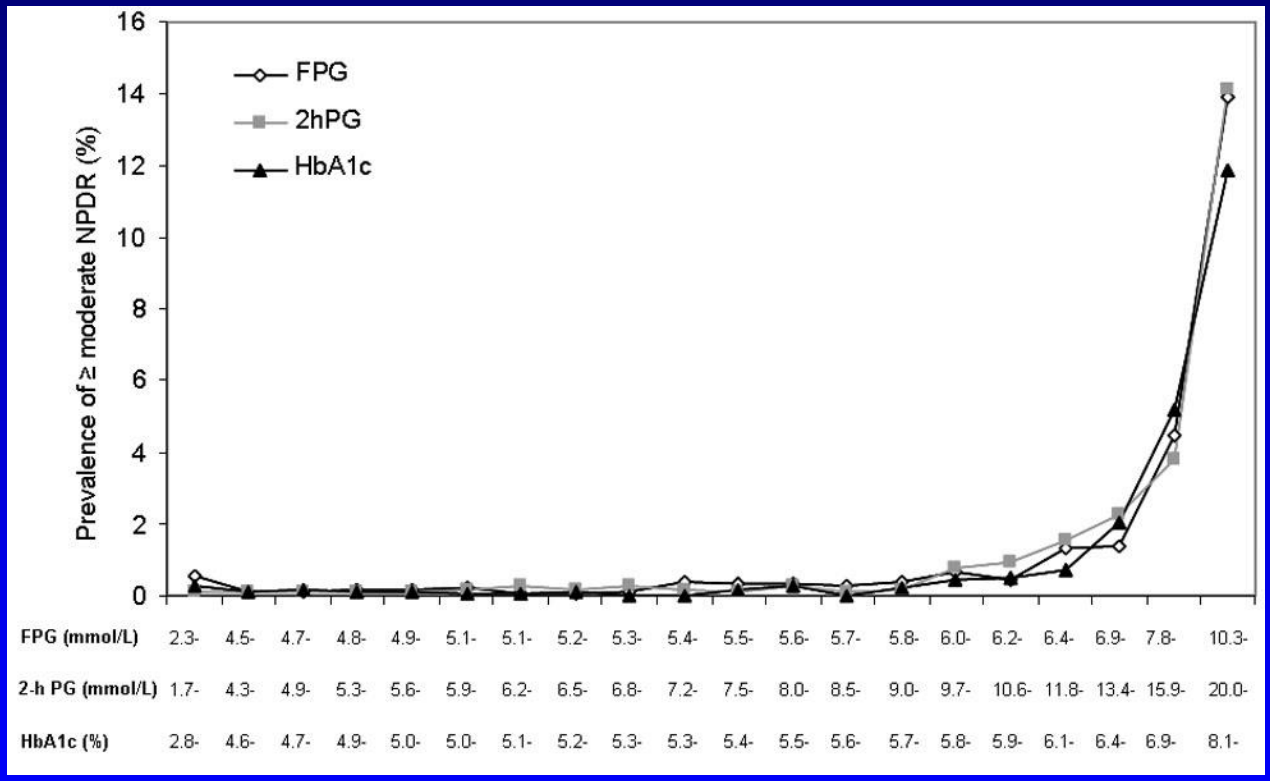


From Colagiuri S et al, Diabetes Care January 2011 34:145-150

Prevalence of diabetes-specific retinopathy (moderate non-proliferative retinopathy) by vigintiles of distribution of FPG, 2-h PG and HbA1c from DETECT-2.



From Colagiuri S et al, Diabetes Care January 2011 34:145-150

Recommendation of the International Expert Committee on the role of A1c assay (Part 1)

For the diagnosis of diabetes:

- A1C assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.

- A1C assay has several advantages over laboratory measures of glucose

- Diabetes should be diagnosed when A1C is $\geq$6.5%. Diagnosis should be confirmed with a repeat A1C test. Confirmation is not required in symptomatic subjects with plasma glucose levels $\geq$200 mg/dl (11.1 mmol/l)

- If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.

2011 WHO: Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

Recommendation

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes.

A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

http://www.who.int/diabetes/publications/report-hba1c_2011.pdf

Some of the factors that influence HbA1c and its measurement*. Adapted from Gallagher et al (*24*)

1. Erythropoiesis Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis. Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.
2. Altered Haemoglobin Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.
3. Glycation Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH. Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. Variable HbA1c: genetic determinants.
4. Erythrocyte destruction Increased HbA1c: increased erythrocyte life span: Splenectomy. Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.
5. Assays Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. Variable HbA1c: haemoglobinopathies. Decreased HbA1c: hypertriglyceridaemia.

* Some of the above interfering factors are "invisible" in certain of the available assays