



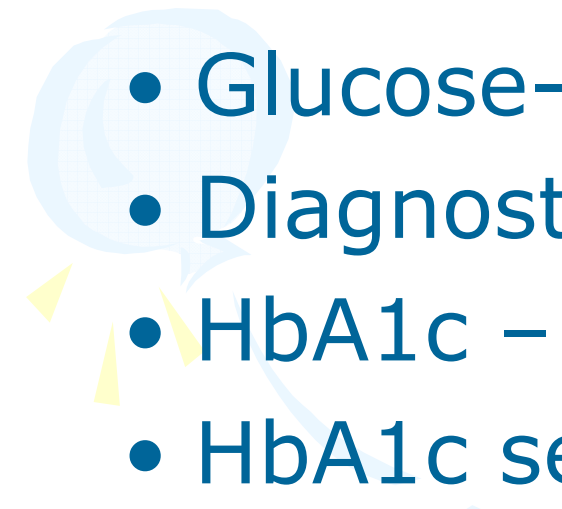
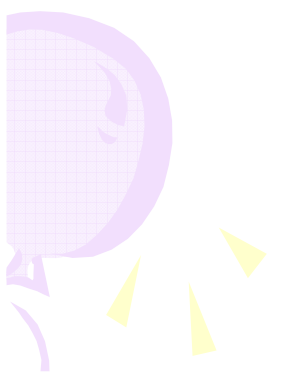
HbA1c for diagnosis of Diabetes

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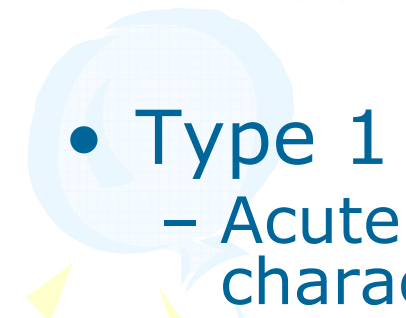
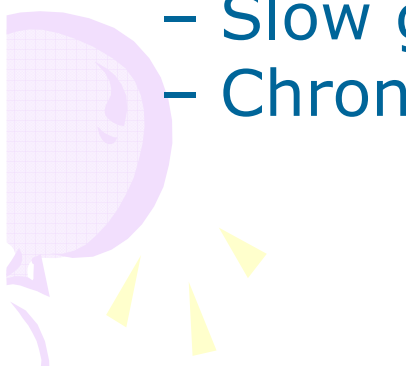


Overview

- Background of Guidelines
 - Need to change
 - Glucose-based tests
 - Diagnostic criteria
 - HbA1c – time to change
 - HbA1c selection as diagnostic test
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Introduction

- Diabetes
 - Inability to properly use Insulin (Insulin resistance)
 - Inadequate production of Insulin (β cell failure)
 - Type 1 DM
 - Acute onset with elevated glucose and characteristic symptoms
 - Type 2 DM
 - Slow gradual onset
 - Chronic increase in glucose
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History of guidelines for the diagnosis of diabetes

- 1979: NDDG recommendations

- FPG ≥ 7.8 mmol/L
- 2PP ≥ 11.1 mmol/L for Diabetes

- FPG < 7.8 mmol/L
- 2PP 7.8 to 11.1 mmol/L for IGT

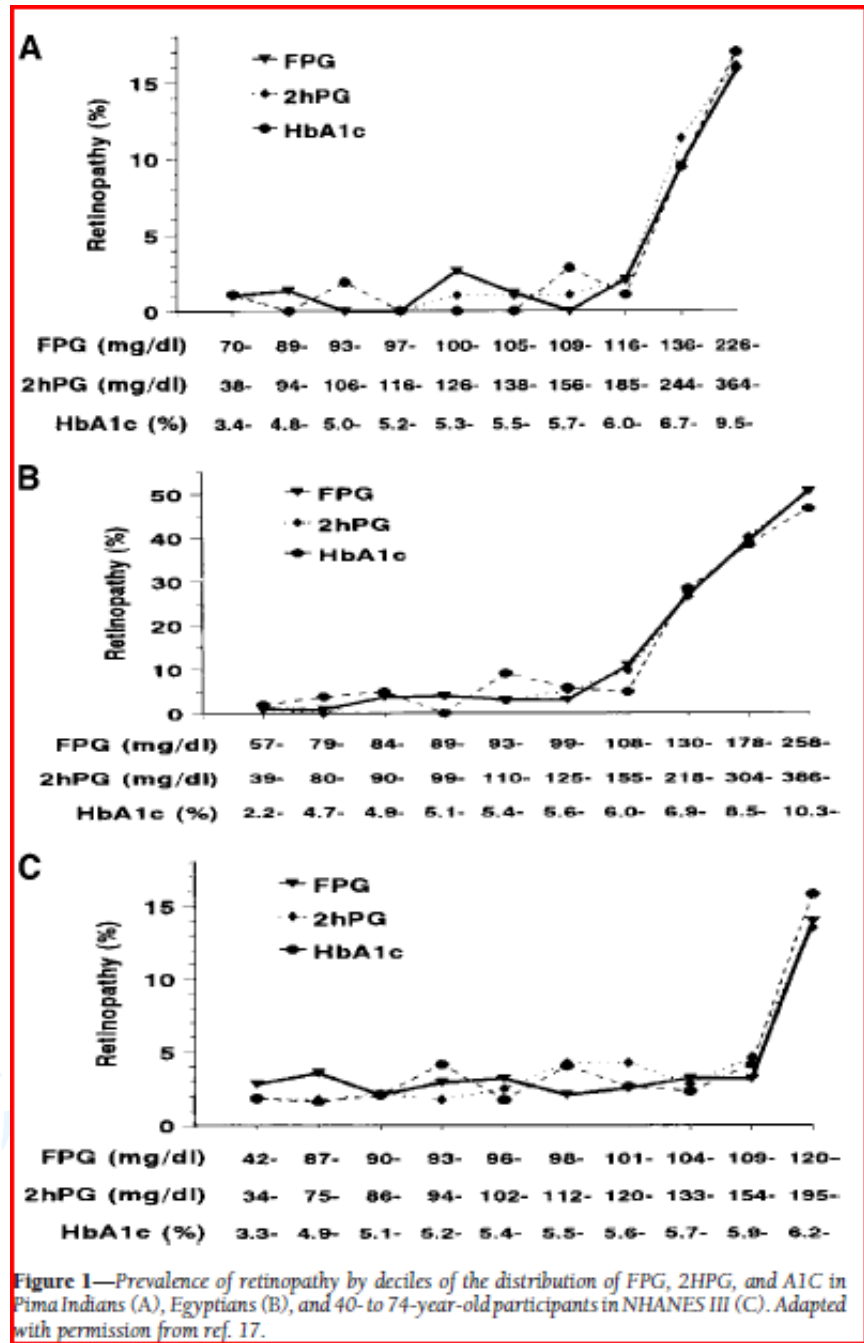
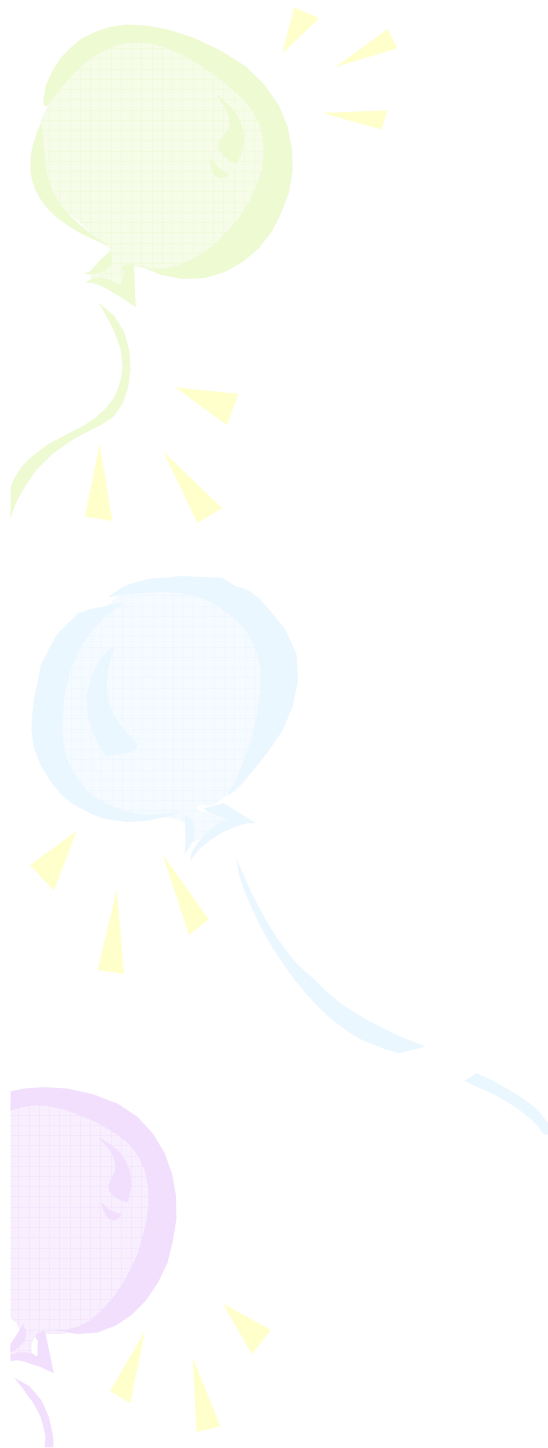
- 1979: WHO report

- FG ≥ 7.8 mmol/L
- 2PP ≥ 11.1 mmol/L for Diabetes

- 2PP 8.0 to 11.1 mmol/L for IGT

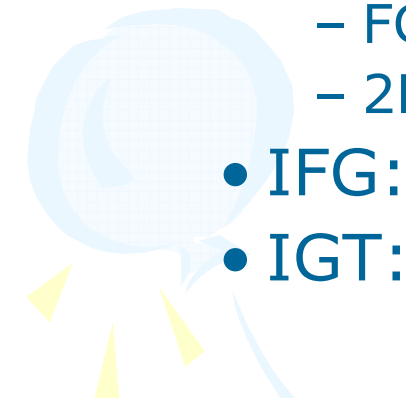

1997 Expert Committee on the Diagnosis & Classification of DM

- 2 seminal contributions:
 - Relationship between glucose levels and the presence of long-term diabetic complications
 - Data negates the wide-spread hypothesis that the 2PP was the gold standard test
- Reduced the FPG cutoff to ≥ 7.0 mmol/L for diabetes
 - This represents a degree of hyperglycaemia similar to 2PP value for diagnosis
 - Either test would result in a similar prevalence of diabetes in the population
 - Acknowledged that FPG and 2PP were not perfectly concordant





History of Guidelines contd


- 1999: WHO criteria revised (similar to ADA 1997)
 - FG cut-off 7.0 mmol/L
 - 2PP cut-off 11.1 mmol/L
 - IFG: $FG \geq 6.1$ mmol/L and < 7.0 mmol/L
 - IGT: $FG < 6.1$ mmol/L and 2PP 7.8 to 11.1 mmol/L
 - Individuals with IFG should be given an OGTT to exclude the presence of diabetes that would otherwise be missed
 - OGTT remains the gold standard
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History of Guidelines contd

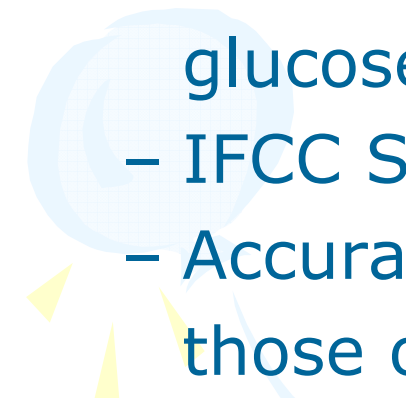
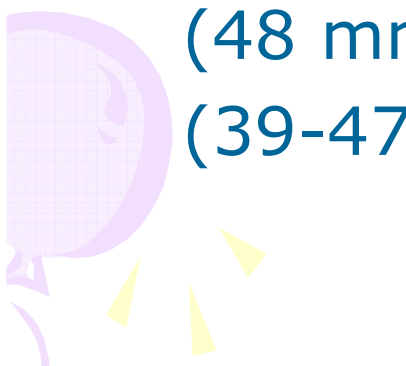


Expert committee 2003:

- FG revised from 6.1 to 5.6 mmol/L
 - IFG ≥ 5.6 but < 7.0 mmol/L
 - Recommended against using HbA1c values for diagnosis in part because of the lack of assay standardisation
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- WHO did not change their 1999 recommendations
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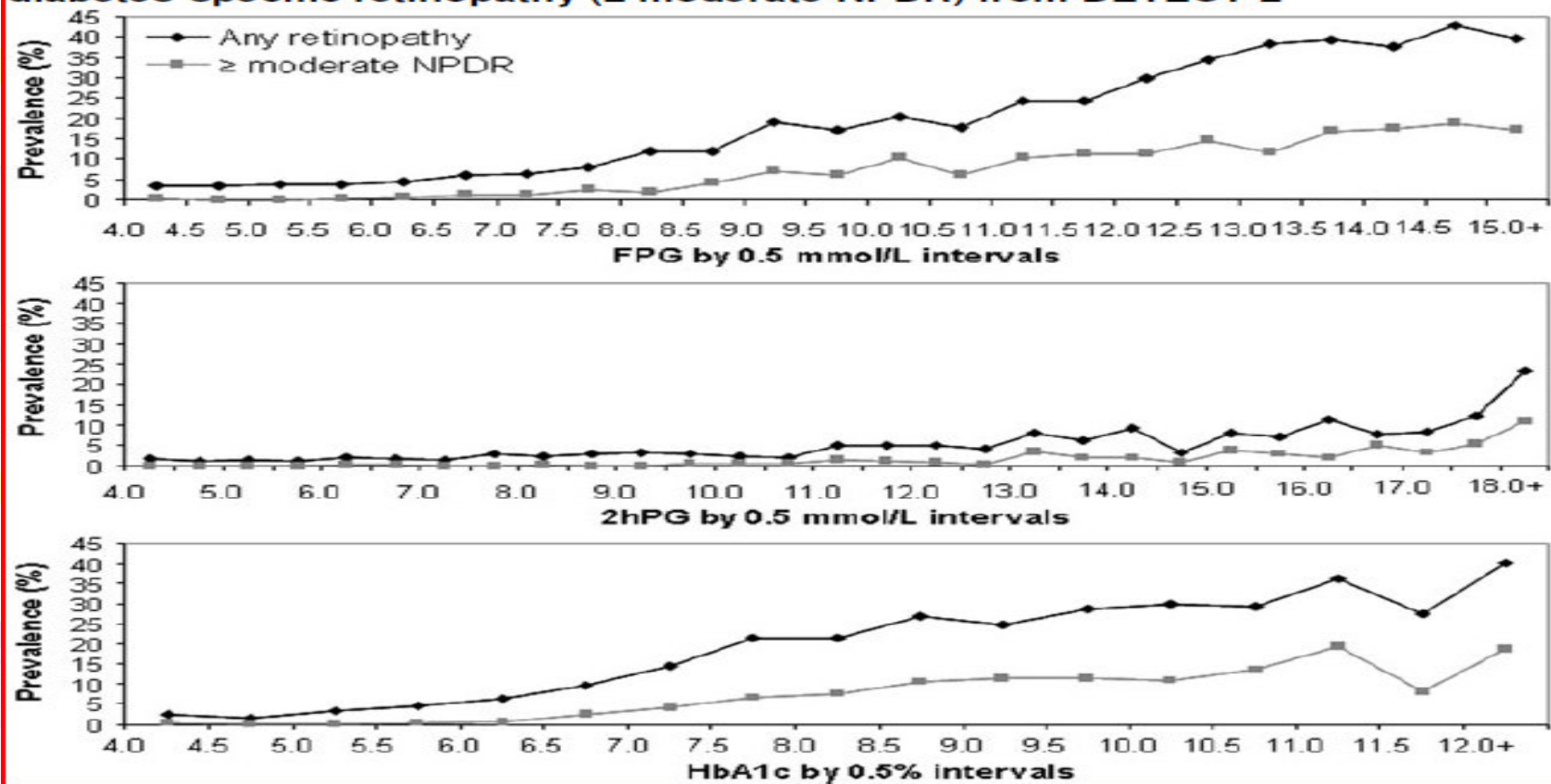


History of guidelines contd

- International Expert Committee 2010:
 - Examined the laboratory measurement of glucose and HbA1c
 - IFCC Standardisation of HbA1c
 - Accuracy and precision of HbA1c assays match those of glucose assays
 - Recommended HbA1c using the cut-off of 6.5% (48 mmol/mol) in DM and between 5.7-6.4% (39-47mmol/mol) in intermediate hyperglycaemia
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Evidence based clinical thresholds

Figure 2. Prevalence of retinopathy by 0.5 mmol/L intervals for FPG and 2-h PG and by 0.5% intervals for HbA1c for any retinopathy and diabetes-specific retinopathy (\geq moderate NPDR) from DETECT-2



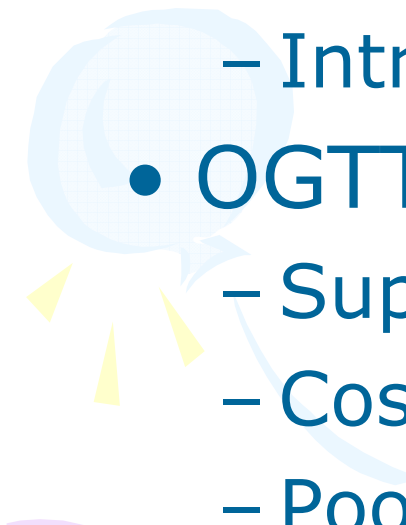
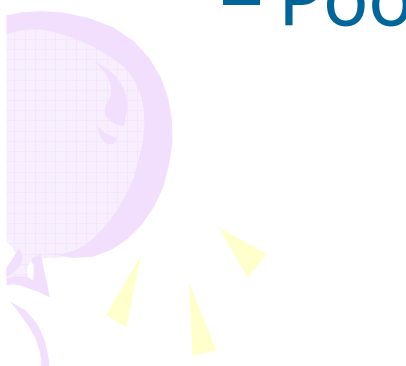


WHO report 2011

- Addendum to the diagnostic criteria published in 2006
 - HbA1c could be used as a diagnostic test provided the assay is standardised & stringent QA is in place
 - HbA1c value of 6.5% (48mmol/mol) is the diagnostic cut point
 - HbA1c value <6.5% does not exclude Diabetes diagnosed using glucose tests
 - Assay not available throughout the world
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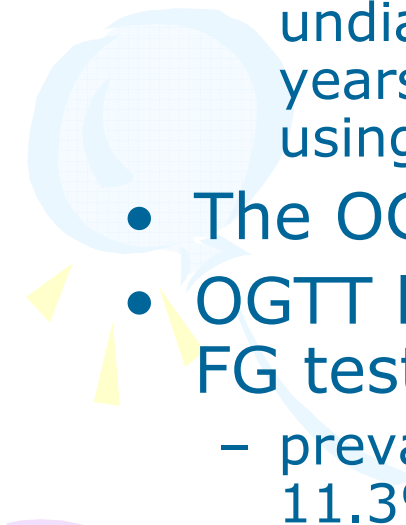
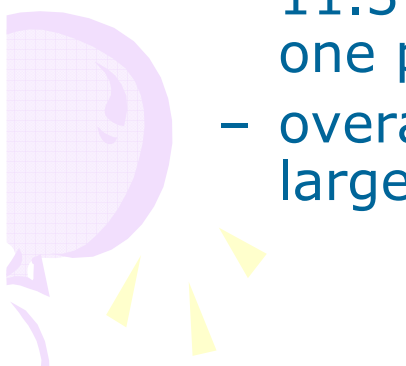


Glucose-based tests

- Fasting Glucose:
 - 8 hr fast with no caloric intake
 - Intra-individual variability (12-15%)
 - OGTT:
 - Supraphysiological glucose challenge
 - Cost and time impact
 - Poor reproducibility (~65%)
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Glucose-based criteria

- Estimates of the prevalence of diabetes and prediabetic depends on the cutoffs and tests used
 - the population-based estimate of prevalence of undiagnosed diabetes among U.S. persons 40 to 74 years of age is 6.4% by using the OGTT and 4.4% by using a FG
 - The OGTT is more sensitive than FG
 - OGTT has considerably worse reproducibility than FG testing
 - prevalence decreased from 19.3% with one OGTT to 11.3% on repeated testing of initial positive results in one population-based study
 - overall test–retest reproducibility of the OGTT in one large study was 65.6%
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Analysis of Glucose

- **Preanalytical:**

- Type of sample
- Rate of Glycolysis
- Inhibitor of Glycolysis

- **Analytical:**

- Method bias compared to reference method
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Table 1. Glucose Changes with Increasing Hematocrit (Hct) and Time

	Hct	Time after blood collection, h				
		0	1	2	4	6
Adult group 1	0.43	89 ± 4 ^a	83 ± 3	78 ± 3	67 ± 3	57 ± 3
Adult group 2	0.51	89 ± 4	82 ± 3	76 ± 2	63 ± 2	52 ± 2
Infant group 1	0.51	101 ± 2	90 ± 5	78 ± 6	63 ± 10	48 ± 7
Adult group 3	0.60	89 ± 4	80 ± 3	73 ± 3	58 ± 3	42 ± 3
Infant group 2	0.60	101 ± 2	87 ± 4	73 ± 5 ^b	56 ± 5 ^b	36 ± 6 ^b
Adult group 4	0.68	89 ± 4	79 ± 3	70 ± 2	51 ± 2	31 ± 3
Infant group 3	0.71	101 ± 2	83 ± 5	66 ± 5 ^b	40 ± 6 ^b	19 ± 5 ^b
Adult group 5	0.75	89 ± 4	78 ± 3	68 ± 2	45 ± 2	20 ± 3
Infant group 4	0.81	101 ± 2	77 ± 5 ^b	55 ± 5 ^b	24 ± 5 ^b	5 ± 3 ^b

^a All glucose values expressed in mg/dL (mean ± SEM). ^b Difference between the adult group and infant group at comparable time and hematocrit is significant: $p < 0.05$ or less.

Table 2. Effect of Heparin, Fluoride, or No Anticoagulant on Glucose Values (mg/dL, mean ± SEM)

	Time after blood collection, h				
	0	1	2	4	6
<i>Infants</i>					
Heparin	101 ± 2	90 ± 5	78 ± 6	63 ± 10	48 ± 7 ^a
NaF	101 ± 2	93 ± 7	89 ± 6	88 ± 6	87 ± 6
Clotted serum	101 ± 2	^b	90 ± 8	83 ± 7	80 ± 6
<i>Adults</i>					
Heparin	89 ± 4	83 ± 3	78 ± 3	67 ± 3 ^c	57 ± 3 ^a
NaF	89 ± 4	82 ± 3	80 ± 3	77 ± 3	75 ± 4
Clotted serum	89 ± 4	^b	81 ± 3	73 ± 4	70 ± 4

^a Decrement in glucose significantly greater in heparin-treated samples than in either NaF-treated or clotted samples, $p < 0.05$. ^b Not measured. ^c Decrease in glucose significantly greater in the heparin-treated samples than in the NaF-treated samples, $p < 0.05$.

CLIN. CHEM. 28/1, 190-192 (1982)

Glucose Determinations in Plasma and Serum: Potential Error Related to Increased Hematocrit

Richard A. Sidebottom,¹ Paul R. Williams,² and Keith S. Kanarek

Effectiveness of Sodium Fluoride as a Preservative of Glucose in Blood

A.Y.W. Chan, R. Swaminathan, and C. S. Cockram¹

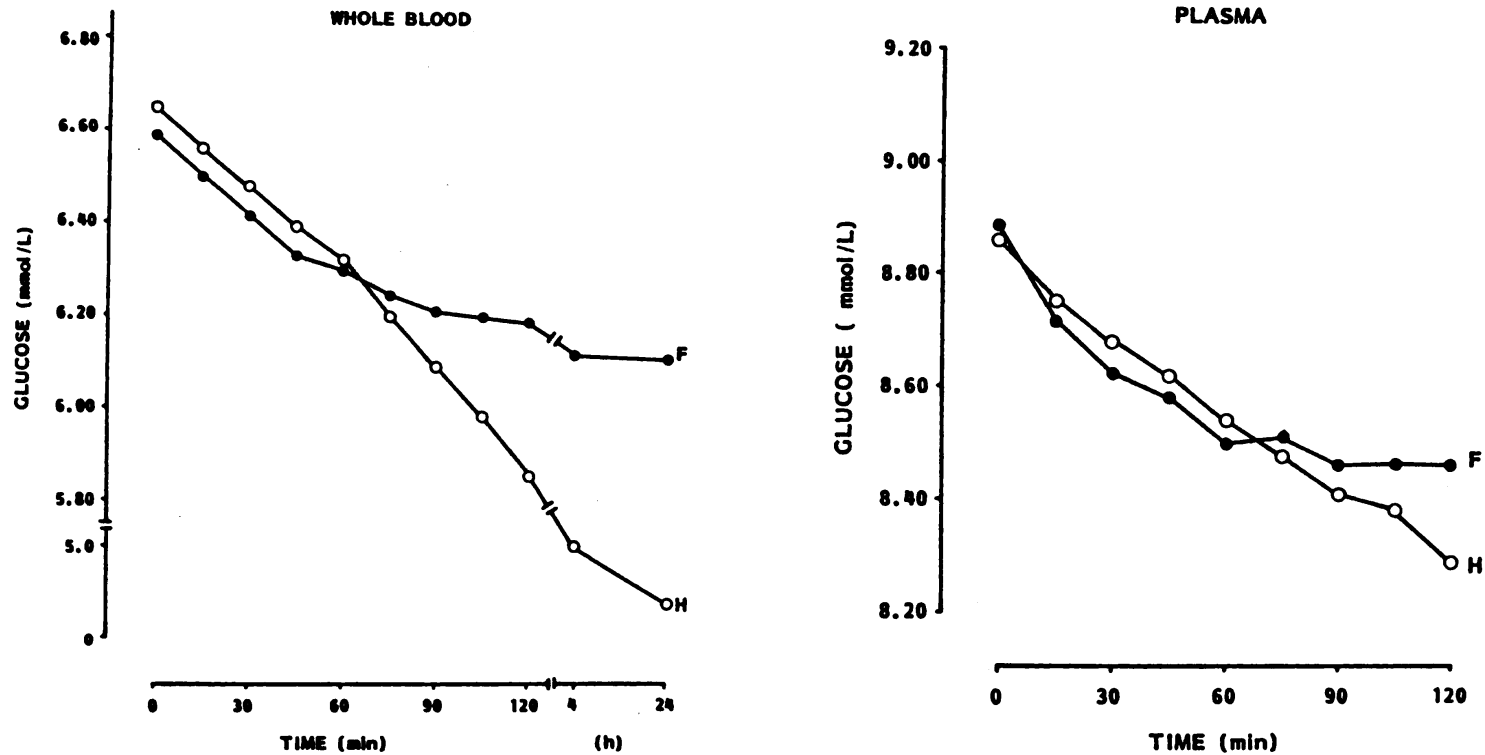
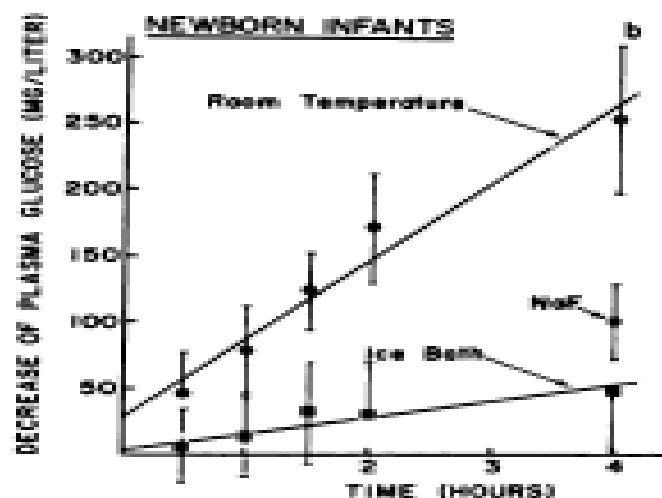
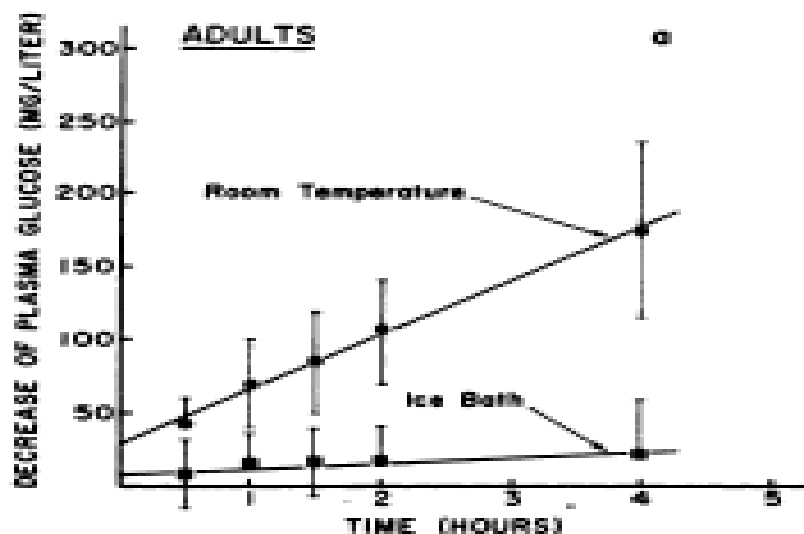


Fig. 1. Representative changes in mean whole-blood glucose concentration with time in whole-blood (*left*) or plasma (*right*) samples kept in fluoride-containing (*F*) or heparin-containing (*H*) tubes

Stabilization of Blood Glucose by Cooling with Ice: An Effective Procedure for Preservation of Samples from Adults and Newborns

Yuan Ly Lin, Carl H. Smith, and David N. Dietzler

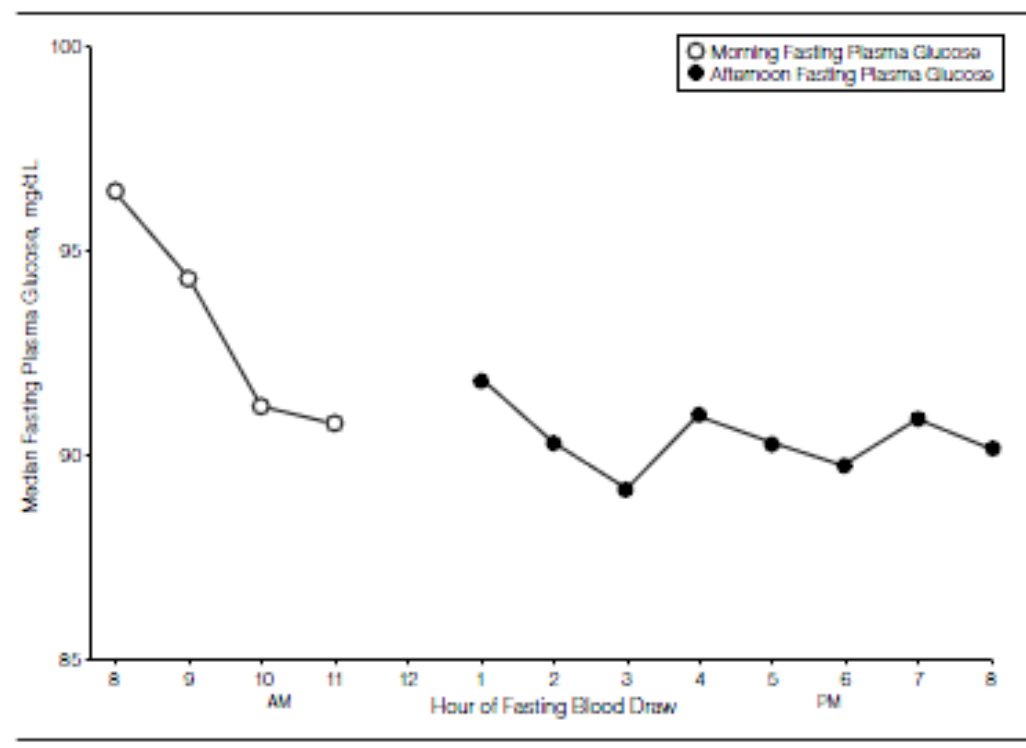


Diurnal Variation in Fasting Plasma Glucose

Implications for Diagnosis of Diabetes in Patients Examined in the Afternoon

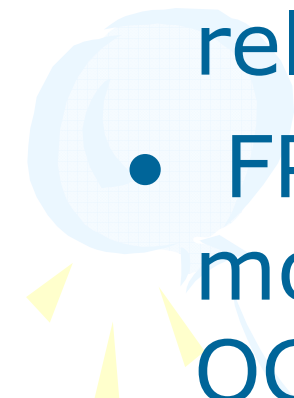
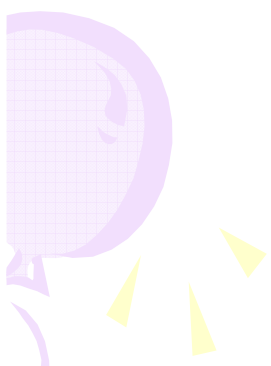
JAMA, December 27, 2000—Vol 284, No. 24

Figure. Median Fasting Plasma Glucose by Hour of Blood Draw







Glucose-based criteria

- FPG levels vary considerably within individuals over the long term but are relatively stable over the short term.
 - FPG measurement are substantially more reproducible than those of the OGTT.
 - intra-individual CVs of 6.4% to 11.4% for measurement of FPG and 14.3% to 16.7% for measurement of 2PP glucose
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Need for an alternative

- USA diagnosis is based on FPG, while in Europe and in clinical trials OGTT is the preferred method
 - Both tests have rather limited overlap
 - Both tests can produce different values for the same patient on different days
 - The level of hyperglycaemia for diagnosis, by either test, is arbitrary
 - Diagnosis based on prevalence of diabetic complications
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Evidence for HbA1c cutoff 6.5% (48 mmol/mol)

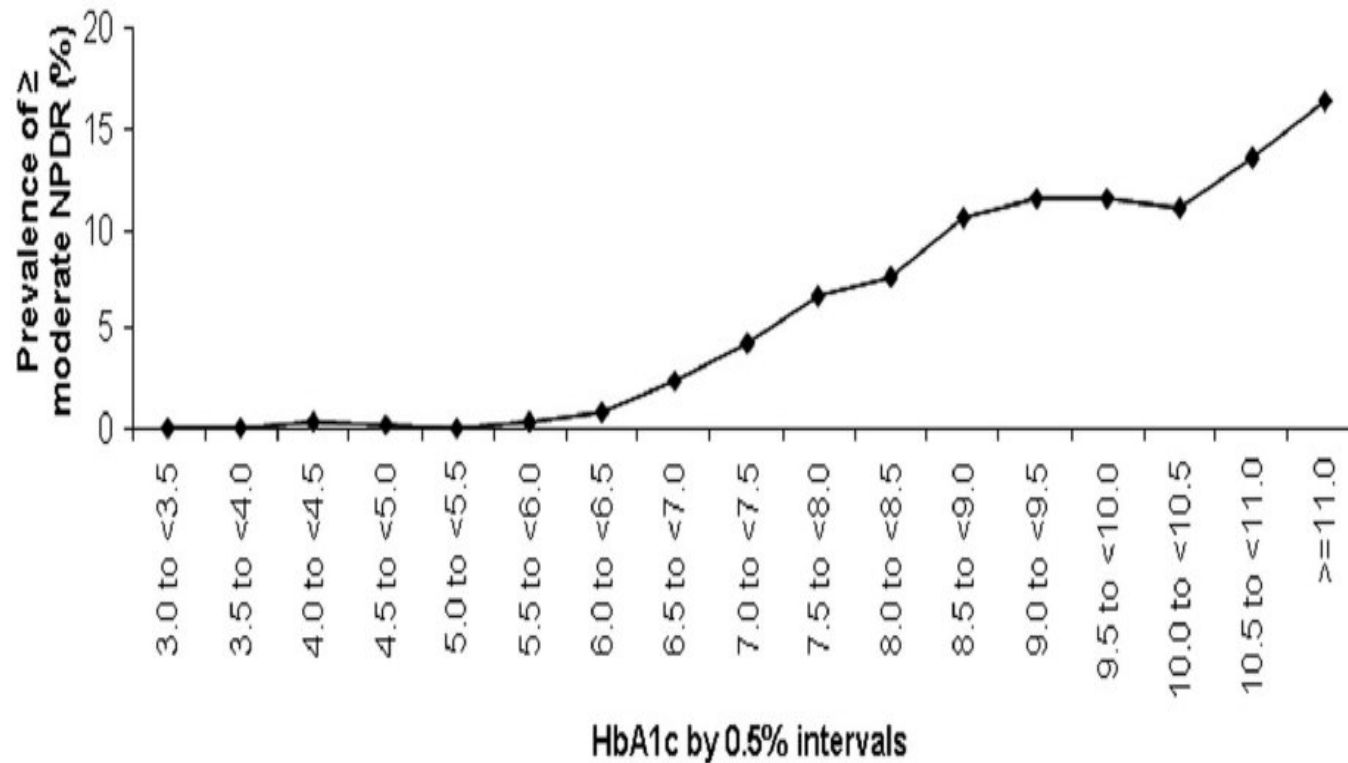
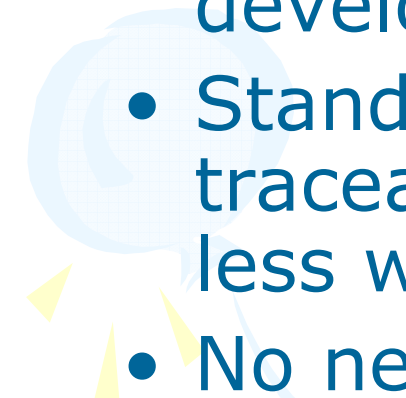



Figure 2—Prevalence of retinopathy by 0.5% intervals and severity of retinopathy in participants aged 20–79 years. NPDR, nonproliferative diabetic retinopathy. Adapted with permission from (S.C., personal communication).



HbA1c - Pros

- Has lower intra-individual variation (<2%)
 - Is the cornerstone of assessing risk of developing diabetic complications
 - Standardised assays with improved traceability; measurement of glucose is less well standardised
 - No need for fasting or timed samples
 - Stability of HbA1c in whole blood
 - Relatively unaffected by acute (stress or illness related) perturbations in glucose
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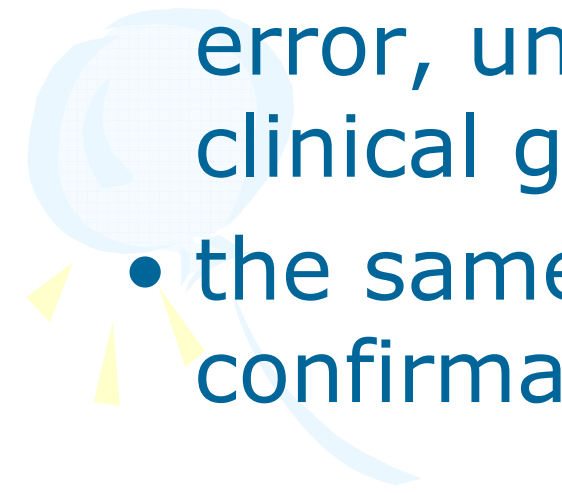
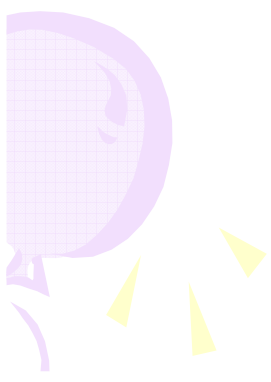


HbA1c - Cons

- Misleading results in:
 - Haemoglobin traits
 - Conditions that change red cell turnover (IDA, Haemolytic anaemia, chronic malaria, blood loss or blood transfusions)
- Differences in glycation rates
- Glycation increases with age
- Racial differences in HbA1c levels
- Rare clinical settings such as rapidly evolving type 1 diabetes


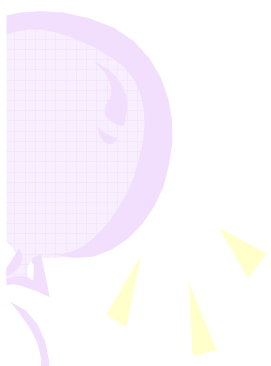


What test (1)

- a test result diagnostic of diabetes should be repeated to rule out lab error, unless the diagnosis is clear on clinical grounds
 - the same test must be repeated for confirmation
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What test (2)


- results of two different tests (e.g., FPG and HbA1c) are available for the same patient
 - if the two different tests are both above the diagnostic threshold, the diagnosis of diabetes is confirmed.
 - if the two different test results are discordant, the test whose result is above the diagnostic cutoff point should be repeated, and the diagnosis is made on the basis of the confirmed test.
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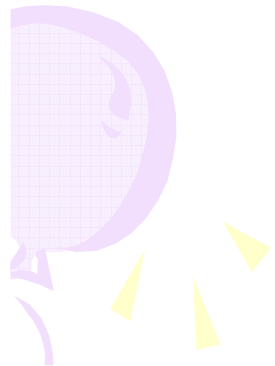
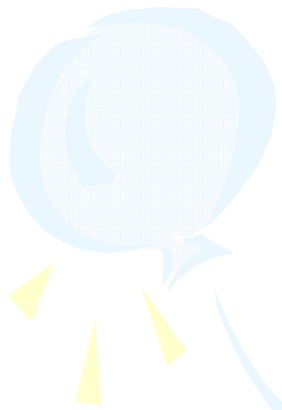
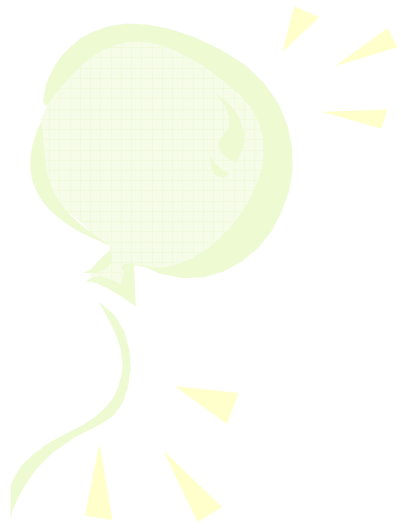
Criteria for the diagnosis of diabetes

- **1.** HbA1c \geq 6.5% (\geq 48 mmol/mol) The test should be performed in a laboratory using a standardised method
OR
 - **2.** FPG \geq 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h
OR
 - **3.** Two-hour plasma glucose 200 mg/dl (11.1 mmol/l) during an OGTT (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 (11.1 mmol/l).
- *In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing



Conclusion

- Factors supporting the use of HbA1c as a diagnostic test
 - Exclude the test in the setting of anaemia
 - Equivocal HbA1c values could require confirmation
 - HbA1c makes the diagnosis of diabetes efficient
 - Single test to both diagnose & manage diabetes
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Thank You!