

DEFINITION AND DIAGNOSIS OF  
DIABETES MELLITUS AND  
INTERMEDIATE HYPERGLYCAEMIA



World Health  
Organization



International Diabetes Federation

# DEFINITION AND DIAGNOSIS OF DIABETES MELLITUS AND INTERMEDIATE HYPERGLYCEMIA

**REPORT OF A WHO/IDF CONSULTATION**



**World Health  
Organization**



**International Diabetes Federation**

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# SUMMARY OF TECHNICAL REPORT AND RECOMMENDATIONS

Since 1965 the World Health Organization (WHO) has published guidelines for the diagnosis and classification of diabetes. These were last reviewed in 1998 and were published as the guidelines for the *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications*. Since then more information relevant to the diagnosis of diabetes has become available. In November 2005 a joint WHO and International Diabetes Federation (IDF) Technical Advisory Group met in Geneva to review and update the current WHO guidelines.

After consideration of available data and recent recommendations made by other organisations, the Group made the following recommendations:

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**Recommendation 1** The current WHO diagnostic criteria for diabetes should be maintained – fasting plasma glucose  $\geq 7.0$ mmol/l (126mg/dl) or 2-h plasma glucose  $\geq 11.1$ mmol/l (200mg/dl).

Despite the limitations with the data from which the diagnostic criteria for diabetes are derived, the current criteria distinguish a group with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications.

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**Recommendation 2** Since there are insufficient data to accurately define normal glucose levels, the term 'normoglycaemia' should be used for glucose levels associated with low risk of developing diabetes or cardiovascular disease, that is levels below those used to define intermediate hyperglycaemia.

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**Recommendation 3** The current WHO definition for Impaired Glucose Tolerance (IGT) should be maintained for the present.

Consideration should be given to replacing this category of intermediate hyperglycaemia by an overall risk assessment for diabetes, cardiovascular disease, or both, which includes a measure of glucose as a continuous variable.



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**Recommendation 4** The fasting plasma glucose cut-point for Impaired Fasting Glucose (IFG) should remain at 6.1mmol/l.

This decision was based on concerns about the significant increase in IFG prevalence which would occur with lowering the cut-point and the impact on individuals and health systems. There is a lack of evidence of any benefit in terms of reducing adverse outcomes or progression to diabetes and people identified by a lower cut-point eg 5.6mmol/l (100mg/dl) have a more favourable cardiovascular risk profile and only half the risk of developing diabetes compared with those above the current WHO cut-point. Lowering the cut-point would increase the proportion of people with IGT who also have IFG but decreases the proportion of people with IFG who also have IGT.

Consideration should be given to replacing this category of intermediate hyperglycaemia by an overall risk assessment for diabetes, cardiovascular disease, or both, which includes a measure of glucose as a continuous variable.

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**Recommendation 5**

1. Venous plasma glucose should be the standard method for measuring and reporting glucose concentrations in blood. However in recognition of the widespread use of capillary sampling, especially in under-resourced countries, conversion values for capillary plasma glucose are provided for post-load glucose values. Fasting values for venous and capillary plasma glucose are identical.
2. Glucose should be measured immediately after collection by near-patient testing, or if a blood sample is collected, plasma should be immediately separated, or the sample should be collected into a container with glycolytic inhibitors and placed in ice-water until separated prior to analysis.

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**Recommendation 6** The oral glucose tolerance test (OGTT) should be retained as a diagnostic test for the following reasons:

- fasting plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed diabetes,
- fan OGTT is the only means of identifying people with IGT,
- fan OGTT is frequently needed to confirm or exclude an abnormality of glucose tolerance in asymptomatic people.

An OGTT should be used in individuals with fasting plasma glucose 6.1–6.9mmol/l (110–125mg/dl) to determine glucose tolerance status.



**Recommendation 7** Currently HbA1c is not considered a suitable diagnostic test for diabetes or intermediate hyperglycaemia.

The following Table summarises the 2006 WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycaemia.

### Diabetes

Fasting plasma glucose	≥7.0mmol/l (126mg/dl)
2-h plasma glucose*	<b>or</b> ≥11.1mmol/l (200mg/dl)

### Impaired Glucose Tolerance (IGT)

Fasting plasma glucose	<7.0mmol/l (126mg/dl)
2-h plasma glucose*	<b>and</b> ≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)

### Impaired Fasting Glucose (IFG)

Fasting plasma glucose	6.1 to 6.9mmol/l
2-h plasma glucose*	(110mg/dl to 125mg/dl) <b>and (if measured)</b> <7.8mmol/l (140mg/dl)

\* Venous plasma glucose 2-h after ingestion of 75g oral glucose load

\* If 2-h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded



# INTRODUCTION

**Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030<sup>1</sup>. Diabetes is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It 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. The American Diabetes Association (ADA) estimated the national costs of diabetes in the USA for 2002 to be \$US132 billion, increasing to \$US192 billion in 2020<sup>2</sup>.**

Since 1965 the World Health Organization (WHO) has published guidelines for the diagnosis and classification of diabetes. These were last reviewed in 1998 and were published as the guidelines for the Definition, Diagnosis and Classification of Diabetes Mellitus<sup>3</sup>. Since then more information relevant to the diagnosis of diabetes has become available. In addition, in 2003, the ADA reviewed its diagnostic criteria<sup>4</sup>. While the criteria for the diagnosis of diabetes and Impaired Glucose Tolerance (IGT) remained unchanged, the ADA recommended lowering the threshold for Impaired Fasting Glucose (IFG) from 6.1mmol/l (110mg/dl) to 5.6mmol/l (100mg/dl)<sup>4</sup>. In view of these developments WHO and the International Diabetes Federation (IDF) decided that it was timely to review its existing guidelines for the definition and diagnosis of diabetes and intermediate hyperglycaemia.

Accordingly, WHO appointed an internal Guideline Steering Group and convened a Technical Guideline Development Group. Membership of these committees is shown in Appendix 1. A meeting of the Technical

Guideline Development Group was held at WHO headquarters in Geneva on November 4–6, 2005. The specific aims of the meeting were to review relevant data which addressed and could inform the review of the diagnostic criteria for:

- Diabetes
- Impaired glucose tolerance (IGT)
- Impaired fasting glucose (IFG) (in particular the 2003 ADA revised criteria).

The definition of the Metabolic Syndrome was outside the brief of this review and was therefore not considered.

In addressing these aims and in formulating recommendations, the Technical Guideline Development Group took into account the following WHO guiding values for guideline development:

- A population perspective, not primarily an individual perspective
- Scientific integrity with evidence on efficacy
- Feasibility
- Cost-effectiveness and opportunity costs
- Sensitivity to local contexts
- Transparency
- A primary audience of health policy makers

# BACKGROUND

**WHO has published four previous Technical Reports relating to diabetes in 1965<sup>5</sup>, 1980<sup>6</sup>, 1985<sup>7</sup> and 1999<sup>8</sup>. Over this period there have been significant changes in the diagnostic criteria and classification of diabetes and intermediate hyperglycaemia. The diagnostic criteria used over this period are summarised in Appendix 2.**

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## **Current diagnostic criteria**

The current diagnostic criteria used for the diagnosis of diabetes and intermediate hyperglycaemia have been in place globally for almost a decade and are widely accepted. However, in 2003 the ADA modified its recommendations resulting in discrepancies between its recommendations and those of the WHO.

Although attention has focussed on the difference in fasting plasma glucose levels for defining IFG, there are a number of important differences between the ADA and WHO recommendations which may result in differences in an individual's classification of glucose tolerance (see Appendix 3). These include:

- fasting plasma glucose value used to define IFG
- inclusion of 2-h plasma glucose value in defining IFG
- requirement for fasting plasma glucose level in defining IGT

fasting plasma glucose as the recommended method for diagnosing asymptomatic diabetes by ADA whereas WHO recommends the oral glucose tolerance test.

These discrepancies have implications for the individual and for population prevalence estimates. For example people who fall into the ADA category of IFG could include people with IGT or diabetes if a 2-h plasma glucose is not measured, and ADA defined IGT could include diabetes if a fasting plasma glucose is not measured.

The objective of the Technical Guideline Development Group meeting was to examine the evidence on the following issues related to the diagnosis of diabetes and intermediate hyperglycaemia:

- Should the current diagnostic criteria for diabetes be changed?
- How should normal glucose levels be defined?
- How should impaired glucose tolerance be defined?
- How should impaired fasting glucose be defined?
- What diagnostic tests should be used to define glucose tolerance status?

The Technical Guideline Development Group accepted the 1999 WHO “classification and aetiological” framework for diabetes (Appendix 4).

# SHOULD THE CURRENT DIAGNOSTIC CRITERIA FOR DIABETES BE CHANGED?

**There are important differences between (i) defining diabetes to identify an individual with diabetes and the consequent clinical and social implications of this diagnosis and (ii) defining diabetes for epidemiological purposes. In the former the diagnosis requires careful substantiation with retesting on another day unless the person is symptomatic and the plasma glucose is unequivocally elevated whereas in epidemiological studies repeat testing is rarely performed. When repeat testing is performed, approximately 75% of people with diabetes detected in epidemiological studies are confirmed to have clinical diabetes<sup>8,9</sup>.**

In the absence of a more specific biological marker to define diabetes, plasma glucose estimation remains the basis of diagnostic criteria. Other considerations also impact on how a diagnosis of diabetes should be made. Does diabetes represent the upper end of a continuous distribution of glucose or a discrete entity? While hyperglycaemia is an important prognostic parameter, is it the central or most important feature determining prognosis in people with hyperglycaemia? In terms of screening asymptomatic people, how can we best balance the medical, social and economic benefits and costs?

Although such questions are still debated, knowledge on diagnostic cut-points for diabetes has been derived from two sets of information:

- plasma glucose levels associated with risk of diabetes specific microvascular complications, particularly retinopathy
- the population distribution of plasma glucose.



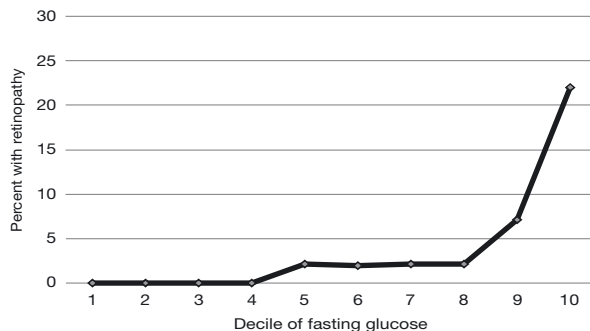
## 1. Diabetes complications

The occurrence of diabetes-specific complications has been used to derive diagnostic cut-points for diabetes, particularly using data from epidemiological studies which have examined both prevalent and incident retinopathy across a range of plasma glucose levels.

Figure 1 shows an example of the data typically used to examine this relationship in which deciles of plasma glucose are plotted against prevalence of retinopathy. The diagnostic cut-point is determined as the level at which the risk of retinopathy increases. Few studies have been ideal for this purpose and most have limited statistical power. Studies have differed in the methods used to diagnose retinopathy and whether or not people with previously diagnosed diabetes are included in the analysis. If people with diagnosed diabetes who are receiving blood glucose lowering treatment are included, the population-based characteristics of the study sample are maintained but a bias associated with treatment-induced effects on plasma glucose is introduced. Excluding people with treated diabetes from analyses eliminates the bias related to treatment effect but changes the characteristics of the population with diabetes<sup>10</sup>. Furthermore, the specific methodology used to derive cut-points (eg based on decile of the inflection point, or Receiver Operator Characteristic [ROC] curve analyses) influences the result. Figure 1 shows that the prevalence of retinopathy rises markedly in the 9th decile of plasma glucose. Most studies have used the lower limit of the decile as the cut-point, but the median within the decile might also be an appropriate choice for the cut-point.

Data from Pima Indians, a study in Egypt and unpublished NHANES III data were cited in the 1997 ADA report<sup>11</sup>. These analyses included people with medication-treated diabetes. Using the lower limit of the decile in which prevalent retinopathy increases significantly, the cut-points from these three studies are 10.3mmol/l, 8.6mmol/l and 8.5mmol/l respectively for 2-h plasma glucose and 6.1mmol/l, 6.0mmol/l and 5.9mmol/l respectively for fasting plasma glucose. Using data which excluded people with diabetes gives somewhat different results: – 9.0mmol/l, 8.9mmol/l and 9.9mmol/l respectively for 2-h plasma glucose and 6.0mmol/l, 6.1mmol/l and 6.4mmol/l respectively for fasting plasma glucose.

**Figure 1. Prevalence of retinopathy by decile of fasting glucose**



One study has reported fasting and 2-h plasma glucose cut-points and incident retinopathy. Over an 11-yr follow up, development of retinopathy increased at a baseline fasting plasma glucose cut-point of 7.0mmol/l and at a baseline 2-h post-glucose load plasma glucose of 13.3mmol/l<sup>12</sup>.

In the review of the evidence to prepare this report, attempts to find data which examined the relationship between plasma glucose and biopsy proven diabetic renal disease were unsuccessful. Studies which have examined the relationship between plasma glucose and the less specific marker of diabetic renal disease, proteinuria, have reported some association but not as strong as with retinopathy<sup>13</sup>.

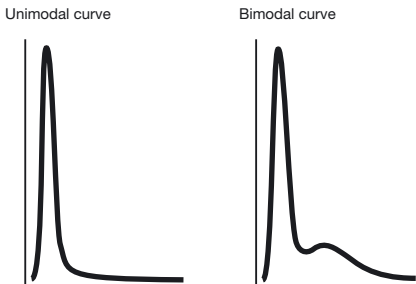
Numerous studies have examined the relationship between plasma glucose and mortality and cardiovascular complications but have failed to show a definite threshold which could be used to define diabetes (see Issues 2-4 below).

## 2. Population distribution of plasma glucose

Figure 2 shows two different distributions of plasma glucose – a unimodal distribution in which the entire population is represented by a single curve, and a bimodal distribution in which the populations can be divided into two separate but overlapping groups. With a bimodal distribution, the point at which the two curves intersect is used to separate abnormal from normal. It should be noted that adopting a cut-point for separating two components of a bimodal distribution of plasma glucose does not necessarily have any biological or pathogenic implications for adverse health outcomes which may be attributable to diabetes.

A bimodal distribution of plasma glucose concentrations was first described in a 1971 study in Pima Indians<sup>14</sup> and subsequently in other populations with a high prevalence of diabetes, including Pacific Islanders<sup>15,16</sup>, Asian Indians<sup>17</sup>, Mexican Americans<sup>18</sup>, Egyptians<sup>10</sup> and Malaysians<sup>19</sup>. Recently bimodality has also been reported in an elderly white population living in Southern California<sup>20</sup>.

Figure 2. Illustration of unimodal and bimodal distribution of plasma glucose



In populations with a bimodal distribution, the plasma glucose cut-point (defined as the point where the two curves intersect) shows variation between studies. For example the Rancho Bernardo study<sup>20</sup> and the Malaysian study<sup>19</sup> reported a similar 2-h plasma glucose cut-point range of 11.0 to 13.3mmol/l (depending on age group). However an analysis of the DETECT-2 data from 26 different countries with plasma glucose measured during an oral glucose tolerance test (OGTT) found a wide variation in cut-points. The cut-point for fasting plasma glucose for the different countries ranged from 5.7 to 8.5mmol/l (median 7.1mmol/l) and for 2-h plasma glucose ranged from 9.1 to 17.9mmol/l (median 12.4mmol/l)<sup>21</sup>.

In summary there are an abundance of data indicating that hyperglycaemia is harmful. However there are limitations in the data and the methodologies used to derive cut-points at which this level of harm is specifically increased and which clearly differentiate diabetes from non-diabetes.

**Recommendation 1** The current WHO diagnostic criteria for diabetes should be maintained – fasting plasma glucose  $\geq 7.0$ mmol/l (126mg/dl) or 2-h plasma glucose  $\geq 11.1$ mmol/l (200mg/dl).

Despite the limitations with the data from which the diagnostic criteria for diabetes are derived, the current criteria distinguish a group with significantly increased premature mortality and increased risk of microvascular and cardiovascular complications.

# HOW SHOULD NORMAL PLASMA GLUCOSE LEVELS BE DEFINED?

One approach to addressing the issue of defining categories of intermediate hyperglycaemia is to define normal glucose tolerance. However, this seemingly simple question is difficult to answer. Each of the ADA publications on the diagnostic criteria for diabetes has defined normal plasma glucose levels. The 2003 ADA statement<sup>4</sup> defined a normal fasting plasma glucose as  $<5.6\text{mmol/l}$  (down from  $6.1\text{mmol/l}$  in 1997) and a normal 2-h plasma glucose as  $<7.8\text{mmol/l}$ . The 1999 WHO report used a fasting plasma glucose of  $<6.1\text{mmol/l}$  and a 2-h plasma glucose of  $<7.8\text{mmol/l}$  as normal<sup>5</sup>.

The difficulty with defining normality mirrors that of defining diagnostic cut-points for intermediate hyperglycaemia i.e. placing a specific cut-point on a continuous variable. Furthermore other factors such as age, gender and ethnicity are relevant to defining normality. Also, as data from new outcomes studies become available, what is considered normal may change.

The following approaches can be used to define normal glucose levels.

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## 1. Statistical approach – population distribution of plasma glucose

This method is commonly used in clinical practice to define a normal level for a laboratory test. Application of this method requires the 'healthy' population to have a unimodal distribution. The upper limit of normal is typically defined as the mean + 2SD and by definition this approach means that 2.5% of the population is considered abnormal, a situation which is not in keeping with a condition of high prevalence such as diabetes.

## 2. Clinical approach – risk of adverse outcomes

Prospective population studies provide information on the relationship between plasma glucose and risk of death, cardiovascular disease and cancer, and of developing diabetes.

Levitan et al<sup>22</sup> performed a meta-analysis of thirty eight prospective studies and confirmed that hyperglycaemia in the non-diabetic range was associated with increased risk of fatal and non-fatal cardiovascular disease, with a similar relationship between events and each of fasting and 2-h plasma glucose. From twelve studies reporting fasting plasma glucose levels and six studies reporting post-challenge glucose, cardiovascular events appeared to increase in a linear fashion with 2-h post-challenge plasma glucose in the range below levels diagnostic of diabetes without a threshold, whereas for fasting plasma glucose there was a possible threshold at 5.5mmol/l.

The Paris Prospective study showed J-shaped relationships for all-cause mortality with both fasting and 2-h glucose concentrations, and the lowest observed death rates were in the intervals centred on 5.5mmol/l for fasting glucose and 5.0mmol/l for 2-h glucose. For ischaemic heart disease death for fasting glucose, the hazards ratio was best modelled by a positive linear relationship but for 2-h glucose, it was modelled by a J-shaped curve and the lowest observed death rate was in the interval centred on 6.0mmol/l<sup>23</sup>.

The DECODE study, after adjusting for other cardiovascular risk factors, reported a J-shaped relationship between mortality and glucose with the lowest rates for a fasting plasma glucose of 4.50–6.09mmol/l. A J-shaped relationship was also observed between 2-h plasma glucose and all-cause mortality and non-cardiovascular disease mortality with the lowest rates at a 2-h plasma glucose of 4.51–5.50mmol/l<sup>24</sup>. There was a graded relationship between cardiovascular mortality and 2-h plasma glucose with the lowest rates at the lowest 2-h plasma glucose distribution<sup>24</sup>.

A 33-yr follow-up of the Whitehall study in which a 50g OGTT was performed at baseline in 1967–1969 in 17869 male civil servants aged 40–64 years reported a threshold model with linear slope as best describing the relationship between 2-h post-load blood glucose and mortality risk. The hazard of coronary mortality rose in a linear fashion from a threshold 2-h blood glucose of 4.6mmol/l. At a 2-h blood glucose of 11.1mmol/l, age-adjusted hazard ratio was 3.6 (95% CI 2.3–5.6) compared with a level of 4.6mmol/l. The graded relationship persisted but was attenuated by 45% after adjustment for baseline ischaemic heart disease, BMI, systolic blood pressure, blood cholesterol, smoking, physical activity, lung function, and employment grade<sup>25</sup>.

In the Baltimore Longitudinal study, all cause mortality increased significantly from a fasting plasma glucose above 6.1mmol/l but not lower levels. For 2-h plasma glucose, risk increased significantly above 7.8mmol/l<sup>26</sup>.

Plasma glucose levels are also associated with cancer risk. Jee et al reported increased risk for all cancers in a cohort of 1.3 million people

followed for upto 10 years with increasing fasting serum glucose above 6.1mmol/l<sup>27</sup>.

There is also no level of plasma glucose at which risk of developing diabetes is clearly increased. In a group of young Israeli men, risk of incident diabetes progressively increased with a fasting plasma glucose  $\geq 4.8$ mmol/l compared with a fasting plasma glucose of  $< 4.5$ mmol/l<sup>28</sup>.

These studies do not provide a definitive answer to what might be considered a normal plasma glucose but it is clear that risk is lowest at levels which are commonly found in apparently healthy people.

### 3. Physiological approach

A number of studies have examined physiological function in people with non-diabetic fasting plasma glucose levels ( $< 7.0$ mmol/l) and have described a range of abnormalities.

Godsland et al<sup>29</sup> reported that first phase insulin response in non-diabetic individuals begins to decrease from a fasting plasma glucose of 5.0–5.4mmol/l and late-phase insulin response declines at a fasting plasma glucose above 6.0mmol/l. Piche et al<sup>30</sup> reported a progressive decline in indices of  $\beta$ -cell function and insulin sensitivity even within the fasting plasma glucose range considered normal. Compared with subjects with a fasting plasma glucose of  $< 4.9$ mmol/l, people with a fasting plasma glucose between 5.3 and 6.1mmol/l were more insulin resistant, had higher insulin and C-peptide responses during an OGTT and had reduced insulin secretion. Even people with a fasting plasma glucose of 4.9 to 5.3mmol/l were characterized by impaired insulin secretion and decreased insulin sensitivity compared with subjects with the lowest fasting plasma glucose.

#### Recommendation 2

Since there are insufficient data to accurately define normal glucose levels, the term 'normoglycaemia' should be used for glucose levels associated with low risk of developing diabetes or cardiovascular disease, that is levels below those used to define intermediate hyperglycaemia.





# HOW SHOULD IMPAIRED GLUCOSE TOLERANCE BE DEFINED?

**In 1979 the US National Diabetes Data Group<sup>31</sup> recommended the category of Impaired Glucose Tolerance (IGT) to denote a state of increased risk of progressing to diabetes, although it was also noted that many would revert to normal. This term was introduced to remove the stigma of diabetes from the other terms in use at the time to denote the range between 'normal' and diabetes. The increased risk of cardiovascular disease in people with IGT was also recognised. This category and definition also featured in the 1980 WHO report<sup>6</sup>. IGT is not a clinical entity but is a risk factor for future diabetes and/or adverse outcomes. Studies suggest that IGT is associated with muscle insulin resistance and defective insulin secretion, resulting in less efficient disposal of the glucose load during the OGTT<sup>32</sup>.**

The prevalence of IGT varies between populations and across different age groups. Prevalence rates in the order of 10% or more are common and it is typically more common in women than in men. The increasing prevalence with increasing age was illustrated in the DECODE study which showed the prevalence of isolated IGT increasing from 2.9% in 30–39yr old men to 15.1% in 70–79yr old men and from 4.5% in 30–39yr old women to 16.9% in 70–79yr old women<sup>33</sup>. A similar pattern is generally seen in Asian populations with prevalence of IGT increasing with age up to 70–89 years. However in the Indian population the prevalence of IGT is higher and does not change much with age<sup>34</sup>.

Data from Mauritius indicate that in people with IGT at baseline, 30% reverted to normal, 35% remain as IGT, 5% changed to IFG and 30% developed diabetes over the 11-yr follow up period<sup>35</sup>.

The reproducibility of IGT with retesting within 6 weeks is only moderate<sup>36</sup>. The proportion of people classified with IGT on the first OGTT and on retesting ranged from 33% to 48% with 39% to 46% being reclassified as normal and 6–13% as having diabetes on repeat testing.

IGT was initially defined as a category of glycaemia associated with an increased risk of developing diabetes but is now increasingly recognised as being associated with a significantly increased risk of premature mortality and cardiovascular disease. The McMaster review<sup>36</sup> reported the following:

- the annualized relative risk of a person with IGT progressing to diabetes was increased 6-fold compared with people with normal glucose tolerance. This relative risk was even higher in people with both IFG and IGT being increased 12-fold.
- the relative risk of all-cause mortality is 1.48-fold higher in people with IGT compared with people with normal glucose tolerance. The relative risk of a fatal cardiovascular outcome was 1.66-fold higher.

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### Validity of the current definition of IGT

The validity of the current definition centres on the risk of developing diabetes or risk of adverse outcomes associated with 2-h plasma glucose levels. The 2-h post-load plasma glucose cut-point of 7.8mmol/l for defining IGT was derived primarily from Pima Indian data which examined the risk of incident diabetes<sup>37</sup>. The incidence ranged from less than 2.0 percent/yr in those with 2-h plasma glucose levels of <5.6mmol/l to 6.8 percent/yr in those with 2-h values of 7.8–11.0mmol/l. A subsequent analysis of six prospective studies showed incidence rates of diabetes in people with IGT that ranged from 35.8 to 87.3/1000 person-yrs<sup>38</sup>. The rates increased with higher fasting plasma glucose and body mass index.

Unlike data reviewed in the section on IFG, there has been relatively little research on the appropriateness of the widely used 2-h plasma glucose level of 7.8mmol/l (140mg/dl) for defining IGT. The study by Gabir et al<sup>39</sup> in Pima Indians showed that the risk of future diabetes increases gradually over most of the glucose distribution but risk is markedly higher in the upper 10% of the glycaemic distribution. The 5-yr incidence rate for new diabetes was 24% for IGT compared with 4% in people with 2-h plasma glucose <7.8mmol/l.

As reviewed in the section on 'normoglycaemia', there is no consistent threshold for 2-h plasma glucose and adverse outcomes. Increasing 2-h plasma glucose levels across the diabetic and non-diabetic range are associated with increased risk of fatal and non-fatal cardiovascular disease. Cardiovascular events appeared to increase in a linear fashion with post-challenge plasma glucose in the non-diabetic range without a

threshold<sup>22</sup>, or in a J-shaped relationship with the lowest observed death rates centred on 5.0mmol/l for 2-h glucose for all-cause mortality and 6.0mmol/l for coronary heart disease death<sup>23</sup>. The DECODE study also reported a J-shaped relationship between all-cause and non-cardiovascular mortality and glucose with the lowest rates at a 2-h plasma glucose of 4.51–5.50mmol/l, and a graded relationship between cardiovascular mortality and 2-h plasma glucose<sup>24</sup>. The Whitehall study showed that coronary mortality rose in a linear fashion from a 2-h blood glucose of 4.6mmol/l<sup>25</sup>.

In summary, although there are limited data to support the current 2-h plasma glucose value used to define IGT, the current cut-point seems to be operationally adequate. However, it is important to note that the risk of future diabetes, premature mortality and cardiovascular disease begins to increase at 2-h plasma glucose levels below the IGT range. Since the rationale for this category is to define a risk state for future diabetes and/or future cardiovascular disease and premature mortality, a risk score combining known risk factors which includes a measure of glucose as a continuous variable, would seem a more logical approach.

**Recommendation 3**

The current WHO definition for Impaired Glucose Tolerance (IGT) should be maintained for the present.

Consideration should be given to replacing this category of intermediate hyperglycaemia by an overall risk assessment for diabetes, cardiovascular disease, or both, which includes a measure of glucose as a continuous variable.



# HOW SHOULD IMPAIRED FASTING GLUCOSE BE DEFINED?

In 1997 the ADA Expert Committee<sup>11</sup> introduced the category of Impaired Fasting Glucose (IFG) to describe the zone between the upper limit of normal fasting plasma glucose and the lower limit of the diabetic fasting plasma glucose. This was believed at that time to be analogous to the zone between the upper limit of a normal 2-h plasma glucose and the lower limit of the diabetic 2-h plasma glucose described by IGT. This recommendation was adopted by WHO in 1999<sup>3</sup>. IFG, as with IGT, is a not clinical entity but rather a risk factor for future diabetes and adverse outcomes. IFG is associated with impaired insulin secretion and impaired suppression of hepatic glucose output. It should be noted that all data in this section refer to IFG as defined by the WHO 1999 report i.e. fasting plasma glucose 6.1–6.9mmol/l (110–125mg/dl) inclusive, unless otherwise stated.

DECODE data show that of all European people with IFG defined by a fasting plasma glucose of 6.1–6.9mmol/l alone, 64.8% have isolated IFG, 28.6% have IGT and 6.6% have diabetes<sup>33</sup>. Similarly, DECODA data show that Asian people with IFG defined by a fasting plasma glucose of 6.1–6.9mmol/l alone, 45.9% have isolated IFG, 35.2% have IGT and 18.9% have diabetes<sup>34</sup>.

The prevalence of IFG varies between populations and across different age groups within populations. Overall prevalence rates in the order of 5% or more are common. IFG is typically more common in men than in women. The DECODE study showed an increase in prevalence of isolated IFG from 5.2% in 30–39yr old men upto 10.1% in 50–59yr old men and then a decrease to 3.2% in 80–89yr old men, whereas in women prevalence increased from 2.6% in 30–39yr olds to 5.9% in 70–79yr olds<sup>33</sup>.

In Asian populations prevalence of isolated IFG generally increases with age, except in the Indian population where prevalence does not change much with age<sup>34</sup>.

Data from Mauritius<sup>35</sup> indicate that in people with IFG at baseline, 40% reverted to normal, 15% remained as IFG, 20% changed to IGT and 25% developed diabetes over an 11-yr follow up period.

Two studies which assessed the reproducibility of IFG with retesting within 6 weeks showed that the proportion of people classified as IFG on the first test and on retesting was 64% and 51% respectively with the majority being reclassified as normal and less than 10% as having diabetes on repeat testing<sup>36</sup>.

The annualized relative risk of people with isolated IFG progressing to diabetes compared with people with normal glucose tolerance showed a 4.7-fold increase in the three studies included in the review by the McMaster group<sup>33</sup>. IFG was associated with increased risk of adverse outcomes with a relative risk ranging from 1.19–1.28 for non-fatal myocardial infarction, non-fatal cardiovascular disease, cardiovascular mortality and all-cause mortality<sup>36</sup>.

### Validity of current WHO definition for IFG

The adoption of a cut-point for fasting plasma glucose of 6.1mmol/l (110mg/dl) by the ADA<sup>11</sup> and WHO<sup>3</sup> as the upper limit of 'normoglycaemia' was based on this being the level above which first phase insulin secretion is lost in response to intravenous glucose and which is associated with progressively greater risk of developing micro – and macrovascular complications. Since then, there has also been an increased focus on the risk of the future development of diabetes. While the ADA Committee noted that the ideal method for selecting the cut-point for IFG would be by the identification of a threshold of fasting plasma glucose at which the risk of adverse clinical or metabolic outcomes rises sharply, available data do not show a definite or consistent threshold for fasting plasma glucose and adverse outcomes<sup>4</sup>.

The risk of developing diabetes is increased even with fasting plasma glucose levels which are considered normal. Tirosh and colleagues<sup>28</sup> reported that in a group of young Israeli men, risk of incident diabetes progressively increased with a fasting plasma glucose  $\geq 4.8$ mmol/l compared with a fasting plasma glucose of  $< 4.5$ mmol/l. These findings confirm the continuous risk even in the plasma glucose range considered normal and underline the difficulty in determining a specific cut-point for increased risk.

In 2003, the ADA revised the cut-point for IFG to 5.6mmol/l (100mg/dl)<sup>4</sup>. This was based on ROC curve analyses of Pima Indian, Mauritius, San Antonio and Hoorn study data which identified the baseline fasting plasma glucose levels which maximised sensitivity and specificity for predicting diabetes over a 5-yr period<sup>4</sup>. ROC curve analyses indicated that a cut-point of 5.4–5.5mmol/l gives the best combination of sensitivity and

specificity for predicting future diabetes. However there is a difference in the actual incidence of diabetes at different fasting plasma glucose levels. In the Mauritius study the 5-yr incidence of diabetes was in the order of 15% for a fasting plasma glucose of 5.5–5.7mmol/l compared with 30% for a fasting plasma glucose of 6.1–6.9mmol/l<sup>40</sup>. In the ARIC study a fasting plasma glucose  $\geq$  5.6mmol/l had a sensitivity of 70% in predicting incident diabetes compared with 50% for  $\geq$  5.9mmol/l. However this increased sensitivity occurred at the expense of a marked increase in the percentage of the population identified as being abnormal (40% v 20% respectively) in this middle-aged US population<sup>41</sup>.

In the European Diabetes Epidemiology Group position statement on the threshold for diagnosing IFG, Forouhi et al examined the magnitude of the association between different thresholds for IFG and diabetes from published data, or derived it from the published data<sup>42</sup>. Overall, the magnitude of the association between diabetes and IFG is greater for IFG defined as FPG 6.1–6.9mmol/l than for FPG 5.6–6.0mmol/l. For example in the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study, diabetes incidence rates per 1,000 person-years for IFG categories of <5.6, 5.6–6.0 and 6.1–6.9mmol/l were, respectively, 1.8, 5.7, and 43.2 in men and 0.7, 6.2 and 54.7 in women<sup>43</sup>.

Increasing fasting plasma glucose in the non-diabetic range is associated with increased risk of fatal and non-fatal cardiovascular disease, however the level at which risk begins to increase has varied between studies. From twelve studies reporting fasting plasma glucose levels, cardiovascular events increased above threshold at 5.5mmol/l<sup>22</sup>. The Paris Prospective study showed increased all-cause mortality above 5.5mmol/l for fasting glucose<sup>23</sup>. The DECODE study reported a J-shaped relationship between mortality and glucose with the lowest rates for a fasting plasma glucose of 4.50–6.09mmol/l but with risk significantly increasing only above 7.0mmol/l<sup>24</sup>. However, after adjusting for 2-h plasma glucose there was no relation between fasting plasma glucose and the risk of premature mortality and cardiovascular disease. In the Baltimore Longitudinal study, all-cause mortality increased significantly from a fasting plasma glucose above 6.1mmol/l<sup>26</sup>. Jee et al<sup>27</sup> reported an increased risk for all cancers in a Korean cohort of 1.3 million people with increasing fasting serum glucose beginning at a level of 6.1mmol/l.

In summary, the various approaches for deriving the most appropriate specific cut-point for defining IFG do not provide a consistent and unequivocal answer. Therefore, as discussed in the following section, other considerations will need to be taken into account in deciding an appropriate cut-point. Similar to the situation with IGT, since the rationale for IFG is to identify a risk state for future diabetes and/or future cardiovascular disease and premature mortality, a risk score combining known risk factors which includes a measure of glucose as a continuous variable, would seem a more logical approach.



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### Should the current WHO criteria for defining IFG be changed?

Since risk of adverse outcomes and future diabetes is continuous across the fasting plasma glucose range, the cut-point chosen to define IFG will be somewhat arbitrary. Therefore other considerations should be taken into account in recommending a cut-point. The Group considered the following points relevant to reaching its recommendation:

- Outcomes
  - Mortality, cardiovascular disease, microvascular complications
  - Incident diabetes
- Prevention of
  - premature mortality and cardiovascular disease
  - progression to diabetes
- Impact on prevalence of IFG
- Concordance of IFG and IGT
- Risk profile of individuals identified with IFG
- Economic considerations and cost implications
- Implications for health services and policy

Each of these points is considered below.

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### Outcomes

As reviewed above, available data do not point to a specific and consistent cut-point for adverse cardiovascular outcomes or mortality.

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### Incident diabetes

The Group expressed reservations about using incident diabetes as the only end point for recommending a cut-point for IFG. The Group also has reservations about the method used by the ADA to derive the cut-point of 5.6mmol/l (i.e. maximising the sum of sensitivity and specificity). The Group was of the opinion that a cut-point should include clinical and public health considerations, and not merely statistical ones.

Actual incidence rates of diabetes are an important consideration. For example, Mauritius<sup>40</sup> and Pima Indian<sup>39</sup> data indicate that risk of progression of IFG in the additional people identified by the recently recommended ADA criteria is half that of WHO defined IFG (approximately 15% v 30% over 5 years).

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### Prevention of premature mortality and cardiovascular disease

Unfortunately there are no data on clinical outcomes of interventions in people with IFG.

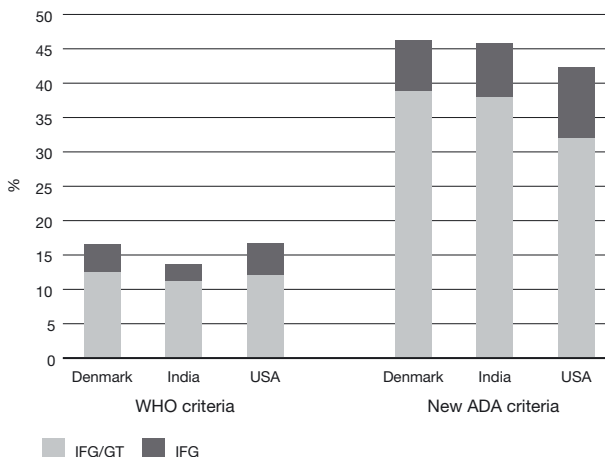
**Prevention of progression to diabetes**

Unlike IGT where there is extensive evidence from well conducted randomised controlled studies that lifestyle and pharmacological interventions can prevent or delay progression to diabetes<sup>44,45,46,47,48,49,50</sup>, there are currently only limited data on the preventability of progression of IFG to diabetes. The recently reported DREAM study showed that the thiazolidinedione, rosiglitazone, was associated with a similar risk reduction of progression from WHO defined IFG and IGT to diabetes or death – hazards ratio 0.30 (0.19–0.49) for isolated IFG and 0.45 (0.36–0.55) for isolated IGT<sup>51</sup>. There are no data for prevention of progression to diabetes from ADA defined IFG.

**Impact on prevalence of IFG**

A number of studies have reported a 2–3-fold increase in IFG prevalence using the new ADA recommended criteria compared with WHO defined IFG, highlighted by data from the DETECT-2 study<sup>52</sup>. Figure 3 shows the prevalence of IFG increasing from 11.8% to 37.6% in Denmark, from 10.6% to 37.6% in India and from 9.5% to 28.5% in the US. Such increases have major consequences in countries such as in India and China where the number of people with IFG in the 40–64-yr age range would increase by 13 million and 20 million respectively using the 2003 ADA criteria to define IFG.

**Figure 3. Comparison of prevalence of IFG diagnosed with 1999 WHO criteria and 2003 ADA criteria**



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**Concordance of IFG and IGT**

One of the reasons cited by the ADA Committee for lowering the IFG cut-point was to increase concordance with IGT<sup>4</sup>. Data from the Danish INTER-99 study<sup>53</sup> show that the percentage of people with IGT who also have IFG increases from 25% using the WHO criteria (FPG 6.1–6.9mmol/l) to 60% with the 2003 ADA criteria (FPG 5.6–6.9mmol/l). However, the overall percentage of people with IFG who have IGT decreases from 25% with the WHO criteria to 20% with the 2003 ADA criteria. While the *number* of people with ADA defined IFG who also have IGT increases, the *proportion* of people with ADA defined IFG who have IGT decreases. Therefore of people identified with IFG by the new ADA definition, there is an increase in the number of people who have IFG but do not have IGT compared with WHO defined IFG. Furthermore, intervening in people with ADA defined IFG with prevention strategies which have been shown to benefit people with IGT will include intervening in a greater number of people who do not have IGT and for whom there is no evidence of benefit.

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**Risk profile of individuals identified**

Studies have reported that the cardiovascular risk profile of people with WHO defined IFG is worse than the additional people identified with IFG using the 2003 ADA criteria<sup>52,54,55</sup>.

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**Economic considerations and cost implications**

These are important for policy makers, public health agencies, insurers, health care providers and consumers. However there are currently no analyses comparing the economic impact of WHO and ADA IFG criteria or the modelled impact of different cut-points as there have been for assessing different diabetes screening strategies.

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**Impact on health services and policy**

The large increase in prevalence of IFG which would result from lowering the cut-point has significant implications for the health system of many countries which are struggling to cope with caring for people with established diabetes. There is also concern that increasing the focus on IFG would divert prevention resources from IGT, where there is more extensive evidence of benefit.

**Recommendation 4** The fasting plasma glucose cut-point for Impaired Fasting Glucose (IFG) should remain at 6.1mmol/l.

This decision was based on concerns about the significant increase in IFG prevalence which would occur with lowering the cut-point and the impact on individuals and health systems. There is a lack of evidence of any benefit in terms of reducing adverse outcomes or progression to diabetes and people identified by a lower cut-point eg 5.6mmol/l (100mg/dl) have a more favourable cardiovascular risk profile and only half the risk of developing diabetes compared with those above the current WHO cut-point. Lowering the cut-point would increase the proportion of people with IGT who also have IFG but decreases the proportion of people with IFG who also have IGT.

As discussed in the section on IGT, consideration should be given to replacing this category of intermediate hyperglycaemia by an overall risk assessment for diabetes, cardiovascular disease, or both, which may include a measure of glucose as a continuous variable.

The recommendation on IFG threshold in this report is identical to the position statement of the European Diabetes Epidemiology Group which also recommends that the diagnostic threshold for IFG should remain at 6.1mmol/l<sup>42</sup>.

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### **Implications of not changing the current WHO diagnostic criteria for IFG**

The Group was mindful of the implications of having different WHO and ADA criteria for IFG. The ADA recommendations are targeted to health care providers in one country compared with the global WHO recommendations. It was also noted that other significant discrepancies already exist between the ADA and WHO recommendations including the method for diagnosing diabetes eg fasting plasma glucose versus oral glucose tolerance test. Although these different recommendations for IFG may lead to some confusion initially it should stimulate research to provide data to resolve the discrepancy and other issues associated with defining cut-points for fasting plasma glucose.



THERE ARE  
TWO THINGS THAT  
ARE CERTAIN:  
THERE IS CHANGE  
AND THERE IS DEATH.

# WHAT DIAGNOSTIC TESTS SHOULD BE USED TO DEFINE GLYCAEMIC STATUS

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## 1. Measurement of glucose in blood

Measurement of glucose in blood remains the mainstay of testing for glucose tolerance status. There are a number of important considerations which can influence this measurement which require careful attention in order to ensure an accurate result.

Most portable devices measure the glucose concentration directly in the plasma component of the blood by filtering out the red blood cells. The signal is then calibrated to produce a readout either as blood or plasma glucose. Laboratory measures normally now use separated plasma, with determination of the amount or concentration of glucose in a fixed volume. Only devices which measure out a fixed volume of blood, and then determine the glucose within that volume, measure true whole blood glucose concentration. As glycolysis inhibitors take time to penetrate into red blood cells, only immediate separation of plasma will avoid some lowering of glucose levels in the sample, though rapid cooling can reduce this loss. Accordingly modern recommendations are for laboratory plasma measurements on appropriately handled samples, and matched calibration of portable devices.

Glucose measured in plasma is approximately 11% higher than glucose measured in whole blood. However this difference is dependent on haematocrit, increasing to 15% at a haematocrit of 0.55 and decreasing to 8% at a haematocrit of 0.30<sup>56</sup>. For this and other reasons the conversion of whole blood glucose to plasma glucose is problematic and the previously published WHO conversion tables may be inaccurate in some situations. It should also be noted that many portable glucose measuring devices are still calibrated to whole blood despite the International

Federation of Clinical Chemistry (IFCC) recommendation that all glucose measuring devices report in plasma values<sup>57</sup>.

Measurement differences may also arise depending on the site of collection of the blood sample. Venous and capillary samples will give the same result in the fasting state but in the non-fasting state capillary will give higher results than venous samples.

The processing of the sample after collection is important to ensure accurate measurement of plasma glucose. This requires rapid separation of the plasma after collection (within minutes) but it is recognised that this seldom occurs. Collection into a container with glycolytic inhibitors (eg NaF) is only partially effective. A minimum requirement is that the sample should be placed immediately in ice-water after collection and before separating but even so separation should be within 30min<sup>58</sup>.

#### Recommendation 5

1. Venous plasma glucose should be the standard method for measuring and reporting. However in recognition of the widespread use of capillary sampling, especially in under-resourced countries, conversion values for capillary plasma glucose are provided for post-load glucose values. Fasting values for venous and capillary plasma glucose are identical.
2. Glucose should be measured immediately after collection by near patient testing, or if a blood sample is collected, plasma should be immediately separated, or the sample should be collected into a container with glycolytic inhibitors and placed on ice-water until separated prior to analysis.

## 2. Oral glucose tolerance test (OGTT)

There is continuing debate about the place of the OGTT for clinical and epidemiological purposes. The test is recommended by the WHO<sup>3</sup>. Although ADA acknowledges the OGTT as a valid way to diagnose diabetes, the use of the test for diagnostic purposes in clinical practice is discouraged in favour of fasting plasma glucose for several reasons, including inconvenience, greater cost and less reproducibility<sup>11</sup>. Some of this variation can be minimised with attention to dietary preparation and taking care to collect the 2-h sample within 5 min of 120 min<sup>59</sup>.

Many studies have reported that fasting plasma glucose and 2-h post-glucose plasma glucose do not identify the same people as having diabetes. In the DECODE study<sup>60</sup>, of the 1517 people with newly diagnosed diabetes, 40% met only the fasting plasma glucose criterion, 31% met only the 2-h plasma glucose criterion and 28% met both criteria. Therefore using only the fasting plasma glucose will fail to diagnose approximately 30% of people with diabetes. Data from the NHANES III study cited in the 1997 ADA report show similar findings for newly diagnosed diabetes<sup>11</sup>. This discrepancy is more obvious in an older population. Barrett-Conner et al<sup>61</sup>



reported that 70% of women and 48% of men aged 50–89 years had new diabetes diagnosed solely by an elevated 2–h plasma glucose.

Does this matter and are there any differences in outcomes for people diagnosed on the basis of the fasting or 2–h plasma glucose or both? Many studies have documented increased rates of mortality in people with diabetes. Studies which have compared these rates in relation to diabetes diagnosed on the basis of fasting or 2–h plasma glucose have consistently shown worse outcomes in those diagnosed on the basis of the 2–h plasma glucose result.

The Hoorn study showed that all-cause and cardiovascular mortality over an 8-yr follow-up was significantly elevated in those with 2–h plasma glucose  $\geq 11.1$ mmol/l but not in those with a fasting plasma glucose  $\geq 7.0$ mmol/l<sup>62</sup>. In the DECODE study, hazard ratios (HR) (95% CI) for diabetes diagnosed on a fasting plasma glucose  $\geq 7.0$ mmol/l was 1.6 (1.4–1.8) for all-cause mortality, 1.6 (1.3–1.9) for cardiovascular mortality, and 1.6 (1.4–1.9) for non-cardiovascular mortality, respectively. The corresponding HRs for diabetes diagnosed on a 2–h plasma glucose  $\geq 11.1$ mmol/l were 2.0 (1.7–2.3), 1.9 (1.5–2.4) and 2.1 (1.7–2.5), respectively. The HR for previously undetected diabetes defined by the 2–h plasma glucose was not significantly different from that for known diabetes, but was significantly higher than that for undetected diabetes based on the fasting plasma glucose<sup>24</sup>. A further DECODE analysis has shown that while mortality is increased in people with newly diagnosed diabetes based on either the fasting plasma glucose or 2–h plasma glucose, this increased risk is no longer significant for fasting plasma glucose  $\geq 7.0$ mmol/l when adjusted for 2–h plasma glucose but risk based on 2–h plasma glucose  $\geq 11.1$ mmol/l remains significant when adjusted for fasting plasma glucose<sup>63</sup>.

Shaw et al<sup>64</sup> reported a 2.7-fold increased risk of all-cause mortality in men and a 2-fold increase in women from three population-based longitudinal studies (in Mauritius, Fiji and Nauru) in people with newly diagnosed diabetes on the basis of an elevated 2–h plasma glucose compared with people with normal glucose tolerance. In contrast people with diabetes diagnosed on the basis of fasting plasma glucose alone did not have an increased risk. However, not all studies have observed this finding<sup>65</sup>.

The 2–h plasma glucose also seems important for microvascular complications. Ito et al<sup>12</sup> reported that the incidence of retinopathy in people with newly diagnosed diabetes increased substantially only in those with 2–h plasma glucose levels above 11.1mmol/l, even in those with fasting plasma glucose  $\geq 7.0$ mmol/l. In people with fasting plasma glucose  $\geq 7.8$ mmol/l but 2–h plasma glucose  $< 11.1$ mmol/l, none developed retinopathy. E

In summary, there is some evidence that diabetes diagnosed solely on the basis of an elevated 2–h plasma glucose is associated with a worse prognosis than diabetes diagnosed on the basis of an elevated fasting plasma glucose alone for both mortality and retinopathy. Therefore, diagnosing the 30% of individuals who have diabetes only on the basis of an elevated 2–h plasma glucose may have prognostic implications. Diagnosing such



people can only be achieved with an OGTT. In addition, IGT can only be diagnosed with an OGTT.

**Recommendation 6** The oral glucose tolerance test (OGTT) should be retained as a diagnostic test for the following reasons

- fasting plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed diabetes
- an OGTT is the only means of identifying people with IGT
- an OGTT is frequently needed to confirm or exclude an abnormality of glucose tolerance in asymptomatic people

An OGTT should be used in individuals with fasting plasma glucose 6.1–6.9mmol/l (110–125mg/dl) to determine glucose tolerance status.

### 3. Glycated Haemoglobin (HbA1c)

HbA1c reflects average plasma glucose over the previous 2–3 months in a single measure which can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the gold standard for assessing glycaemic control in people with diabetes and have resulted in its consideration as an option for assessing glucose tolerance in people without diagnosed diabetes.

The relationship between HbA1c and prevalent retinopathy is similar to that of plasma glucose as illustrated in Figure 1. This relationship was originally reported in Pima Indians<sup>66</sup> and has also been observed in several populations including Egyptians<sup>10</sup>, Americans<sup>11</sup> and Japanese<sup>67</sup>. Overall the performance of HbA1c has been similar to that of fasting or 2–h plasma glucose but the actual HbA1c threshold value has differed between studies.

These favourable aspects of HbA1c need to be balanced against the reality that HbA1c measurement is not widely available in many countries throughout the world. Furthermore there are aspects of its measurement which are problematic. Although in reference laboratories the precision of HbA1c measurement is similar to that of plasma glucose, global consistency remains a problem. Furthermore the HbA1c result is influenced by several factors including anaemia, abnormalities of haemoglobin, pregnancy and uraemia. Some of these factors may be a bigger problem in under-resourced countries due to a higher prevalence of anaemia and of haemoglobinopathies. The precise effect of these factors on the HbA1c result varies with the laboratory method used<sup>68</sup>.

Taking all of these considerations into account, the Group concluded that the role of HbA1c in the diagnosis of diabetes and intermediate hyperglycaemia is not established and that it could not be recommended as a diagnostic test at this time.

**Recommendation 7** Currently HbA1c is not considered a suitable diagnostic test for diabetes or intermediate hyperglycaemia.

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**Terminology**

The Group recommends using the term Intermediate Hyperglycaemia to describe glycaemic levels between 'normal' glucose tolerance and diabetes. Use of 'pre-diabetes' is discouraged to avoid any stigma associated with the word diabetes and the fact that many people do not progress to diabetes as the term implies. In addition this focus on diabetes may divert attention from the important and significantly increased cardiovascular risk.

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**Future directions**

Studies are required to guide future deliberations about diagnostic criteria which go beyond plasma glucose considerations and take into account various aspects of benefits and costs. Uniform methodologies and approaches to analyses would assist in producing universally comparable results and interpretation of findings. Pooling of data from studies which individually have insufficient power may help to resolve some outstanding issues eg defining cut-points for diabetes at which risk of retinopathy increases.

Retaining the risk categories of IFG and IGT in clinical practice should be reconsidered. Defining specific levels for intermediate hyperglycaemia may not be the most appropriate way of defining future risk of diabetes or cardiovascular disease. This risk might be better assessed by the use of prediction scores which, in addition to plasma glucose, also include other risk factors.



# APPENDIX 1

## MEMBERSHIP OF GUIDELINE DEVELOPMENT COMMITTEES

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### Guideline Steering Group

- G Roglic, Department of Chronic Diseases and Health Promotion, Geneva, Switzerland (Chair)
  - S Resnikoff, Department of Chronic Diseases and Health Promotion, Geneva, Switzerland
  - K Strong, Department of Chronic Diseases and Health Promotion, Geneva, Switzerland
  - N Unwin, Department of Chronic Diseases and Health Promotion, Geneva, Switzerland
- 

### Technical Guideline Development Group

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- D Vistisen, Steno Diabetes Center, Gentofte, Denmark (Statistical Advisor)
- P Zimmet, International Diabetes Institute, Caulfield, Australia (corresponding member)

K Borch-Johnsen also represented the European Association for the Study of Diabetes. The American Diabetes Association was asked to provide a representative but was unable to do so.

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### WHO Secretariat

- G Roglic, Department of Chronic Diseases and Health Promotion, Geneva, Switzerland
- N Unwin, Department of Chronic Diseases and Health Promotion, Geneva, Switzerland

# APPENDIX 2

## SUMMARY OF WHO DIAGNOSTIC CRITERIA FOR DIABETES AND INTERMEDIATE HYPERGLYCAEMIA

	1965	1980	1985	1999
<b>Normal</b>				
Fasting glucose	Not specified	Not defined	Not defined	<6.1mmol/l
2-h glucose	<6.1mmol/l			Not specified but <7.8mmol/l implied
<b>Diabetes</b>				
Fasting glucose	Not specified	≥8.0mmol/l and / or	≥7.8mmol/l or	≥7.0mmol/l or
2-h glucose	≥7.2mmol/l	≥11.0mmol/l	≥11.1mmol/l	≥11.1mmol/l
<b>IGT</b>				
Fasting glucose	Referred to as borderline state	<8.0mmol/l and	<7.8mmol/l and	<7.0mmol/l and
2-h glucose	6.1 7.1mmol/l	≥8.0 and <11.0 mmol/l	≥7.8 and <11.1 mmol/l	≥ 7.8 and <11.1mmol/l
<b>IFG</b>				
Fasting glucose	Not defined	Not defined	Not defined	≥6.1 and <7.0mmol/l and
2-h glucose				<7.8mmol/l (if measured)

Values represent venous plasma glucose

# APPENDIX 3

## COMPARISON OF 1999 WHO AND 2003 ADA DIAGNOSTIC CRITERIA

	WHO 1999	ADA 2003
<b>Diabetes</b>		
Fasting glucose	≥7.0mmol/l	≥7.0mmol/l
	<b>or</b>	<b>or</b>
2-h glucose*	≥11.1mmol/l	≥11.1mmol/l
<b>IGT</b>		
Fasting glucose	<7.0mmol/l (if measured)	Not required
	<b>and</b>	
2-h glucose	≥7.8 and <11.1mmol/l	≥7.8 and <11.1mmol/l
<b>IFG</b>		
Fasting glucose	6.1 to 6.9mmol/l	5.6 to 6.9mmol/l
	<b>and (if measured)</b>	
2-h glucose	(measurement recommended)	Measurement not recommended (but if measured should be <11.1 mmol/l)

\* Venous plasma glucose 2-h after ingestion of 75g oral glucose load



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