

## Evidence for current diagnostic criteria of diabetes mellitus

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### Abstract

Diabetes mellitus is a non-communicable metabolic

derangement afflicting several millions of individuals globally. It is associated with several micro and macro-vascular complications and is also a leading cause of mortality. The unresolved issue is that of definition of the diagnostic threshold for diabetes. The World Health Organization and the American Diabetes Association (ADA) have laid down several diagnostic criteria for diagnosing diabetes and prediabetes based on the accumulating body of evidence. This review has attempted to analyse the scientific evidence supporting the justification of these differing criteria. The evidence for diagnosing diabetes is strong, and there is a concordance between the two professional bodies. The controversy arises when describing the normal lower limit of fasting plasma glucose (FPG) with little evidence favouring the reduction of the FPG by the ADA. Several studies have also shown the development of complications specific for diabetes in patients with prediabetes as defined by the current criteria though there is a significant overlap of such prevalence in individuals with normoglycemia. Large multinational longitudinal prospective studies involving subjects without diabetes and retinopathy at baseline will ideally help identify the threshold of glycemic measurements for future development of diabetes and its complications.

**Key words:** Diabetes; Prediabetes; Post glucose; Microvascular complications; Macrovascular complications

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**Core tip:** The diagnostic criteria for diabetes and prediabetes have evolved along the timeline taking into account new evidences which had developed. The major professional bodies have converged on to a consensus in developing the different thresholds for diagnosis of diabetes and associated states. Nevertheless, controversy remains on certain issues. There

is need to review the evolution of these criteria, the logistics behind their adoption and their association with different complications.

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## INTRODUCTION

Diabetes mellitus (DM) is a classic non-communicable disease that contributes to morbidity, mortality and poor quality of life apart from imposing economic burden on the health care system. The prevalence of type 2 DM is rising steadfast at an alarming rate and is estimated to affect 592 million individuals globally by the year 2035<sup>[1]</sup>. The International Diabetes Federation projections of the prevalence of prediabetes are expected to reach 471 million by 2035<sup>[1]</sup>. It is essential to make an early diagnosis and begin intervention to avoid complications of DM. But, defining the diagnostic threshold for diabetes and prediabetes has been a matter of intense debate. In this regard, several professional bodies have published differing diagnostic criteria over the last few decades. Below, is a review of the evolution of various diagnostic criteria and their validity.

## EVOLUTION OF DIAGNOSTIC CRITERIA FOR DIABETES

In ancient times, DM was diagnosed by tasting urine. Then the diagnosis was made by estimation of glucose in urine. But urine glycosuria did not correlate with glucose level in blood and was replaced by estimation of plasma glucose.

### **World Health Organization criteria (1965)**

The World Health Organization (WHO) in 1965 proposed the first widely accepted laboratory standard for diagnosing DM (Table 1). The committee recommended diagnosing DM in persons under the age of 45 years if 2 h venous plasma glucose was  $\geq 7.22$  mmol/L after loading with oral glucose of 50 or 100 g<sup>[2]</sup>. In persons aged more than 45 years, the committee considered that other clinical data should be the main guide to the diagnosis. Borderline state was defined if 2 h plasma glucose level was between 6.11 to 7.17 mmol/L.

### **National Diabetes Data Group criteria (1979)**

The National Diabetes Data Group (NDDG) in 1979 proposed new diagnostic criteria for DM<sup>[3]</sup>. It was based on the bimodal distribution of plasma glucose observed in Pima Indians and Nauruan population and the risk of

progression to DM and its complications<sup>[4,5]</sup>. A subject was diagnosed as having DM if fasting plasma glucose (FPG) was  $\geq 7.78$  mmol/L and/or 2-h plasma glucose (2-h PG) after 75 g of glucose was  $\geq 11.11$  mmol/L.

A study on Pima Indians revealed that the 2-h PG level differentiated those with DM from those without<sup>[4]</sup>. Subjects fall into two groups, one with a distribution of 2-h PG levels below 11.11 mmol/L, and the other with a distribution above 13.33 mmol/L. Diabetic retinopathy was mainly confined to the second group, i.e., in subjects whose 2-h PG level  $\geq 13.33$  mmol/L and this value divided the subjects with diabetes from nondiabetics. This bimodal distribution was further confirmed in Nauruan population<sup>[5]</sup>. Similar bimodal distribution also exists for FPG, where the glycemic threshold of about 7.78 mmol/L divides the two groups. Later, the bimodal glycemic distribution was reconfirmed from other populations with a high prevalence of DM like Mexican Americans<sup>[6]</sup>, Pacific Islanders<sup>[7]</sup>, South African Indians<sup>[8]</sup>, Egyptians<sup>[9]</sup>, Malaysians<sup>[10]</sup> and Americans in the United States<sup>[11]</sup>. However, for some populations, no such bimodality could be documented<sup>[12]</sup>.

With accumulating evidence from further studies, it was recognized that several individuals had 2-h PG levels that were intermediate between the normal and diabetic range. This group of individuals had 1%-5% risk of progression to DM per year though the majority continued to remain in this state and a few reverted to normalcy. It was also noted that there was an increased prevalence of atherosclerotic disease and electrocardiographic abnormalities and death in this population. This provided a window of opportunity to identify such individuals to intervene early and prevent progression to DM and its complications. To lay emphasis on this, the terminology "impaired glucose tolerance" (IGT) was first introduced by the NDDG of the National Institute of Health, United States. It was defined as a state of having venous FPG level of less than 7.8 mmol/L and a 2-h PG oral glucose tolerance test (OGTT) value between 7.8 mmol/L and 11.1 mmol/L<sup>[3]</sup>.

This group also aimed to standardize the protocol for OGTT internationally and recommended using 75 g of anhydrous glucose load for testing in nonpregnant adults. This was based on the observation that 50-g dose was not adequate in many individuals to identify IGT detected using the larger dose. Also, 100-g dose resulted in significant nausea in several study subjects. In subjects without diabetes it was reported that 50 g or 100 g result in approximately similar plasma glucose levels, the only difference was that 2 h PG was 0.83 mmol/L higher for 100 g as compared to 50 g oral glucose load<sup>[13,14]</sup>. Also there were no significant differences between 75- and 100-g doses. But in subjects with IGT there was higher difference (up to 2.78 mmol/L) in 2-h PG value between the 50 and 100 g oral glucose<sup>[3]</sup>.

### **WHO criteria (1980 and 1985)**

The WHO technical recommendation released in 1980

**Table 1** Evolution of diagnostic criteria of diabetes mellitus

	WHO 1965	WHO 1980	WHO 1985	ADA1997 WHO 1999	ADA 2003	IEC 2009 ADA 2010 WHO 2011
IFG	Not defined	Not defined	Not defined	Fasting ≥ 6.11 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L	Fasting ≥ 5.5 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L	Fasting ≥ 5.5 to < 7 mmol/L and post glucose (if measured) < 11.1 mmol/L or HbA1c (5.7%-6.4%)
IGT	Post glucose 6.11-7.1 mmol/L	Fasting < 8 mmol/L and/or post glucose ≥ 8 to < 11.1 mmol/L	Fasting < 7.8 mmol/L and/or post glucose ≥ 7.8 to < 11.1 mol/L	Fasting (if measured) < 7 mmol/L and post glucose ≥ 7.8 to 11.1 mmol/L	Fasting (if measured) < 7 mmol/L and post glucose 7.8 to 11.1 mmol/L	Fasting (if measured) < 7 mmol/L and post glucose 7.8 to 11.1 mmol/L or HbA1c (5.7%-6.4%)
DM	Post glucose ≥ 7.22 mmol/L	Fasting ≥ 8 mmol/L and/or post glucose ≥ 11.1 mmol/L	Fasting ≥ 7.8 mmol/L and/or post glucose ≥ 11.1 mmol/L	Fasting ≥ 7 mmol/L and/or post glucose ≥ 11.1 mmol/L	Fasting ≥ 7 mmol/L and/or post glucose ≥ 11.1 mmol/L	Fasting ≥ 7 mmol/L or Post glucose ≥ 11.1 mmol/L and/or HbA1c ≥ 6.5%

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; DM: Diabetes mellitus; IEC: International Expert Committee; ADA: American Diabetes Association; WHO: World Health Organization; HbA1c: Glycated hemoglobin.

modified the criteria for diagnosing DM (Table 1). A venous FPG value above 8 mmol/L and a post glucose load 2-h PG value above 11 mmol/L were considered diagnostic of DM. This 2-h PG value was chosen based on observations that specific complications of DM rarely developed below this threshold. The term "IGT" suggested by the NDDG was also endorsed by WHO and became a part of the recommendation<sup>[15]</sup>. This was further slightly modified in the subsequent recommendations in 1985 and fasting and 2-h post glucose load venous plasma glucose thresholds were redefined as 7.8 mmol/L and 11.1 mmol/L respectively (Table 1)<sup>[16]</sup>.

#### **American Diabetes Association criteria (1997) and WHO criteria (1999)**

In 1997, the American Diabetes Association (ADA) lowered the threshold for FPG from 7.8 to 7.0 mmol/L and the 2-h post glucose load value was retained (Table 1)<sup>[17]</sup>. Impaired fasting glucose (IFG) was defined as FPG ≥ 6.1 mmol/L and < 7.0 mmol/L (Table 1). WHO adopted these criteria for the diagnosis of diabetes and prediabetes in 1999. In the second National Health and Nutrition Examination Survey (NHANES-II), only 26% of people with newly diagnosed DM by 1985 WHO had FPG ≥ 7.8 mmol/L, whereas 97% had 2-h PG ≥ 11.1 mmol/L<sup>[18]</sup>. Other studies also reported that as many as 80% of DM cases discovered in population screening by OGTT have FPG < 7.8 mmol/L<sup>[19-25]</sup>. Thus, the cutpoint of FPG > 7.8 mmol/L defined a greater degree of hyperglycemia than did the cutpoint of 2-h PG > 11.1 mmol/L. Thus, FPG appeared to be an insensitive test in population screening for undiagnosed DM.

This revision of the diagnostic criteria for the FPG from 7.8 to 7.0 mmol/L was based on the assumption that the threshold of the FPG and 2-h PG should identify

similar conditions. In Pima Indians<sup>[26]</sup>, Egyptians<sup>[9]</sup> and NHANES-III, both FPG and 2-h PG were strongly associated with retinopathy. The cutpoint for the 2-h PG was justified largely because of the dramatic increase in the prevalence of retinopathy approximately around that point. The equivalent cutpoint of FPG for 2-h PG level predicting retinopathy was computed in population studies of the Pima Indians, Egyptians, Pacific population, and NHANES III participants.

#### **ADA criteria (2003)**

A controversial change was brought out in the 2003 ADA guidelines, and it was the reduction in the cut-off point for defining the upper limit of FPG (Table 1). Based on four population-based epidemiological studies, the ideal cut-off point was shown to fall between 5.22-5.72 mmol/L and based on this data, an arbitrary cut-off of 5.55 mmol/L was chosen as the new threshold<sup>[27]</sup>. The lower threshold value of IFG was reduced from 6.11 to 5.55 mmol/L.

The phases of IFG and IGT represent metabolic states intermediate between normal glucose homeostasis and diabetic hyperglycaemia. The physiological basis of IFG and IGT are different. IFG is associated with insulin resistance at liver while IGT is associated with peripheral insulin resistance, at the level of skeletal muscle. The rationale for establishing the intermediate categories of impaired glucose regulation was based on their ability to predict future diabetes and its complications. The idea behind selecting the lower limit of IFG would be the identification of a threshold of FPG at which the risk of development of DM and complication or metabolic rises sharply. Data from Mauritius<sup>[28]</sup> and DECODE study<sup>[29]</sup> indicate that such a threshold of FPG does not exist for cardiovascular risk factors, all-cause mortality, or future DM. This criterion was based on

receiver operating characteristics (ROC) curve analyses of Pima Indian, Mauritius, San Antonio and Hoorn study data, which identified the baseline FPG levels, which maximised sensitivity and specificity for predicting DM over a 5-year period<sup>[25]</sup>. The ROC curve analyses indicated that a cut-point of 5.4-5.5 mmol/L gives the best combination of sensitivity and specificity for predicting future DM.

#### ADA criteria (2010) and WHO criteria (2011)

International Expert Committee (IEC 2009)<sup>[30]</sup>, ADA in 2010 and WHO in 2011 recommended a glycated hemoglobin (HbA1c) level of  $\geq 6.5\%$  as a diagnostic cut-off for DM (Table 1). HbA1c level reflects the average plasma glucose level over preceding three months. HbA1c is more convenient than glucose because it does not require fasting samples and is also not affected by recent changes in diet or activity. Another limitation of plasma glucose assay is lack of consistent accuracy of assay<sup>[31]</sup>. HbA1c has a greater analytic stability and less day-to-day variability in comparison to plasma glucose<sup>[32]</sup>. Selvin *et al*<sup>[33]</sup> evaluated the variabilities of glycemic measurement and found that 2-h PG levels [within-person coefficient of variation (CV), 16.7%; 95%CI: 15.0-18.3] and FPG (CV, 5.7%; 95%CI: 5.3-6.1) had substantially more variability compared with HbA1c (CV, 3.6%; 95%CI: 3.2-4.0) levels.

### HbA1c VS GLUCOSE CUTPOINTS FOR DIAGNOSIS OF DM

Lorenzo *et al*<sup>[34]</sup> compared 1999 WHO (2-h PG  $\geq 11.11$  mmol/L) and 2003 ADA criteria (FPG  $\geq 7$  mmol/L) with an HbA1c of  $\geq 6.5\%$ . It was found that sensitivity of HbA1c is poorer than plasma glucose because HbA1c diagnosed 5.2% of subjects as having diabetes compared to FPG (7.1%) and the 2-h PG (15.4%). Kramer *et al*<sup>[35]</sup> reported the sensitivity and specificity of HbA1c cutoff of 6.5% were 44% and 79% respectively based on the Rancho Bernardo Study. According to the ADA criteria, for this given HbA1c cut point of 6.5%, 85% of participants were classified as nondiabetic. Olson *et al*<sup>[36]</sup> compared HbA1c and standard OGTT for diagnosis of DM in three datasets from the prospective Screening for IGT study ( $n = 1581$ ), NHANES-III ( $n = 2014$ ), and NHANES 2005-2006 ( $n = 1111$ ) and reported that HbA1c criterion failed to recognize upto 70% of cases of DM. In conclusion, from above studies, HbA1c had the least sensitivity for diagnosis of DM in comparison to FPG and 2-h PG. Several studies have shown that HbA1c levels, as the plasma glucose levels, can predict the development of future DM<sup>[37,38]</sup>.

A limitation of HbA1c is that it is affected by red blood cell disorders<sup>[39]</sup>. Another limitation of HbA1c is that its levels depend on genetic factors<sup>[40,41]</sup>. It also suffers from analytic imprecision if methods other than high-performance liquid chromatography is used

for estimation and if such tests are not standardized. Measurement of HbA1c is currently well standardized with the adaptation of "national glycohemoglobin standardization program" protocols.

### OPTIMAL THRESHOLD OF THE HbA1c FOR RETINOPATHY

The most important question is how well HbA1c predicts retinopathy. IEC suggested a cutoff of the HbA1c of 6.5% for the diagnosis of DM because it was presumed that diabetic retinopathy sharply increased above this level. Unfortunately, most of the studies are cross-sectional and only a few prospective studies looked at the relationship between HbA1c and retinopathy (Table 2). Longitudinal prospective studies with subjects without DM and retinopathy at baseline will ideally give the association of HbA1c with retinopathy.

### CROSS-SECTIONAL STUDIES OF HbA1c FOR RETINOPATHY PREDICTION

Colagiuri *et al*<sup>[42]</sup> analysed the pooled data of nine studies and find that diabetes-specific retinopathy (after exclusion of mild retinopathy) was observed over the HbA1c range of 6.3% to 6.7% based on vignitile distribution and 6.4% by ROC analysis. He concluded that HbA1c  $\geq 6.5\%$  is a suitable alternative diagnostic criterion for DM. In the Australian Diabetes Obesity and Lifestyle study (AusDiab), retinopathy was assessed in 2182 participants aged  $\geq 25$  years. DM was not excluded in this study. The thresholds for increasing the prevalence of retinopathy was 6.1% for HbA1c<sup>[43]</sup>. Sabanayagam *et al*<sup>[44]</sup> examined the relationship of HbA1c to retinopathy in population-based sample of 3190 Malay adults aged 40-80 years in Singapore. HbA1c cut-off point of 6.6% detected mild retinopathy [87.0% sensitivity, 77.1% specificity and area under curve (AUC) 0.899] and 7.0% detected moderate retinopathy (82.9% sensitivity, 82.3% specificity and AUC 0.904). The prevalence of mild and moderate retinopathy was  $< 1\%$  below the optimal cut-off points. Xin *et al*<sup>[45]</sup> in Chinese population and Cho *et al*<sup>[46]</sup> in South Korean population found a threshold of 6.5% for detection of retinopathy. In ARIC study<sup>[47]</sup>, lower AUC was found (0.561 for any retinopathy, 0.543 for mild retinopathy and 0.658 for moderate) to severe retinopathy. These studies show that though there is an association between HbA1c and retinopathy, an optimal threshold could not be established.

### LONGITUDINAL STUDIES OF HbA1c FOR RETINOPATHY PREDICTION

Tsugawa *et al*<sup>[48]</sup> analyzed longitudinal data of 19897 Japanese adults who underwent a health checkup in 2006 and were followed up three years later. Logistic



**Table 2** Longitudinal studies assessing the glycated hemoglobin thresholds for retinopathy

Ref.	Study population characteristics	Assessment of retinopathy	Method of determining cutoff	Cut off
Tsugawa <i>et al</i> <sup>[48]</sup>	3 yr follow-up; number = 19987 Japanese subjects; age ≥ 21 yr; diabetes not excluded	Nonmydriatic 45° retinal photograph	Test for nonlinearity in multivariate logistic regression models with restricted cubic spline Multivariate logistic regression with categories of HbA1c as independent variable	Possible threshold at HbA1c levels between 6% and 7% 6.5%-6.9%
van Leiden <i>et al</i> <sup>[49]</sup> Hoorn study	7.9-11.0 yr follow-up; number = 233; age 50-74 yr; analyses in total study group and in subjects without diabetes	Ophthalmoscopy and fundus photography	Logistic model with categories of HbA1c (adjusted for age, sex, hypertension, glucose metabolism category)	No threshold found

HbA1c: Glycated hemoglobin.

regression analysis found that individuals with HbA1c levels of 6.5%-6.9% were at significantly higher risk of developing retinopathy at 3 years compared with those with HbA1c levels of 5.0%-5.4% [adjusted odds ratio, 2.35 (95%CI: 1.08-5.11)]. The incidence of retinopathy was determined in 233 individuals, aged 50 to 74 years, by ophthalmoscopy and fundus photography at baseline and after an average follow-up of 9.4 years in the Hoorn study<sup>[49]</sup>. Incidence of retinopathy was found to be significantly increased for HbA1c ranging between 5.8%-13.1% compared to HbA1c between 4.3%-5.2% but no optimal threshold of HbA1c was determined as the number of subjects in the study was not adequate.

Thresholds of HbA1c for retinopathy differ widely in the studies because of several reasons. First, different statistical methods were used in different studies. For example, in AusDiab study<sup>[43]</sup>, the cutoff was 6.1% by visual inspection, but cutoff was changed when change-point models were used. Without any adjustment, a threshold of 5.2% was calculated by using a change point model. After adjustment for age, sex and systolic blood pressure, the threshold for HbA1c was observed at 5.6% (95%CI: 3.9-6.2,  $P = 0.092$ ) and after further adjustment for diabetes duration, the threshold rose to 6.0% (3.9-7.0,  $P = 0.064$ ). Study on Pima Indians, Egyptians and in DETECT-2 study, cutoff of HbA1c were determined without any adjustment. Second, the threshold of HbA1c depends widely on the definition of retinopathy. Mild retinopathy is not specific for DM as it has been documented in non diabetic individuals too. Thresholds of HbA1c for mild, moderate and severe retinopathy can differ. For example, in Malay population thresholds of HbA1c were 6.6% and 7.0% respectively for mild and moderate retinopathy<sup>[44]</sup>. Also, the criteria for grading of retinopathy was different in different studies.

Third, the distributions of HbA1c may not be the same for different ethnicities. For example, Tsugawa *et al*<sup>[48]</sup> in cross-sectional study examined the relationships between a HbA1c level and the prevalence of retinopathy in black and white United States adults. Two thousand eight hundred and four white persons and 1008 black persons above 40 years of age were included in the study. After adjustment for age, sex,

hypertension, body mass index (BMI), family history of DM, and use of antidiabetes medications or insulin, the lowest HbA1c category for which the prevalence of retinopathy was significantly higher than the reference category (< 5.5%) was 6.0% to 6.4% for white persons (risk difference, 4.8% 95%CI: 0.5%-9.1%) and 5.5% to 5.9% for black persons (risk difference, 5.3%CI: 1.0%-9.5%). It was noted that the prevalence of retinopathy was higher at a lower HbA1c level in black Americans when compared white Americans. However, Bower *et al*<sup>[50]</sup> did not find any ethnic differences in the relationship of HbA1c with retinopathy in non-Hispanic white, non-Hispanic black and Hispanic American participants aged ≥ 40 years from the 2005-2008 NHANES. Finally, differences in threshold of HbA1c might be due to lack of standardization of HbA1c measurements, especially in older studies.

## HbA1c AND MACROVASCULAR COMPLICATIONS

Chronic hyperglycemia is a risk factor for adverse cardiovascular outcomes and mortality. A meta-analysis of 26 prospective studies assessed the association between HbA1c and major cardiovascular outcomes including all-cause mortality, incident cardiovascular diseases (CVD), CVD mortality, incident stroke and peripheral arterial disease. Only studies that followed up patients for more than 5 years were included. It was found that for every 1% increase in HbA1c, there was a 15% increase in hazard of all-cause mortality, 25% increase in CVD mortality, 17% in CVD, 17% in fatal coronary heart diseases and 29% increase in peripheral vascular diseases<sup>[51]</sup>. A positive dose response relationship was also noticed between HbA1c and the outcome measures and HbA1c was independent risk factor for adverse cardiovascular outcomes. Similar findings were noted in another meta-analysis by Selvin *et al*<sup>[52]</sup>.

## PREDIABETES AND RISK OF COMPLICATIONS

The association of complications is not restricted to

glucose levels above the diabetic threshold. It is a continuum, which continues in IGT and IFG range. Indeed, complications have also been documented in normal population, although of diminished magnitude. Various studies have looked into the paradigm of prediabetes forecasting the risks of micro and macrovascular complications of diabetes.

## PREDIABETES AND RISK OF DIABETIC RETINOPATHY

The occurrence of microvascular complications associated with established DM is well known. However, such complications of dysglycemia have also been noted in patients who currently fall within the spectrum of prediabetes. The Diabetes Prevention Programme followed up individuals known to have prediabetes and analysed a subset of them for development of diabetic retinopathy. Eight percent of patients had evidence of retinopathy as defined as Early Treatment Diabetic Retinopathy Study (ETDRS) level 20<sup>[53]</sup>. One percent of the study population noted to have mild/moderate diabetic retinopathy as defined by ETDRS level 35-43. The Blue mountains eye study, a population-based survey of common eye diseases conducted in Australia, screened 3275 participants without DM for retinopathy lesions using six field fundus photographs. Microaneurysms were seen in 6.8% of nondiabetic population<sup>[54]</sup>. These studies defined retinopathy based on the presence or absence of microaneurysms, and it is to be noted that they are not specific for diabetic retinopathy and may occur in patients with systemic hypertension. In some studies, they have been shown to be related to atherosclerosis and carotid disease.

A population-based cross sectional survey of prevalence of DM, risk factors and associated conditions was done in the AusDiab study<sup>[55]</sup>. All participants detected to have DM and prediabetes and few with normal glucose tolerance (as defined by WHO 1999 criteria) were screened for retinopathy. Fundus photographs included two fields per eye, namely the macula and nasal to disc were graded according to Wisconsin criteria. The prevalence of diabetic retinopathy was 6.7% (95%CI: 5.3%-8.4%) in patients with prediabetes<sup>[56]</sup>. The prevalence of retinopathy was 5.8% in the population with normal glucose tolerance (95%CI: 3.7%-8.5%)<sup>[57]</sup>.

The Gutenberg health study, is a prospective population-based observational study conducted in a single centre in Germany that initially included 15010 individuals with the aim of studying ocular, cardiovascular, psychosomatic and immune disorders. A sub-cohort of 5000 individuals were analyzed to study the prevalence of retinopathy in those diagnosed to have prediabetes as defined by HbA1c value ranging from 5.7%-6.4% and its association with cardiovascular risk factors. Twenty two percent of participants were diagnosed to have prediabetes based on the HbA1c criteria. Eighty three percent of those with prediabetes were assessed for evidence of retinopathy by 3-field fundus photograph,

and 8.2% were found to have diabetic retinopathy. None of the participants had evidence of proliferative diabetic retinopathy. Though there was no statistically significant difference in the prevalence of cardiovascular risk factors between those with and without retinopathy, the number of participants with retinopathy was too small to draw any conclusion<sup>[58]</sup>.

## DIABETIC RETINOPATHY CHANGES IN NORMOGLYCEMIA

However, the retinal vascular changes seen in diabetic patients, termed isolated retinopathy signs, are often seen in individuals without DM or hypertension. The prevalence of these signs has been documented to range between 2.6%-8.6% in individuals without DM or hypertension. Such isolated retinopathy signs are often transient and on follow-up of these individuals, 40%-70% of such signs may resolve spontaneously<sup>[59,60]</sup>.

The Beaver Dam Eye study was a cross-sectional population-based study that investigated the association between retinopathy lesions and hypertension among non-diabetic individuals. Among the 4926 persons examined, 7.8% had evidence of retinopathy, and there was a significant association with systemic hypertension<sup>[61]</sup>. Similar prevalence was also seen in the Blue Mountains eye study where 3654 individuals from Sydney, Australia were screened for retinopathy using six field fundus photography. Retinal hemorrhages and microaneurysms were noted in 9.9% of individuals, and a significant positive relationship was noted between retinopathy and hypertension. However, DM was defined based on the FPG level > 7.8 mmol/L alone which could have resulted in mislabeling a significant proportion of individuals with DM as non-diabetics according to the current definitions<sup>[54]</sup>.

A follow-up of this cohort, where 2335 persons were re-examined reported a cumulative 5 year incidence of retinopathy as 9.7% and no significant association was found between incident retinopathy and blood glucose level or hypertension. The lack of a demonstrable association with hypertension could have resulted from inadequate power of the study. Among those with retinopathy at baseline, 3.5% had developed DM during the intervening five year period, and the retinopathy lesions had regressed or remained unchanged in 72.3%<sup>[59]</sup>. The ARIC study had reported the three-year incidence of retinopathy in non-diabetic subjects as 2.9% and also showed an association between retinopathy and hypertension and fasting blood glucose levels. Forty-three percent of any retinopathy signs seen among patients at baseline had regressed at the end of three years. This was found to be related to lower levels of cardiovascular risk factors<sup>[60]</sup>.

Whether these changes of retinopathy signify an increased risk of progression to DM is debatable. Most studies have shown no such association. However, retinopathy was predictive of incident DM in persons with a positive family history of DM during the follow-

up of the ARIC cohort. The incidence of DM was 10.4% among those with a family history of DM compared to 4.8% among those without a positive family history after a follow up of 3 years<sup>[62]</sup>. Similarly, the Beaver Dam study assessed the 15-year cumulative incidence of DM and hypertension among those with evidence of any retinopathy at baseline and found a significant association between incident DM and retinopathy among those < 65 years of age (24.3% vs 11.1%)<sup>[63]</sup>.

## PREDIABETES AND RISK OF NEPHROPATHY

The prevalence of nephropathy is increased in individuals diagnosed to have prediabetes compared to normal individuals. The NHANES data analysis revealed the prevalence of chronic kidney disease (CKD) (as defined by glomerular filtration rate (GFR) using "modification of diet in renal diseases" equation) in newly detected prediabetes to be 17.1% compared to 11.8% in those without DM and 24.2% in newly detected DM, after adjustment for age, gender and race. However, the diagnosis of prediabetes was based on measurement of FPG alone which could have underestimated the prevalence of prediabetes in the study. The other important risk factor for CKD, namely hypertension was documented based on self-reporting by study participants which could have again biased the results of the study. Nevertheless, the prevalence of CKD increased across the spectrum of dysglycemia<sup>[64]</sup>.

Few studies have shown that early kidney injury characterized by hyperfiltration is seen in those with prediabetes. Among the 1560 individuals included in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) study, it was seen that individuals with IFG had evidence of hyperfiltration (defined as GFR > 90<sup>th</sup> percentile determined by Iohexol method and adjusted for age, weight, height and use of renin-angiotensin inhibitors) when compared to those with normal glucose<sup>[65]</sup>. Similar results were obtained in the Huaian Diabetes Prevention program from China, where 5431 subjects were included to analyze the association between HbA1c level and renal hyperfiltration. The study had reported a positive correlation between HbA1c level and hyperfiltration independent of other parameters like age, sex, hypertension, BMI and lipid profile. The odds of hyperfiltration was 2.34 times higher in persons with HbA1c level of 6.21%-6.49% compared to those with A1c < 5.7%<sup>[66]</sup>. This indicates that chronic hyperglycemia is associated with hyperfiltration in addition to the acute effect of hyperglycemia that has been even in healthy subjects<sup>[67]</sup>.

Microalbuminuria, another marker of kidney injury, has also been found to be associated with prediabetic state. A study from New Zealand determined the prevalence of microalbuminuria and its association with other risk factors like ethnicity, glycemic status, hypertension, obesity and life style factors. Individuals with IGT had a higher prevalence of microalbuminuria

when compared to those with normal glycemic status (16.1% vs 4.0%) and glycemic status was found to be the most important determining factor of microalbuminuria in multivariate regression analysis<sup>[68]</sup>. However, contrary to the results of the above-mentioned studies, a study from Korea did not find any significant association between microalbuminuria and prediabetes. Forty-five percent of participants were diagnosed to have prediabetes based on ADA criteria for FPG and HbA1c in the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V). Though the prevalence of microalbuminuria was higher in the prediabetic group when compared to the normal group (6.3% vs 3.6%), this difference was not seen following the adjustment for hypertension<sup>[69]</sup>.

## PREDIABETES AND RISK OF NEUROPATHY

Nerve conduction study conducted in 58 subjects from India with prediabetes as defined by the WHO criteria detected evidence of neuropathy in 32.8% of subjects which was evaluated by quantitative sensory testing (QST) and autonomic function tests. Autonomic neuropathy was evident in 8% of individuals, and QST was abnormal in 27.6% of subjects<sup>[70]</sup>.

## PREDIABETES AND RISK OF CARDIOVASCULAR DISEASES

Both IGT and IFG are associated with an increased risk of developing adverse cardiac events. A few studies have shown that patients with IGT have a greater risk when compared to patients with IFG. The risk also seems comparable to those with DM. Individuals with prediabetes were shown to have evidence of subclinical arteriosclerosis as measured by cardio-ankle vascular index (CAVI) in a recent study from Japan. CAVI is a sensitive indicator of arterial wall stiffness that is independent of blood pressure changes<sup>[71]</sup>. The odds of having high CAVI score among those with prediabetes was 1.29 (95%CI: 1.11-1.48) in men and 1.14 (95%CI: 1.01-1.28) for women compared to 2.41 (95%CI: 1.97-2.95) in men and 2.52 (95%CI: 1.94-3.28) for women with DM<sup>[72]</sup>.

Subclinical myocardial infarctions, defined as those unrecognized by the patient and the physicians are harbingers of major cardiovascular events in the future. The multi-ethnic study of atherosclerosis was instituted to study the prevalence and progression of subclinical cardiovascular disease in a population-based cohort from the United States<sup>[73]</sup>. In this cohort, the prevalence of unrecognized myocardial infarction detected based on electrocardiographic changes was found to be higher among those with IFG when compared to those with normal fasting glucose level (3.5% vs 1.4%) and this relationship persisted even after adjusting for other confounding risk factors<sup>[74]</sup>.

Increased risk of cardiovascular disease and all-cause mortality with abnormal glucose metabolism was documented in the AusDiab study after a median follow-up of 5.2 years. IFG was found to be an independent predictor of CVD mortality with a hazard ratio of 2.5 (95%CI: 1.2-5.1) after adjusting for other risk factors for CVD. However, IGT was not found to be associated with increased CVD mortality<sup>[75]</sup>.

A meta-analysis of studies evaluating the risk of coronary artery disease (CAD) associated with IFG as defined by the ADA and the WHO included 17 prospective studies. The risk of CAD was found to be increased in participants with IFG as defined by both criteria. The relative risk of CAD with IFG was 1.11 (95%CI: 1.02-1.21) using the ADA criteria and was 1.18 (95%CI: 1.10-1.28) when applying the WHO criteria. However, sub group analysis showed that the increased risk of CAD with IFG was not seen in studies that had excluded individuals with elevated 2-h plasma glucose. And further, the risk of CAD with IFG was not found to be significant when adjusted for other CAD risk factors<sup>[76]</sup>. A similar meta-analysis of studies analyzing the risk of stroke with prediabetes, an increased risk was seen in those studies which had defined prediabetes according to the WHO criteria (FPG 6.11-6.94 mmol/L). The risk was found to be increased in those with IGT and those with both IGT and IFG<sup>[77]</sup>.

## CONCLUSION

Current diagnostic criteria for DM or intermediate hyperglycemia is based on threshold of FPG, 2-h PG and HbA1c for diabetic complications, especially retinopathy. Controversies in diagnostic criteria are due to differences in inclusion criteria, different ethnic populations being studied, background prevalence of DM, definition of retinopathy used and statistical methods utilized. Therefore, there is a need to adopt uniform methodologies in studies across the globe to get universally comparable and interpretable results. Possibly, large longitudinal prospective studies involving subjects from different ethnicities, without diabetes and retinopathy at baseline will ideally help to identify the threshold of glycemic measurements (FPG, 2 h-PG and HbA1c) for future development of diabetes and its complications. Definition of retinopathy especially related to diabetes must be standardized universally. Further research is needed to understand better the pathophysiology of IFG and IGT. It is not well understood whether IFG and IGT are distinct metabolic abnormalities or they are parts of continuum. The factors predicting the development of future diabetes and its complications from IGT and IFG is also not well understood. This risk might be better assessed by the use of prediction scores which are weighted according to the glycemic measurements, other risk factors, and clinical features including complications. Finally, the extent to which future DM and its complications, especially cardiovascular diseases can be prevented

by adoption of modification of thresholds are not yet known.

New data from properly designed studies may help in revision of diagnostic criteria in future.

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