

Prediabetes: Prevalence, Screening, Risk factors, and interventions: A review

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Abstract

Prediabetes (intermediate hyperglycaemia) is a high-risk state for diabetes that is defined by glycaemic variables that are higher than normal, but lower than diabetes thresholds. 5-10% of people per year with prediabetes will progress to diabetes, with the same proportion converting back to normoglycaemia. Prevalence of prediabetes is increasing worldwide and experts have projected that more than 470 million people will have prediabetes by 2030. Observational evidence shows associations between prediabetes and early forms of nephropathy, chronic kidney disease, small fibre neuropathy, diabetic retinopathy, and increased risk of macrovascular disease. Tabak A.G. (2012). Multifactorial risk scores using non-invasive measures and blood-based metabolic traits, in addition to glycaemic values, could optimise estimation of diabetes risk. For prediabetic individuals, lifestyle modification is the cornerstone of diabetes prevention, with evidence of a 40-70% relative-risk reduction.

Keywords: Prediabetes, ADA, CDC, Risk score, Screening, Prevalence, Risk factors Intervention.

Introduction

Prediabetes is a condition of elevated blood glucose, including impaired fasting glucose and impaired glucose tolerance (IGT), that often precedes the onset of type 2 diabetes (T2D). ADA (2016). Although asymptomatic, prediabetes is an independent risk factor for cardiovascular disease and if untreated is likely to progress to T2D within 5 years of onset. Schup. (2016). Prediabetes is a term used to describe the states of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Prediabetes is indicated by higher-than-normal blood glucose levels which suggest a high risk for progression to diabetes mellitus. Cynthia et al (2017). The number of diabetics worldwide in 1995 was 135 million people and is predicted to be 300 million people in 2025 prediabetes is a high-risk state for developing diabetes and associated complications Seidel et al (2008).

The term prediabetes has been criticised because many people with prediabetes do not progress to diabetes, and it might imply that no intervention is necessary because no disease is present. Furthermore, diabetes risk does not necessarily differ between people with prediabetes and those with a combination of other diabetes risk factors indeed, WHO use the term intermediate hyperglycaemia and an international expert committee convened by the ADA prefers the "high-risk state of developing diabetes" to prediabetes. WHO, IDF (2009)

Prevalence of Prediabetes

India has a high prevalence of diabetes mellitus and the numbers are increasing at an alarming rate. The prevalence of diabetes for all age-groups Worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030 Sarahwild, et al (2004). The total of people with diabetes is projected to rise from 171million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The prevalence of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) were 8.3% Tamilnadu, 12.8%

Maharashtra, 8.15% Jharkhand and 14.6% Chandigarh. Anjana et al (2011).

Definition for Prediabetes

Prediabetes, in which blood glucose concentrations are higher than normal but not meeting the absolute definition of diabetes, represent a high-risk state for diabetes development. According to World Health Organization(WHO), individual at risk have one or both prediabetic conditions: impaired fasting glucose (IFG), definition as a fasting plasma glucose (FPG) concentrations ≥ 6.1 (110mg/dl) and < 7.0 mmol/l (126mg/dl), and/or impaired glucose tolerance (IGT), define by a FPG concentration < 6.1 mmol/l(110mg/dl) and a 2 hrs post-load plasma glucose concentrations between ≥ 7.8 (140mg/dl) and < 11.1 mmol/l (199mg/dl) measured during a 75g oral glucose tolerance test (OGTT).WHO(2006). The American Diabetes Association (ADA) applies the same post-load threshold values for IGT, but uses a lower cutoff value for IFG with a IFG with a FPG 5.6-6.9 mmol/l (100-125mg/dl. Furthermore, the ADA recommends that a glycated hemoglobin A1c (HbA1c) between 5.7 and 6.4% as other measures for diagnosing prediabetes.

Prediabetes was defined as individuals with IFG or both. Impaired fasting (IFG) was defined as a fasting CBG ≥ 6.1 mmol/l (≥ 110 mg/dl) and < 7.0 mmol/l (< 126 mg/dl) and a 2 hrs post-glucose value < 8.9 mmol/l (< 160 mg/dl). Impaired glucose tolerance (IGT) was defined as a 2 hrs post glucose CBG ≥ 8.9 mmol/l (≥ 160 mg/dl) but < 12.2 mmol/l (< 220 mg/dl) and a fasting value < 7 mmol/l (< 126 mg/dl). Expert Committee report (1997). More recently the term 'prediabetes' or intermediate 'hyperglycaemia' has evolved irrespective of terminology, all are defined by parameters that are higher than normal physiology but lower than the threshold limits set of diagnosis of T2DM.

Screening and diagnostic criteria for prediabetes Guidelines for Screening

Numerous national and interventional health care organizations promote evidence based screening for Diabetes and prediabetes for adults and children those who are at risk and asymptomatic. It was noted that only 46 % of asymptomatic adults with risk factors for prediabetes receive screening for the condition. National diabetes statistical report (2014). Although many guidelines recommend laboratory screening only for those who at risk for prediabetes. According to American Diabetes Association ADA recommends screening for all adults at age 45 and younger adults who are overweight or obese with 1 additional risk factor. ADA (2016). Hence it is advisable that screen at risk adults for every 3 yrs and individual monitoring once in a year for people with prediabetes increasing hyperglycaemia & multiple risk factors. AACE (2015).

Screening Methods

FPG, 2hrs Plasma glucose after a 75g oral glucose Tolerance test, and hemoglobin A1C are all appropriate for screening for prediabetes. ADA (2016). The fasting test is the lower cost most widely available screening

Table 1A: Diagnostic Criteria for IFG & IGT By Various Organization diabetes.co.uk (The global diabetes community)

Normal	Pre - Diabetes	Diabetes
FPG: <5.5	FPG: 5.2 -7.0	FPG: >7.0
OGTT: <7.8	OGTT: 7.8 -11.1	OGTT: >11.1
HbA1c: ≤6.0%	HbA1c: 6.0 -6.4 %	HbA1c: >6.4 %

Table 1B: Diagnostic criteria for pre diabetes according to WHO and ADA

WHO	ADA
FPG	FPG
110-125mg/dl	100-125 mg/dl
6.1-6.9mmol/L	5.6-6.9 mmol/L
2hrs OGTT Glucose	2hrs OGTT Glucose
140-198mg/dl	140-198 mg/dl
7.8-11.0 mmol/L	7.8-11.0 mmol/L
HbA1c	HbA1c
5.7-6.4 %	5.7-6.4 %

method. NIDDK (2014). It was predicted that FPG indicates a single point blood glucose level which requires 8-hours fast. And it does not assess long term glycaemic load. 2hrs PG referred as oral glucose tolerance test is more expensive while comparing to FPG & HbA1c. and it is an early marker of IGT. Short term life style changes stress, illness and some medications affect the results. HbA1c reflects long term glycaemic load and the results are not affected by short term factors such as stress and illness. The test requires no fasting and is most convenient method for patients. The test is expensive. NIDDK (2014).

To our knowledge, there are different scores from centres for disease control and prevention CDC, Poltavskiy et al (2016). American Diabetes Association ADA, Indian Diabetic Risk score Saleem et al (2017). That had been developed to help screening DM as well as prediabetes. BMI is a good predictor of prediabetes in indian adults says Pandey (2017).

Diagnostic Criteria

There are different diagnosing criteria for prediabetes which is seen in Table –1A, Table – 1B, Table 1C.

Any abnormality must be repeated and confirmed on a separate day. The diagnosis of diabetes can also be made based on unequivocal symptoms and a random glucose >200mg/dl (American Diabetes Association. Diabetes Care. 2014;37 Suppl1: S81- 90).

Table 1C: Diagnostic criteria for pre diabetes

Venous plasma glucose				
International Panel	Fasting (mmol/L)	2 h post load/OGTT* (mmol/L)	Classification/ Subcategory	HbA _{1c} % (mmol/mol)
WHO, 1965		7.1-8.2		-
WHO, 1980	<8.0	= 8.0 and <11		-
WHO, 1985	<7.8	= 7.8 and <11.1		-
WHO, 1999 and 2006 (most recent)	<7.0 = 6.1 and <7.0	= 7.8 and <11.1 <7.8 (if measured*)	IGT IFG	-
ADA, 1997	<7.0	= 7.8 and <11.1	IGT	-
	6.1-6.9	N/A	IFG	
ADA, 2003	<7.0	7.8-11.0	IGT	-

		(if measured*)		
	5.6-6.9 †	N/A	IFG	
ADA, 2010 (most recent)	<7.0	7.8-11.0	IGT	5.7-6.4 (39-47)
	5.6-6.9 †	N/A	IFG	

(www.the lancet.com vol.379 Jun 16,2012).

Cutaneous marker of skin

Due to Insulin resistance there is a chance of acanthosis nigricans and skin tag among pre diabetes. Skin lesions include increased skin tags and a condition called acanthosis nigricans – a darkening and thickening of the skin especially in fold areas such as the neckline and axilla. This condition is directly related to the insulin resistance, though the exact mechanism is not known. Acanthosis nigricans is a cosmetic condition strongly associated with insulin resistance in which there is darkening of the skin in areas where there are increases such as the neck and arm pits. Skin tags: Skin tags are also seen with increased frequency in patients with insulin resistance. A skin tag is a common, benign condition which consists of a bit of skin that projects from the surrounding skin and may appear attached to the skin. Skin tags can vary quite a bit in appearance. They may be smooth or irregular, flesh coloured or more deeply pigmented and either (Joseph 2000)

Risk factors associated with prediabetes Family History

Veera et al (2012) carried out a study on prediabetes in young adults at Visakhapatnam and confirms that if one of the parents is having diabetes mellitus and the offspring is suffering with hypertriglyceridemia, central adiposity and hypercholesterolemia definitely leads to prediabetes and type 2 diabetes.

IDF, (2006) carried out a population based study in Chennai to analyse co-segregation of obesity with familial aggregation of type 2 diabetes mellitus. This study involved a total of 2463 subjects (M:F 1196:1267) with normal glucose tolerance (NGT). They observed that a positive family history of obesity were significantly higher in families with a positive family history (group 2) vs. families with no family history (group 1). They concluded that general and central obesity are associated with a family history of diabetes.

Abbas ali et al.,(2008) conducted a study to find the association between familial risk of type 2 diabetes mellitus (T2DM) and the prevalence of metabolic syndrome (MS) in 448(>30 years) (257 males and 191 females) adult Asian Indians. Familial risk of T2DM was classified into three groups viz., 1=both parents affected; 2=parent and/or siblings affected and 3=none or no family history for T2DM. Family history of T2DM had significant effect on individuals with MS as compared to their counterparts (individuals having no family history of T2DM). It therefore seems reasonable to argue that family history of T2DM could be useful as a predictive tool for early diagnosis and prevention of MS in Asian Indian population.

Obesity

One of the study reveals that increase in body weight causes insulin resistance so this may lead to the condition of prediabetes. The consumption of junk food having high content of saturated fatty acids may lead to the overweight and cause insulin resistance. Veera et al (2012). There is a link between higher degree of obesity. And prediabetes postulates sequence for progression from prediabetes to diabetes, the beneficial effects of change in diet, an increase in exercise and securing a weight loss need to be the primary measures for early intervention in this condition. Philips (1994).

Body Mass Index and waist circumference

In recent decades, men and women around the globe have gained weight, largely due to changes in dietary patterns and decreased physical activity levels. Sarahwild (2004). Excess adiposity reflected by higher body mass index (BMI) is the strongest risk factor for diabetes, and Asians tend to develop diabetes at a much lower BMI than those of European ancestry. Bullard (2013). The risk of diabetes rises as excessive body fat increases, starting from the lower end of a healthful BMI or waist circumference. WHO (2009). A meta-analysis of prospective cohort studies suggests that the risk associated with a higher waist circumference is slightly stronger than the risk associated with a higher BMI. The expert Committee (1997). In clinical practice, it is important to monitor both BMI and waist circumference. Weight gain since young adulthood is another independent predictor of diabetes risk even after adjusting for current BMI.

Recent study said that B.M.I. & WC are easy to use tools that can be applied for screening of prediabetes in adolescents

Physical Activity

Hannaon (2014) observed the glucose intolerance representing a spectrum of abnormalities including impaired fasting glucose, impaired glucose tolerance and type 2 diabetes. This global epidemic of diabetes is largely driven by the globalisation of western culture and lifestyles. It is estimated that more than 90% cases of type 2 diabetes could be prevented with the adoption of a prudent diet (high in cereal fibre and polyunsaturated fatty acids and low in trans fatty acids and glycaemic load), avoidance of overweight and obesity (BMI<25 kg/m²), engagement in moderate to vigorous physical activity for at least 0.5 hour per day, non smoking and moderate alcohol consumption.

A study conducted on Japanese adults to investigate the association between daily physical activity and metabolic risk factors mng prediabetes and found daily physical activity is beneficially associated with WC, Triglycerides and

insulin resistance in individuals with prediabetes and hence light intensity daily physical activity is important in the management of Prediabetes & type 2 dm. Hamasaki et al (2011).

Hypertension

Kivity et al (2012) conducted a prospective cohort study in 1152 white male medical students to evaluate elevated Blood Pressure as a long term predictor of type 2 diabetes with a median follow up period of 38 years. After adjustment for BMI and other risk factors for diabetes, SBP and DBP at age 30 years remained significantly higher in individuals who developed diabetes than in their nondiabetic counterparts; however, the difference in the rate of increase in SBP was no longer significant following multivariate adjustment. They concluded that BP elevations precede the development of type 2 diabetes in middle age by 20–25 years. Higher BP in the prediabetic state might contribute to the presence of vascular disease at the time of diagnosis of type 2 diabetes.

Khambalia et al (2011) conducted a study in 1871 women aged 35–68 years to examine waist circumference as a risk factor for having hypertension only, impaired fasting glucose only, or both, and assess whether the associations vary according to overweight status. Each cm increase in waist circumference increased the odds of hypertension by 5% for non overweight women and 3% for overweight women; impaired fasting glucose by 9 and 3% for non-overweight and overweight women, respectively; and hypertension and impaired fasting glucose by 17% among non-overweight versus 9% for overweight women. They concluded waist

circumference was significantly associated with impaired fasting glucose and both hypertension and impaired fasting glucose, and the associations vary by overweight status.

Cardiovascular risk

A search in PubMed database using cardiovascular risk assessment in prediabetes for the articles published shows that A meta analysis confirms that holistic interventions including diet, exercise and pharmacotherapy successfully delayed or prevented the progression of prediabetes to DM. Ezekial et al (2013). while a systemic review affirmed that prediabetes increases the risk for cardiovascular disease. **NDS (2014)** These Reports show ever increasing evidence of CVD risk in prediabetes

Kivity et al., (2012) conducted a study in 10,913 men and women to assess whether normoglycemic fasting plasma glucose (FPG) is associated with increased risk of CVD outcomes in healthy patients. A total of 1119 incident cases of CVD occurred during a mean follow-up of 4.3 years. Subjects with fasting glucose levels in the high normal range (95–99 mg/dl) had an increased CVD risk when compared with levels <80 mg/dl. A multivariate model, adjusted for age, serum triglycerides, and high-density lipoprotein and low-density lipoprotein cholesterol levels, revealed an independent increased risk of CVD with

rising FPG levels in the normal range. They concluded that elevated CVD risk is strongly and independently associated with glucose levels within the normoglycemic range. Fasting plasma glucose may help in identifying apparently healthy persons with early metabolic abnormalities who are at increased risk for CVD before progression to prediabetes and overt diabetes mellitus.

Smoking and Alcohol

Kowall et al., (2010) conducted a 7 year study in 1223 subjects aged 55–74 years at baseline in 1999–2001 to evaluate the effect of passive and active smoking. They found that among never smokers, subjects exposed to ETS (Environmental Tobacco Smoke) had an increased diabetes risk in the total sample and in a subgroup of subjects having prediabetes at baseline. Active smoking also had a statistically significant effect on diabetes incidence and in prediabetic subjects. This study provides us evidence that both passive and active smoking is associated with T2DM.

Cullmann et al., (2012) had, done a study to investigate the influence of alcohol consumption and specific alcoholic beverages on the risk of developing prediabetes and type 2 diabetes. Subjects, who at baseline had normal glucose tolerance (2070 men and 3058 women) or prediabetes (70 men and 41 women), aged 35–56 years, were evaluated in this cohort study. Total alcohol consumption and binge drinking increased the risk of prediabetes and Type 2 diabetes in men, while low consumption decreased diabetes risk in women. Men showed higher risk of prediabetes with high beer consumption and of type 2 diabetes with high consumption of spirits. Women showed a reduced risk of prediabetes with high wine intake and of type 2 diabetes with medium intake of both wine and spirits whereas high consumption of spirits increased the prediabetes risk. They concluded that high alcohol consumption increases the risk of abnormal glucose regulation in men. In women the associations are more complex: decreased risk with low or medium intake and increased risk with high alcohol intake.

Lifestyle Interventions

Lifestyle intervention involving calorie-restriction and exercise to promote weight-loss, as demonstrated in the Diabetes Prevention Program, significantly reduced conversion to diabetes among high risk patients with impaired glucose tolerance by 58%. **NDS-(2014)**. The beneficial effect of lifestyle modification was documented in various populations including multiethnic American, Finnish, Lindstrom et al (2003) Chinese, and Indian. Pandey et al (2017).

Diabetes is inextricably linked with heart disease, and a healthful diet is a key behavioral target for these serious public health problems. Numerous public and private agencies have adopted health promotion and nutrition education programs to foster healthy eating behaviors.

Numerous studies have shown the importance of lifestyle changes in the prevention of Type 2 Diabetes including weight reduction and exercise programmes.

The Diabetes Prevention Programme outcomes study revealed that intensive lifestyle modification was able to reduce the progression to type 2 diabetes by over 50 %. Hannon et al (2014).

The Da Qing Study showed that combination of both diet and exercise resulted in 42 % reduction. Lig., X., Hu.. (1997).

Pharmacotherapy

Evidence of potential benefits from pharmacotherapy is accumulating. The biguanides are a class of drug that include metformin, used for decades to treat diabetes. Metformin has beneficial effects on BMI and lipid concentrations and has been proven to be safe by trial evidence showing no serious adverse effects (only minor gastrointestinal side-effects were detected). Veera et al (2012)

It reduces fasting glucose mainly through its effect on hepatic glucose output. According to trial evidence in people with IGT, metformin lowers risk of type 2 diabetes by 45%. Its effect was similar to lifestyle. The beneficial effect of metformin was greater in prediabetic people with a higher baseline BMI and higher FPG than in their leaner counterparts with lower FPG concentrations. Gastrointestinal side-effects of the drug were mostly mild to moderate, so the intervention seemed to be safe.

α -glucosidase inhibitors reduce the rate of polysaccharide digestion from the proximal small intestine. They mainly lower postprandial glucose without causing hypoglycaemia. Since their effect on HbA1c is smaller than that of other oral antidiabetic agents, they are seldom used in the treatment of type 2 diabetes. Bergman. (2012).

Conclusion

Pre diabetes is a serious and often overlooked disease that increases the risk for T2DM and cardiovascular events. Identification and screening of individuals at risk will increase the diagnosis of pre diabetes and facilitate early intervention to prevent disease progression and complications. Health care providers in any practice setting should assess for pre diabetes / diabetes risk in patients presenting for any reason and order laboratory screening for those meeting screening criteria.

Preventive interventions are appropriate for any patient with risk factors for pre diabetes / diabetes with life style modification as the cornerstone of treatment. Intensive lifestyle modification programs are highly effective but not always accessible and health care providers should incorporate preventive interventions as a routine component of primary care.

The evolving epidemic of diabetes represents a critical public health challenge in most developed and many developing countries. Patients with pre diabetes can be easily identified with simple to use widely available clinical measures such patients are at high risk for developing type 2 diabetes and CVD and should be targeted for intensive prevention efforts.

Lifestyle interventions emphasizing modest weight loss and increase in physical activity are appropriate for most patients with IFG and IGT and are safe and effective. Pharmacological intervention can be considered for people at particular risk for developing diabetes.

Abbreviations

IGT-Impaired glucose tolerance, T2D- Type 2 Diabetes, IFG- Impaired fasting glucose, WHO-World Health Organization, ADA-American Diabetes Association, CBG-Capillary Blood glucose, FPG-Fasting Plasma Glucose, OGTT-Oral Glucose Tolerance Test, US-United States, CDC-Centres for Disease Control, DM-Diabetes Mellitus, NGT-Normal Glucose Tolerance, WC-Waist circumference, BMI-Body Mass Index, SBP-Systolic Blood Pressure, DBP-Diastolic Blood Pressure, CVD-Cardiovascular Disease, ETS-Environmental Tobacco Smoke

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