

Prevalence, Risk Factors and Prevention of Prediabetes: A Review

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Abstract: *Prediabetes is a state where the blood sugar levels are higher than normal but lower than the threshold of diabetes. Prediabetes is associated cluster of metabolic changes like dysglycemia, dyslipidemia, hypertension, obesity, insulin resistance, and oxidative stress placing prediabetics at an increased risk of developing diabetes, Various studies are in progress for preventing, controlling, and reversing prediabetes. This article reviews the prevalence, risk factors, and interventions for the prevention of prediabetes and also suggests more research on novel foods for reversing prediabetes.*

Keywords: Impaired glucose tolerance: Impaired Fasting Glucose: Insulin resistance: lifestyle intervention: Prediabetes. Novel foods

1. Introduction

Diabetes is a rapidly growing metabolic disorder globally. According to World Health Organization, about 422 million people have diabetes and the majority of them live in low - income and middle - income countries (1). India is a fast - developing country and so is its diabetic population. Prediabetes is a state of prolonged hyperglycemia that may progress to Type 2 Diabetes if not intervened.

1.1 Diagnosis

The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1 - 6.9mmol/L (110 to 125 mg/dl) and impaired glucose tolerance (IGT) defined as 2 h plasma glucose of 7.8 - 11.0 mmol/L (140 - 200mg/dl) after ingestion of 75g of oral glucose load or a combination of two based on a 2 h oral glucose tolerance test (OGTT).

The American Diabetes Association (ADA) on the other hand has the same cut - off value for IGT (140 - 200mg/dl) but has a lower cut - off value for IFG (100 - 125 mg/dl) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of Prediabetes (2).

Several studies have shown a poor correlation between IGT, IFG, HbA1c, and diagnosis of prediabetes or diabetes and indicate overlapping of groups having IGT and IFG with different pathophysiology.

HbA1c is substantially determined by genetic factors independent of blood glucose levels and may be an inaccurate tool to measure average blood sugar and they are of valid concern to diagnosis (3)

2. Prevalence

According to International Diabetes Federation comprehensive statistics of the present and future trends of prediabetes prevalence based on impaired glucose tolerance is as below. The worldwide prevalence of impaired glucose tolerance was estimated at 7.3% of adult population in 2017 and is predicted to increase to 8.3% by 2045.

There have been various reports of increasing incidences of prediabetes. According to an ICMR - INDIAB Population - based cross - sectional study, prevalence of diabetes and prediabetes in 15 states of India varied from 4.3% in Bihar to 10.0% in Punjab and was higher in urban areas than in rural areas and higher in mainland states than in the northeast.

Prevalence of prediabetes varied from 6.0% (5.1 - 6.8) in Mizoram to 14.7% (13.6 - 15.9) in Tripura and the prevalence of impaired fasting glucose was generally higher than the prevalence of impaired glucose tolerance and indicating that the prevalence of prediabetes is higher than the prevalence of Diabetes in India. (4)

According to " Incidence of Type 2 Diabetes Mellitus and Prediabetes in Kerala, India: Results from a 10 year prospective cohort study" A High incidence of prediabetes over diabetes is observed which shows an epidemic trend of Type 2 Diabetes in Kerala, India (5)

In a study conducted in Tamilnadu by Logaraj Muthunarayanaetal, it was observed that out of 544 participants over the age of 20 years among 30 villages in Tamilnadu, India, Theprevalence of prediabetes was 8.5% and diabetes was 10.1 % which is of high concern (6)

A cross - sectional study conducted in the West Tripura district of India revealed that there is a high prevalence of

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prediabetes than the national average in west Tripura, India (7)

According to a study conducted in Rural Maharashtra, India. Out of 306 surveyed subjects, 5.9%, 16.7% and 77.5% had diabetes, prediabetes, and euglycemia respectively. Where the prediabetes percentage is almost 3 times more than the diabetes population (8)

It is evident through various studies that the prevalence of prediabetes is rapidly increasing worldwide and that it requires appropriate interventions.

3. Risk factors associated with Prediabetes

3.1 Overweight/ Obesity

The present scenario with increased calorie intake and decreased energy expenditure leading to energy imbalance has resulted in obesity which is interrelated to Prediabetes and Diabetes. Excess body fat in overweight and obese individuals may have increased fat degradation resulting in the production of large free fatty acids and a low ability to utilize insulin - mediated glucose resulting in high blood glucose levels causing Insulin resistance. Various studies have also stated that increased waist circumference and increased waist - to - hip ratio are one of the causes of prediabetes and diabetes. (9, 10)

3.2 Dyslipidemia

Various studies have proved that high cholesterol levels and low HDL and VLDL levels are causes of increased blood sugars. According to "The role of lipids in pathogenesis and treatment of Type 2 diabetes and associated comorbidities" of BMB report (11) there is a direct correlation between the metabolism of glucose and lipids. An elevated concentration of triglycerides is also a risk factor for developing prediabetes. These abnormalities can be used as valid biomarkers for predicting prediabetes, several years before the onset of diabetes.

3.3 Hypertension

It is well known that high blood pressure is a direct risk factor for pre - diabetes and cardiovascular diseases. A Korean genome and epidemiology study states that hypertension is an independent risk factor for type 2 diabetes. (12) The latest study also suggests that Beta cell dysfunction and insulin resistance combined together lead to type 2 diabetes. (13). Thus, controlling hypertension becomes a key factor in reducing the risk of Type 2 diabetes.

3.4 Family history of diabetes (FHD)

Family history of diabetes plays a very important role in the onset of diabetes. a positive family history of diabetes increases the chances of prediabetes or diabetes two folds more.

As per a multicenter analysis from the German Center for Diabetes Research conducted by Robert Warner (14), a family history of diabetes is associated with a higher risk for

prediabetes. The result of the study stated that FHD was significantly associated with the risk for prediabetes (IFG and/or IGT, OR 1.40; 95% CI 1.27, 1.54). This association remained significant in multivariable logistic regression models including sex, age, and BMI (OR 1.26; 95% CI 1.14, 1.40). When different prediabetic outcomes were considered separately, the association was found for isolated IFG (OR 1.37; 95% CI 1.20, 1.57), isolated IGT (OR 1.25; 95% CI 1.07, 1.46) as well as for the combination IFG+IGT (OR 1.64; 95% CI 1.40, 1.93). After stratification on BMI, the association between FHD and prediabetes was seen only in non - obese individuals (BMI < 30 kg/m²).

3.5 Polycystic ovarian syndrome (PCOS)

Most women diagnosed with PCOS have insulin resistance which in turn may lead to prediabetes. A study conducted by Dzamal Ibricevic et al (2013) states that approximately 50 - 70% of all women with PCOS (polycystic ovarian syndrome) who participated in the study were found to have a lower or higher degree of insulin resistance, while insensitivity to insulin cells very likely contributed to hyperandrogenaemia which is responsible for the symptoms and signs of PCOS. Insulin resistance, PCOS, and prediabetes are linked clearly pointing out that PCOS is one of the major risk factors for prediabetes. (15)

3.6 Alcohol consumption.

Alcohol intake has a direct effect on blood sugar. When alcohol is consumed it increases hunger and makes one consume more calories, Alcohol leads to increased blood sugar then makes the blood sugars fall which makes one crave high carbohydrates and sugar.

This again increases calorie intake which increases blood sugar, increases body weight resulting in obesity which is also a risk factor for prediabetes and diabetes.

A study conducted by M Cullman et al (2012) on the Swedish population found that Total alcohol consumption and binge drinking increased the risk of pre - diabetes and Type 2 diabetes in men, while low consumption decreased diabetes risk in women (16) explaining the potential risk for prediabetes.

3.7 Smoking

Smoking impairs insulin action by reducing peripheral glucose uptake and leading to insulin resistance. A study conducted by P. Bornemizsa (17) noted an increase in blood sugars of both diabetic and nondiabetic populations after 30 minutes of inhalation of nicotine cigarettes clearly stating that smoking increases the chance of prediabetes.

3.8 Physical Activity

Being physically more active increases insulin sensitivity and helps maintain normal blood sugar levels, lack of physical activity is a known risk factor for developing prediabetes and diabetes. A study conducted in the United state of America stated that increased physical activity decreased fasting blood sugar in many adults. (18). Showing

that there is a strong relation between increased metabolism through physical activity and insulin resistance.

3.9 Gender

Multiple studies on gender and prediabetes report that there may also be gender differences in the manifestation of prediabetes. Impaired fasting glucose is noted more in males and impaired glucose tolerance is noted more in Females. According to a survey conducted by government of India, prevalence of diabetes in males was higher being 12% compared to females being 11.7%. Which indicates that men are more prone to diabetes than women in India. (19)

3.10 Age

Diabetes can occur at any age but the risk of the onset of prediabetes increases as age increases may be due to decreased insulin secretion. It is more often seen in middle age and old age.

According to American Diabetes Association (20), More than 25% of the U. S. population aged ≥ 65 years has diabetes, and the aging of the overall population is a significant driver of the diabetes epidemic. Although the burden of diabetes is often described in terms of its impact on working - age adults, diabetes in older adults is linked to higher mortality, reduced functional status, and increased risk of institutionalization.

3.11 Stress

Research has been going on to estimate a clear link between stress and diabetes since the 17th century. Stress initiates the release of several stress hormones, increasing blood sugar levels and the risk of developing diabetes. According to a review done on Stress - induced diabetes by Kapil Sharma et al (21)

Its indeed evident that prolonged stress and obesity create a vicious cycle that ultimately results in metabolic dysfunction. The development of insulin resistance is the result of this metabolic dysfunction. The hypothalamic - pituitary - adrenal (HPA) axis and the sympathoadrenal system significantly mediate the stress response. In order for the host to survive during periods of high stress, evolutionary preserved responses such as insulin resistance and stress hyperglycaemia are produced in all vertebrates, fishes, worms, and insects. The central and peripheral neurological systems, bone marrow, white and red blood cells, and the reticuloendothelial system are among the tissues that use glucose most extensively and are non-insulin - dependent cells. In animal models of haemorrhagic shock, the injection of a hypertonic glucose solution increased heart function, and blood pressure and enhanced survival.

By promoting angiogenesis and anti - apoptotic pathways, acute hyperglycaemia may prevent cell death following ischemia.

Both in vitro and in vivo research have demonstrated that cardiomyocytes exposed to an insulin-free media with high glucose concentrations are resistant to pathological insults

such as ischemia, hypoxia, and calcium overload, indicating that acute hyperglycaemia represents an innate defence mechanism. In addition to these stressful hyperglycaemia gives the immune system and brain a source of energy during stress, injury, and infection.

Stress - induced Hyperglycaemia may be beneficial at times of crisis but chronic stress leads to insulin resistance due to various factors including hyperglycaemia and leads to prediabetes and Type 2 diabetes in people with chronic stress.

Oxidative stress

Oxidative stress is the state is the imbalance between the production of free radicals and anti - oxidant defences leading to tissue damage. Recent studies reveal that the cellular reduction - oxidation (redox) leads to oxidative stress and subsequent onset of prediabetes and the development of diabetes and complication by regulating certain pathways involved in beta cell dysfunction and insulin resistance (22)

As stated in the Indian Journal of Physiology and Pharmacology, A study conducted by Arwa Abdel Raheem et al, The Hexose monophosphate (HMP) glycolysis pathway is shifted during Diabetes mellitus near glycolysis rather than the HMP pathway to yield energy where the amount of glucose enters the cell is low which causes oxidative stress hence oxidative stress markers can be a good early predictor of Diabetes Complications. (23)

Increased generation of reactive oxygen species (ROS) and oxidative stress occurs in mitochondria as a result of an overload of glucose and oxidative phosphorylation. Endoplasmic reticulum (ER) stress plays an important role in oxidative stress and there is a rigid connection between both organelles through Mitochondrial associated membranes which means that ROS generated in mitochondria promotes ER stress, hence a state of stress and mitochondrial dysfunction are the result of this vicious cycle. The implication of mitochondria in insulin release and exposure of pancreatic beta cells to hyperglycemia make them more vulnerable to oxidative stress and mitochondrial dysfunction. Thus, the interaction of both mechanisms is related to impaired glucose homeostasis and can cause diabetes - associated insulin resistance.

As it is evident that oxidative stress is a major risk factor for pre - diabetes, a new strategy of classic as well as new antioxidants should be used to prevent diabetes and treat diabetes.

3.12 Diet

In addition to the above factors diet also plays an important role as a potential risk factor for prediabetes. High intake of saturated fats increases the risk of impaired glucose regulation. (20) where a high intake of dietary fiber may reduce the risk factor. As a diet high in fat is a risk factor for cardiovascular disease, it is also a major risk factor for prediabetes. Both High - fat diets, as well as high sugar - sweetened beverages, are risk factors for prediabetes.

A meta - analysis study done on Association between sugar-sweetened beverages and type 2 diabetes by Meng Wang et al (2014) found that Sugar-sweetened beverage intake was associated with an increased risk of Type 2 Diabetes and the association was attenuated by adjustment for body mass index (24).

In fact, American Diabetes Association suggests restricting the consumption of refined, highly processed foods and those with added sugars.

4. Health problems associated with prediabetes

4.1 Diabetes

Prediabetes progresses to diabetes gradually over a period of time and worsening of insulin diabetes. Approximately 5 – 10% of prediabetic subjects progress to Diabetes annually (25). Once the stage of diabetes is reached, uncontrolled diabetes can lead to Microvascular complications like Neuropathy, Retinopathy, Nephropathy, and Macrovascular complications like Cardiovascular diseases, Peripheral Arterial Disease, and Stoke.

4.2 Neuropathy

Neuropathy is a common complication of diabetes occurring in more than half the patients with type 2 diabetes. A recent study showed the existence of small fiber neuropathy in Impaired glucose tolerance subjects who progressed to type 2 diabetes. (26)

4.3 Retinopathy

Retinopathy occurs in the prediabetes stage itself even before the onset of type 2 diabetes. A study conducted by Varo Kirthi et al in 2022 stated that the prevalence of retinopathy in prediabetes was 7.1%, this represented an excess prevalence compared to those with normoglycemia, Hyperglycaemia can cause retinal damage prior to the diagnosis of diabetes (27)

4.4 Nephropathy

Constant hyperglycaemia leads to slow renal injury and chronic kidney diseases, many studies have stated that the onset of nephropathy is early in prediabetics. A study conducted in 2019 by Julia Ines F Branda et al, stated that Diabetic Kidney disease occurs in the prediabetes stage itself, and even a mild glucose metabolism disturbance has a major impact on the prevalence of Nephropathy (28).

4.5 Macrovascular Complications

The prevalence of cardiovascular diseases and stroke is high among people with diabetes. A first systemic review done to synthesize global prevalence rates of Cardio Vascular Diseases, including stroke, Myocardial infarction, Angina, Heart failure, Atherosclerosis and Coronary Artery Diseases among people with Type 2 diabetes states that cardiovascular disease is a major cause of comorbidity and

death among patients with Type 2 diabetes with coronary artery diseases having the high prevalence (29).

4.6 Lifestyle interventions for the prevention of diabetes

A well - planned lifestyle intervention that includes physical activity of at least 150 - 175 minutes/week and Dietary energy restriction targeting ideal body weight has shown a reduction of 40%– 70% in the risk of developing type 2 diabetes in people with impaired glucose tolerance.

A randomized controlled trial study found that the intervention of yoga may be helpful to reduce oxidative stress in prediabetes and also beneficial in reducing Body Mass Index, Waist circumference, systolic blood pressure, and fasting glucose (30).

4.7 Pharmacological Interventions

Pharmacological interventions can be adopted when lifestyle interventions are incapable of controlling blood sugars depending on the individual's requirements and necessities.

5. Conclusion

Lifestyle interventions like a customized balanced diet and a structured physical activity regime. Yoga, Meditation, and breathing exercises can be included in one's lifestyle to prevent prediabetes.

Diabetes education is important for people to know about prediabetes, diabetes, and its complication and to adopt the required lifestyle modifications and prevent diabetes.

Well - researched novel foods can also be used to prevent or reverse prediabetes.

If lifestyle interventions are not efficient in getting glycaemic control, then pharmacological interventions can be initiated.

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