

Review article

Prediabetes, Cardiovascular Risk & Life Style Intervention

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Abstract

Prediabetes is an intermediate state of hyperglycemia with glycemic parameters above normal but below the diabetes threshold ,there is always presence of prediabetes before the onset of diabetes, it remains a state of high risk for developing diabetes with yearly conversion rate of 10%-15% .Pre-diabetes can be identified as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The IGT is detected by oral glucose tolerance testing. Both IFG and IGT are risk factors for type 2 diabetes, and risk is even greater when IFG and IGT occur together. The leading risk factor for type 2 diabetes is a condition called pre-diabetes. The prediabetes predisposition to type 2 diabetes makes it a potential risk factor for cardiovascular disease.

Observational evidence suggests Prediabetes is associated with dysglycemia, central obesity, inflammation and endothelial dysfunction, oxidative stress contributing towards the pathogenesis of cardiovascular diseases The preferred clinical approach to cardiovascular prevention is to treat all the risk factors . This article reviews the pathogenesis and diagnostic criteria for pre-diabetes and its relation to cardiovascular risk factors , and potential intervention strategies like physical activity, exercise and yoga which may alter cardiac autonomic functions & arterial stiffness leading to an effective management of prediabetes and reduce the CVD risk factors.

Key words: Impaired fasting glucose ,Impaired glucose tolerance, Diabetes, Lifestyle intervention, Prediabetes, Cardiovascular disease

Background:

Prediabetes is a condition defined as having blood glucose levels above normal but below the defined threshold of diabetes. It is considered to be an at risk state, with high chances of developing diabetes. While, prediabetes is commonly an asymptomatic condition, there is always presence of prediabetes before the onset of diabetes. This paper will reviews the pathogenesis and diagnostic criteria for pre-diabetes and its relation to cardiovascular risk factors , and potential intervention strategies. prediabetic patients have higher risk for cardiovascular diseases (CVDs) which

further increases the rate of mortality [1]. Reason for the rate of increase may be lack of observation, regular follow-up programmes and self awareness about the conditions of disease. Although, the disease manifestations start in the early stages of disease but before it gets established as a full blown condition is the pre-stage called prediabetes. Cardiovascular disease, the most common diabetes-related morbidity, is prevalent in the pre-diabetic state prior to the onset of overt type 2 diabetes [2].

What is Pre-Diabetes?

The World Health Organization (WHO) has defined prediabetes as a state of

intermediate hyperglycemia which is diagnosed with the help of two specific parameters

1. Impaired Fasting Glucose (IFG) also defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and Impaired Glucose Tolerance (IGT) defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load [3].

The American Diabetes Association (ADA), on the other hand has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has an additional Criterion of Hemoglobin A1c (HbA1c) with level of 5.7% to 6.4% for the Diagnosis of prediabetes[4].

Pathogenesis of glucose tolerance :

Prediabetes Precedes development of Type II Diabetes.

Prediabetes, is associated with increased plasma insulin concentration (hyperinsulinemia). This occurs as a compensatory response by the pancreatic beta cells for diminished sensitivity of target tissues to the metabolic effects of insulin, a

condition referred to as insulin resistance in prediabetes.

This is due to derangement of the glucostatic function of the liver, takes up glucose from the bloodstream and stores it as glycogen, but because the liver contains glucose 6-phosphatase it also discharges glucose into the bloodstream. Insulin facilitates glycogen synthesis and inhibits hepatic glucose output. When the plasma glucose is high, insulin secretion is normally increased and hepatic gluconeogenesis is decreased. Glucagon can contribute to hyperglycemia as it stimulates gluconeogenesis. The decrease in insulin sensitivity impairs carbohydrate utilization and storage, raising blood glucose and stimulating a compensatory increase in insulin secretion. Development of insulin resistance and impaired glucose metabolism is usually a gradual process, beginning with excess weight gain and obesity. Most of the insulin resistance appears to be caused by abnormalities of the insulin signalling pathways that link receptor activation with multiple cellular effects. [5-6].

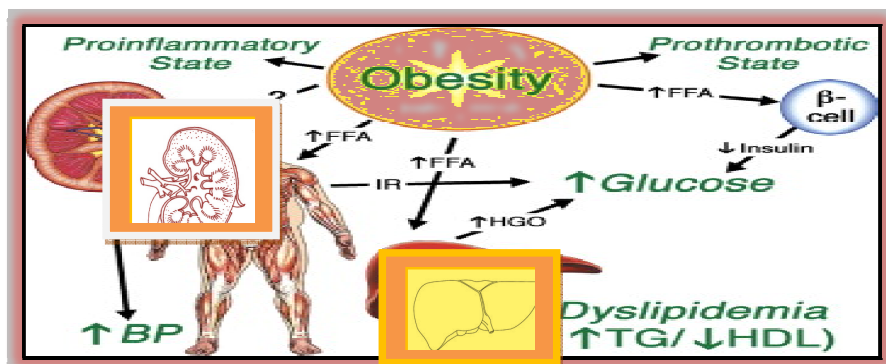


Image 1 : Pathogenesis of Prediabetes

Insulin resistance is part of a cascade of disorders that is often called the “metabolic syndrome” features of the metabolic syndrome include: (1) obesity (2) insulin resistance; (3) fasting hyperglycemia; (4) lipid abnormalities (5) hypertension. The major adverse consequence of the metabolic syndrome is cardiovascular disease, including atherosclerosis..

Factors Insulin Resistance in Prediabetes

- Obesity/overweight
- Excess growth hormone (acromegaly)
- Pregnancy, gestational diabetes
- Polycystic ovary disease
- Lipodystrophy
- Autoantibodies to the insulin receptor
- Mutations of insulin receptor
- Mutations of the peroxisome proliferators’ activator receptor g (PPARg)
- Mutations that cause genetic obesity

- Polycystic ovary disease

Development of Prediabetes During Prolonged Insulin Resistance

With prolonged insulin resistance, even the increased levels of insulin are not sufficient to maintain normal glucose regulation. As a result, moderate hyperglycemia occurs after ingestion of carbohydrates in the early stages of the disease. In the later stages of Prediabetes, the pancreatic beta cells become “exhausted” and are unable to produce enough insulin to prevent hyperglycemia, especially after the person ingests a carbohydrate-rich meal. In many instances, prediabetes can be effectively treated, at least in the early stages, with exercise, caloric restriction, and weight reduction, and no exogenous insulin administration is required.

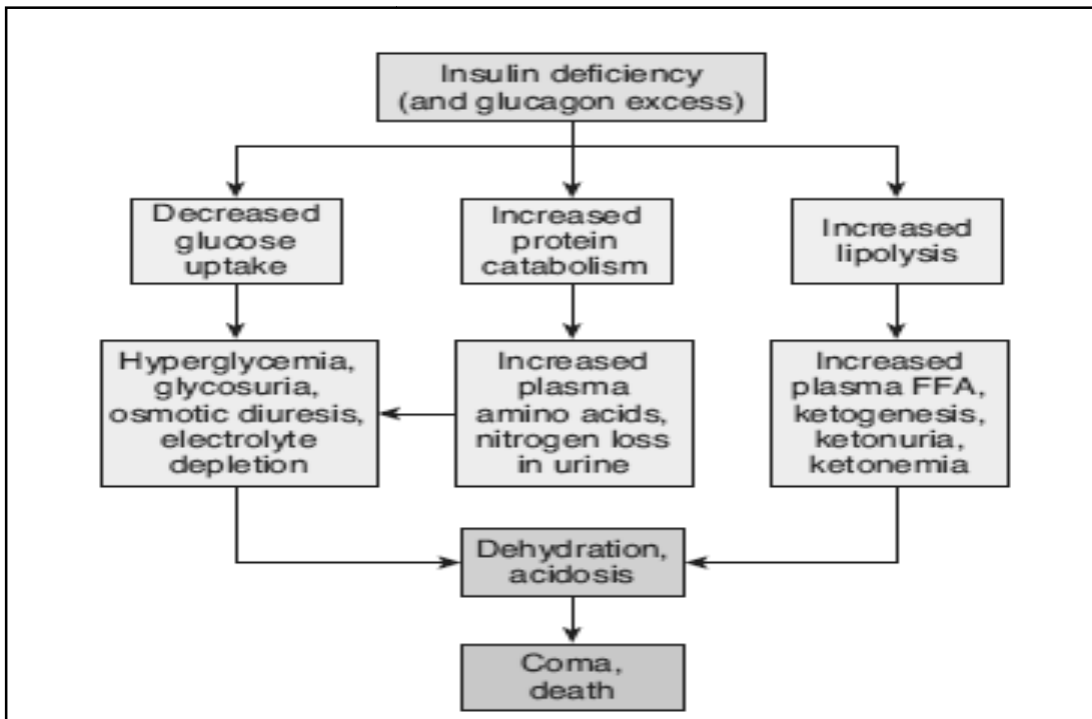


Image 2 : Consequences of Insulin deficiency

Cardiovascular Risks Associated With Prediabetes :

Insulin resistance associated with prediabetes is known to be an important risk factor for cardiovascular disease [7].

In addition to risk for diabetes and cardiovascular risk, prediabetes is associated with nephropathy, neuropathy and other vascular complications [8]

Large epidemiological studies have shown that subjects with nondiabetic hyperglycemia such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are at high risk for developing prediabetes and cardiovascular disease (CVD) which results in mortality [9].

Prediabetes and oxidative stress:

Prediabetes is associated with dysglycemia, central obesity, inflammation and endothelial dysfunction, oxidative stress contributing towards the pathogenesis of cardiovascular diseases [10]. Antioxidant markers like thiol/disulfide homeostasis, which have a critical role in many cellular activities such as antioxidant protection, detoxification, cell growth and apoptosis, may be associated with triglyceride levels in early preclinical atherosclerosis especially when fasting plasma glucose is raised [11-12]

A study by Agarwal et al intended to explore the risk of cardiovascular disease (CVD) related with prediabetes by assessing oxidative stress and inflammation using serum interleukin-6 (IL-6), myeloperoxidase (MPO) and urine microalbumin (MA) and their correlation with fasting plasma glucose (FPG) reported that Prediabetes group had significantly

increased IL-6, MPO and MA as compared to healthy controls [10].

A cross-sectional study by Al-Aubaidy et al included 127 participants attending the Diabetes Screening Clinic, reported that oxidative stress markers like Serum 8-hydroxy-2-deoxy-guanosine (8-OHdG) & triglycerides & Erythrocyte reduced glutathione (GSH) in the IFG group was increased compared to control [11].

A study by Ates et al have shown that thiol oxidation increases in prediabetic patients and there is a positive correlation between the oxidative stress marker like disulfide and blood glucose and HbA1c levels [12].

Atherosclerosis, Coronary Artery disease and Carotid intima-media thickness (CIMT) The association between blood glucose and carotid intima-media thickness (CIMT) seems to be plausible because both hyperglycaemia and CIMT predict cardiovascular outcomes CIMT is accepted as a marker of early atherosclerosis [13].

Endothelial dysfunction precedes the development of atherosclerosis and is believed to play a central role in its pathophysiology. Ludmer and colleagues first demonstrated impaired endothelial-dependent vasodilatation in the presence of atherosclerosis [14].

CIMT has therefore become a valuable research tool in clinical trials in the assessment of therapeutic agents directed against atherosclerosis. Thus, on account of these characteristics, CIMT has been used as an intermediate end point to assess the therapeutic efficacy of various interventions in a number of clinical studies in prediabetes [15].

CIMT is considered as a surrogate marker of cardiovascular disease, an independent risk factor, and a tool for early detection of atherosclerosis and also has the ability to determine the management strategy [16].

The easy accessibility of the carotid arteries, due to their superficial location and size, makes them most suitable for study [17]. B-mode ultrasound assessment of CIMT provides measurements of arterial wall abnormalities and thus a non-invasive assessment of the degree of atherosclerotic change

O' Leary et al highlights the value of the CIMT and the contribution it makes when added to known cardiovascular risk factor in prediabetics[18].

Veller et al compared intima-media thickness (IMT) to the presence of risk factors and the arterial ultrasound score (AUS), a measure of large scale qualitative changes in the vessel wall, a sensitive indicator of asymptomatic coronary artery disease and good predictor for the subsequent development of cardiovascular symptoms [19].

A descriptive, cross-sectional study included 110 prediabetic patients as case, 76 healthy subjects as control group. Measurement of CIMT was performed in the posterior wall of both carotid arteries by mode B ultrasound, Prediabetes group had significantly increased carotid intima media thickness as compared to healthy controls [20].

In recent years, CIMT has been shown as an independent predictor of CV risk and the presence of carotid plaque as a strong predictor of CV events and mortality [21].

Prediabetes and Cardiac autonomic function

The autonomic nervous system (ANS) plays an important role not only in physiological situations, but also in various pathological settings such as diabetic neuropathy, myocardial infarction (MI) and congestive heart failure (CHF). Autonomic imbalance associating increased sympathetic activity and reduced vagal tone has been strongly implicated in the pathophysiology of arrhythmogenesis and sudden cardiac death in prediabetics [22].

Prediabetes is found to be associated with dysfunction of cardiac autonomic activity, reflected by reduced heart rate variability, decreased parasympathetic modulation of the heart and increased prevalence of male erectile dysfunction in individuals with prediabetes [23-24]. Non-invasive evaluation of neural impairment in subjects with IGT has shown significantly greater abnormalities detected by four of five cardiovascular reflex tests, increase prevalence of both hyperesthesia and hypoesthesia, and increased heat detection thresholds [25].

There is also increasing evidence to demonstrate a higher frequency of idiopathic polyneuropathy, painful sensory neuropathy and small fiber neuropathy among prediabetic individuals with IGT. These findings suggest an involvement of the small unmyelinated nerve fibers that carry pain, temperature, and regulate autonomic function during prediabetes, prior to development of diabetes[26].

Heart Rate Variability-

Heart rate variability is a non-invasive electrocardiographic marker reflecting the

activity of the sympathetic and vagal components of the ANS on the sinus node of the heart. It expresses the variations of both instantaneous HR and RR intervals (intervals between QRS complexes of normal sinus depolarisations) [27].

Analysis of HRV consists of a series of measurements of successive RR interval variations of sinus origin which provide information about autonomic tone [28]. They may generally be performed on the basis of 24 hour Holter recordings or on shorter periods ranging from 0.5 to 5 minutes particularly in the field of dynamic electrocardiography [29].

In 1996 a Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) defined and established standards of measurement, physiological interpretation and clinical use of HRV. Time domain indices geometric measures and frequency domain indices constitute nowadays the standard clinically used parameters [30].

Treatment Modalities For Prediabetes

Life style intervention

Prediabetes is now recognized as a reversible condition that increases an individual's risk for development of diabetes. Lifestyle risk factors for prediabetes include overweight and physical inactivity. In view of people embracing sedentary life style, and the effectiveness of treatment becoming less, the role of regular exercise especially 'yoga' seems to be a beneficial and economical adjuvant in the management of the prediabetes. It seems to be the earliest and the most effective method for providing peace and tranquillity. It is

known that yoga induces physiological and biochemical changes in volunteers [31].

A recent review suggested that yoga may reduce the stress, improve metabolic profile, regulate autonomic nervous system and alter hypothalamopituitary adrenal axis which act as neural mediators of hyperglycemia [32].

In 2002, Knowler et al hypothesized that lifestyle intervention would prevent or delay the development of prediabetes. The researchers randomly assigned patients with prediabetes to receive a placebo or a lifestyle modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week. The average follow-up was 2.8 years. The lifestyle intervention reduced the incidence by 58% compared with placebo. Participants assigned to the lifestyle intervention had more weight loss and greater increase in physical activity than did participants in the placebo group [33].

The Finnish Diabetes Prevention Study published in 2003 evaluated the effects of a lifestyle intervention in diet and exercise behavior, and the effect of the intervention on glucose and lipid metabolism. In the study, 522 middle-aged, overweight subjects with impaired glucose tolerance were randomly assigned to receive either usual care or an intensive lifestyle intervention. The subjects in the intervention group received training sessions and advised to increase overall physical activity. The authors found that intensive lifestyle intervention produced long-term beneficial changes in diet, physical activity, and clinical and biochemical parameters and reduced diabetes risk. The incidence of

converting from prediabetes to diabetes was approximately 2% for subjects who lost at least 5% of their body weight vs about 8% for subjects who gained more than 2.5% of their body weight ($p < 0.002$) [34].

In 2012, Perreault et al reported that patients with prediabetes that did not progress to diabetes after they completed an intensive lifestyle intervention. They also discovered that reversion to normal glucose levels even transiently, was associated with a 56% reduced risk of future diabetes [35].

In 2013, Schellenberg et al compared the effectiveness of lifestyle interventions to standard care on minimizing progression of prediabetes to diabetes or reducing all-cause mortality in diabetes. This meta-analysis study identified 9 randomized, controlled trials with prediabetic patients who were at risk of diabetes and 11 randomized, controlled trials with patients who had diabetes. Seven of the 9 studies looking at patients who were at risk of diabetes reported that lifestyle interventions decreased the risk of diabetes up to 10 years after a lifestyle intervention [36].

In 2013, Shreelaxmi V. et al reported that Yoga intervention may be helpful in control of oxidative stress in prediabetes subjects. Yoga can also be beneficial in reduction in BMI, waist circumference, systolic blood pressure and fasting glucose. Effect of yoga on antioxidant parameters was not evident in this study. The findings of this study need to be confirmed in larger trials involving active control groups. [37]

In 2014, Jyotsna, V. P. yoga holds promise as an approach to reducing cardiometabolic risk factors and increasing exercise self-efficacy for this group, Indians with elevated

fasting blood glucose, that participation in an 8-week yoga intervention was feasible and resulted in greater weight loss and reduction in waist circumference when compared to a walking control. Yoga offers a promising lifestyle intervention for decreasing weight-related prediabetes and type 2 diabetes risk factors and potentially increasing psychological well-being [38]. In the 20-year follow-up of the Da Qing Diabetes Prevention Study, those receiving a lifestyle intervention had a 51% lower incidence of diabetes. Group-based lifestyle interventions over 6 years can prevent or delay progression of prediabetes to diabetes for up to 14 years after the active intervention [39].

Pharmacotherapy

Several groups of antidiabetic drugs such as Metformin, Biguanides, Thiazolidinediones, α -Glucosidase Inhibitors, GLP-1 analogies have been studied in context of prediabetes. Metformin was noted to be less effective than lifestyle intervention in the United States DPP trial but in the Indian DPP (IDPP) trial it was noted to be as effective as lifestyle intervention [39]. Metformin has been found to be more beneficial to individuals with higher BMI and higher FPG [40].

The glitazones are synthetic ligands for peroxisome proliferator-activated receptors- γ . They increase glucose uptake and utilization in the peripheral organs and decrease gluconeogenesis in the liver, thereby reducing insulin resistance [41].

GLP-1 analogs exploit the physiological effects of GLP-1, they have been shown to augment post prandial insulin secretion, suppress glucagon and hepatic glucose

production, slow gastric emptying, and reduce appetite [41].

Conclusion

Aim of this review was to describe the diagnosis and pathogenesis of prediabetes and life style modification like physical activity, exercise and yoga may altered cardiac autonomic functions & arterial stiffness lead to an effective management of prediabetes and reduce the CVD risk factors.

yoga intervention will show beneficial effect on glycemic parameters to enhances insulin receptor expression, sensitivity of the β -Cells of pancreas to glucose signal and also the improvement in insulin secretion causing increased glucose uptake and thus

reducing blood sugar, improvement in the lipid levels ,weight reduction and cardiac autonomic functions. Yoga is an ancient discipline designed to bring balance to the physical, mental, emotional, and spiritual dimensions of the individual However, this review article and Majority of published literature and guidelines support Lifestyle interventions focusing on dietary modification and increased physical activity like physical exercise, yoga should be the foundation of therapy for diabetes prevention in patients with prediabetes and early diagnosis of altered cardiac autonomic functions & arterial stiffness may lead to an effective management of prediabetes and reduce the cardio vascular risk factors.

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