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Prediabetes diagnosis and treatment: A review

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Abstract

Prediabetes is an intermediate state of hyperglycemia with glycemic parameters above normal but below the diabetes threshold. While, the diagnostic criteria of prediabetes are not uniform across various international professional organizations, it remains a state of high risk for developing diabetes with yearly conversion rate of 5%-10%. Observational evidence suggests as association between prediabetes and complications of diabetes such early nephropathy, small fiber neuropathy, early retinopathy and risk of macrovascular disease. Several studies have shown efficacy of lifestyle interventions with regards to diabetes prevention with a relative risk reduction of 40%-70% in adults with prediabetes. While there is increasing evidence to prove the efficacy of pharmacotherapy in prevention of diabetes in adults with prediabetes, pharmaceutical treatment options other than metformin are associated with adverse effects that limit their use for prediabetes. There are no reports of systematic evaluation of health outcomes related to prediabetes in children. The effects of pharmacotherapy of prediabetes on growth and pubertal development in children remains unknown. Secondary intervention with pharmacotherapy with metformin is advocated for high-risk individuals but criteria for such consideration benefit of early intervention, long term cost effectiveness of such interventions and the end point of therapy remain unclear. Pharmacotherapy must be used with caution in children with prediabetes. 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. The elevation of blood sugar is a continuum and hence prediabetes can not be considered an entirely benign condition. This aim of this review is to describe the challenges associated with diagnosis of prediabetes, the possible adverse medical outcomes associated with prediabetes and the treatment options and rationale for their use in context of prediabetes.

Key words: Impaired fasting glucose; Impaired glucose tolerance; Diabetes; Metformin; Lifestyle intervention; Prediabetes

Core tip: Prediabetes is a state of intermediate hyperglycemia. While there are several controversies about the diagnosis of prediabetes, it remains an at-risk state for development of diabetes. Several adverse health outcomes have been associated with prediabetes. This review provides a detailed description of the current literature regarding diagnosis, health consequences and treatment of prediabetes and also

provides an insight for clinical management.

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DIAGNOSIS OF PREDIABETES

Various organizations have defined prediabetes with criteria that are not uniform. 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 6.1-6.9 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 or a combination of the two based on a 2 h oral glucose tolerance test (OGTT)[1]. 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 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 poor correlation between HbA1c and IFG and IGT[3-5]. The usefulness of diagnosis of diabetes or prediabetes on basis of IFG and IGT have been challenged due to inability of these blood glucose cut points to capture pathology related to diabetes and probability of developing diabetes in future[6]. These cut-offs further loose their credibility due to poor reproducibility of these tests in adults and children[7,8]. Although, HbA1c is believed to represent an average blood sugar level and should ideally represent hyperglycemia more accurately, this may not be entirely true. HbA1c is substantially determined by genetic factors independent of blood glucose levels and may be an imprecise tool to measure average blood sugar[9,10]. While there are valid concerns about diagnostic criteria of prediabetes, prediabetes remains to have a lower reproducibility (approximately 50%) than diabetes (approximately 70%). Based on the available evidence, it appears that prediabetes defined by various alternative criterions consists of an overlapping group of individuals with one or more abnormalities in their glucose excursions. It is possible that presence of IFG and IGT identifies subjects with different pathological abnormalities in their glucose metabolism and presence of both of these signifies more advanced impairment in overall glucose homeostasis.

PREVALENCE OF PREDIABETES

There have been reports of increased mean FPG and prevalence of diabetes in developed as well as developing countries[11]. The Centers of Disease Control and Prevention National Diabetes Statistics Report suggested that 37% of United States adults older than 20 years and 51% of those older than 65 had prediabetes in 2009-2012 defined by fasting glucose or HbA1c levels[12]. When applied to the entire United States population in 2012, these estimates suggest that, there are nearly 86 million adults with prediabetes in United States alone[12]. The world wide prevalence of IGT in 2010 was estimated to be 343 million (7.8%) ranging from 5.8% in South East Asia to 11.4% in North American and Caribbean Countries of the nation's population[13]. International Diabetes Federation projects an increase in prevalence of prediabetes to 471 million globally by 2035[13].

HEATLH RISKS ASSOCIATED WITH PREDIABETES

Progression to diabetes

The conversion rate of individuals from prediabetes to diabetes changes with population characteristics and the criteria used to define prediabetes[14,15]. In a meta-analysis evaluating the progression of prediabetes to diabetes published in 2007, the annual incidence rate of diabetes was found to be 4%-6% for isolated IGT, for isolated IFG 6%-9% and for both IGT and IFG was 15%-19%[16]. This meta-analysis only consisted of studies published prior to 2004. In subsequently reported major studies, the annual incidence rates of conversation from prediabetes to diabetes were similar. In the Diabetes Prevention Program (DPP) Outcomes Study, the incidence of diabetes was noted to be 11% in the control group[17]. In the United States Multi-Ethnic Study of Atherosclerosis the annual incidence of diabetes in IFG group slightly above 4%[18]. In the The Toranomon Hospital Health Management Center Study the incidence of diabetes was reported as 7% in the group with an HbA1c 5.7%-6.4% and 9% in the IFG group[19]. In the China Da Qing Diabetes Prevention Study (CDQDPS), the cumulative incidence of diabetes over a 20 years period, was noted to be higher than 90% among subjects with IGT defined by repeated OGTT in the control group[20]. The use of ADA *vs* WHO criteria to define prediabetes has also been shown to affect the incidence rate of diabetes with lower incidence in individuals defined by ADA criteria compared to WHO criteria[21].

According to an expert panel, continuous rather than dichotomous risk scores are more useful for predicting the risk of developing diabetes[22]. A diabetes risk score based more easily accessible variable such as age, sex, ethnicity, fasting glucose, systolic blood pressure, HDL cholesterol, BMI and history of diabetes in parents or siblings has been shown to have better predictive value than either IFG or IGT[23].

Nephropathy and kidney disease

Several studies have shown an association of increased risk of chronic kidney disease and early nephropathy with

prediabetes[24-28]. The causal nature of this relationship remains unclear as this association may be due increased incidence of diabetes in this group or the presence of other factors associated with both hyperglycemia and nephropathy rather than the effect of prediabetes itself[29,30].

Neuropathies

Prediabetes is found to be associated with dysfunction of cardiac autonomic activity, reflected by reduced heart rate variability[31-35], decreased parasympathetic modulation of the heart[35] and increased prevalence of male erectile dysfunction in individuals with prediabetes[36]. 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[37]. There is also increasing evidence to demonstrate a higher frequency of idiopathic polyneuropathy, painful sensory neuropathy[38-43] and small fiber neuropathy[38,40,41] 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.

Retinopathy

Nearly 8 percent of participants with prediabetes in the DPP study were found to have evidence of diabetic retinopathy[44]. While prediabetes has been associated with an increased risk of diabetic retinopathy in some studies, these findings vary depending on the method used for detection[24,45-49].

Macrovascular disease

Prediabetes has been associated with increased risk of developing macrovascular disease but whether this elevated risk is due to prediabetes itself or due to development of diabetes remains unclear[50,51]. While cross sectional studies have shown an increased prevalence of coronary heart disease in individuals with prediabetes[52,53] but this relationship may be confounded by the common risk factors present between cardiovascular diseases and prediabetes.

TREATMENT OPTIONS FOR PREDIABETES

Lifestyle interventions

The encompassing theme of lifestyle intervention programs is to change the modifiable risk factors of prediabetes and diabetes by targeting obesity with increase in physical activity and dietary changes. The two largest diabetes prevention studies, the United States DPP and the Finnish Diabetes Prevention Study (DPS) have both shown beneficial effects of lifestyle interventions[54,55]. In the DPP study, after a 3 year follow-up, intensive lifestyle interventions (ILS) lead to a 58% risk reduction. The ILS involved changes in diet and physical activity aimed at producing weight. The biggest determinant of risk reduction was note to be weight loss. This study showed that for every 1 kg decrease in weight, the risk of developing diabetes in future was reduced by 16%[56]. In the DPS, the benefits were found to be dependent on achievement of the number of pre-defined goals of the intervention by the participant. These goals consisted of weight reduction greater than 5 percent, total fat intake less than 30 percent of energy intake, saturated-fat intake less than 10 percent of energy intake, fiber intake greater than or equal to 15 g per 1000 kcal , and exercise greater than 4 h/wk[55]. While both of these studies were largely among Caucasians, studies in Asian population have also shown similar benefits[57,58].

Pharmacotherapy

Several groups of antidiabetic drugs such as Biguanides, Thiazolidinediones, α-Glucosidase Inhibitors, GLP-1 analogies and non-antidiabetic drugs and therapies such as anti-obesity drugs, and bariatric surgery have been studied in context of prediabetes.

Metformin has been used for several decades for treatment of diabetes and has been noted to have additional favorable outcomes such as body mass index (BMI) reduction and improved cholesterol profile. The collective evidence of trials among subjects with IGT, suggests a 45% risk reduction for development of type 2 diabetes[59]. Metformin was noted to be less effective than lifestyle in the United States DPP trial but in the indian DPP (IDPP) trial it was noted to be as effective as lifestyle intervention[54,57]. Metformin has been found to be more beneficial to individuals with higher BMI and higher FPG[54]. Metformin has also been studied in obese children by several investigators. The collective evidence shows a slight benefit in BMI reduction over lifestyle interventions, while the benefit was statistically significant it was noted to be only short term with the greatest benefit at 6 mo and no difference at 12 mo duration[60].

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[61]. In the double blind placebo controlled Diabetes Reduction Assessment with Ramipril and rosiglitazone Medication study, rosiglitazone was found to be effective in decreasing incidence risk of diabetes by 60% over a 3 year period but was associated with significant side effects such as an additional average weight of 2.2 kg in intervention group compared to controls and a higher incidence of heart failure (0.5% *vs* 0.1%) and total cardiovascular events (2.9% *vs* 2.1%)[62,63]. Pioglitazone was found to decrease the risk of diabetes by > 70% in obese subjects with IGT in the ACT NOW study. Some of the added benefits were, decrease

in diastolic blood pressure, reduction in rate of carotid intima-media thickness and a greater increase in HDL cholesterol but it was associated with increased weight gain (approximately 3 kg more than placebo) and edema (13% *vs* 6% in controls)[64]. In the double blinded placebo controlled 3 years prospective IDPP-2 study, there was no difference in incidence of diabetes between subjects receiving lifestyle intervention and placebo and subjects receiving lifestyle intervention and pioglitazone[65]. In the more recent Canadian Normoglycemia Outcomes Evaluation trial, low does combination of rosiglitazone and metformin was tested against placebo to investigate whether low dose combination therapy would decrease the incidence of type 2 diabetes with a lower risk of adverse events. Incident diabetes occurred in significantly fewer individuals in the active treatment group (14%) than in the placebo group (39%). The relative risk reduction was 66% and the absolute risk reduction was 26%, and 80% subjects in the treatment group reverted to normoglycemia compared to 53% in the control group, but the subjects in active treatment group had increased reports of diarrhea (16% *vs* 6% in controls)[66]. Overall, there are safety concerns for thiazolidinedione such as weight gain, liver toxicity, increased cardiovascular risk and possible link with bladder cancer which have limited the use of these mediations for treatment of prediabetes.

α-glucosidase inhibitors such as acarbose and voglibose, prolong the overall carbohydrate digestion time, and reduce the rate of glucose absorption, thus decrease the postprandial rise in blood glucose[67]. In the STOP-NIDDM trial, acarbose was found to decrease the relative risk for diabetes by 25% among subjects with IGT during a 3.3 years of follow-up[68,69]. The medication was associated with several gastrointestinal side effects such as flatulence and diarrhea and 31% of the participants in the acarbose arm dropped out before completion of the study[68]. A Japanese trail found a 40% risk reduction in incidence of diabetes in high-risk individuals with IGT with voglibose over a 48 wk period. Voglibose was noted to have a similar side effect profile as acarbose but only 7% subjects discontinued the use of drug due to adverse effects[70].

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[71]. Exenatide and liraglutide have been demonstrated to have long term efficacy for sustained weight loss in obese subjects and reduce prevalence of prediabetes over a follow-up period of 1-2 years. The most common side effects with these drugs are nausea and vomiting and they remain injectable preparations[72-74].

Anti-obesity drugs Orlistat has also been studied in context of prediabetes. Orlistat is a gastrointestinal lipase inhibitor used for treatment of obesity that acts by inhibiting the absorption of dietary fats by approximately 30%. Research has shown that over a 1.5 year follow-up period, use of Orlistat in conjunction with low energy diet is associated with greater weight loss as compared to placebo (6.7 kg *vs* 3.8 kg) and a decrease in conversion rate from IGT to overt diabetes (7.6% *vs* 3.0%) in obese adults[75]. Similar finding have also been reported by the XENDOS trail regarding the efficacy of Orlistat with a 37% relative risk reduction in development of diabetes after 4 years of treatment[76].

Bariatric surgery

Bariatric surgery includes a variety of procedures aimed at either creating a mal-absorptive state, a restrictive state or a combination of the two to limit caloric intake. The procedures commonly used include Roux-en-Y gastric bypass, Laparoscopic adjustable gastric banding, Sleeve gastrectomy, and Duodenal switch with biliopancreatic diversion. In the Swedish Obese Subject, bariatric surgery was found to result in sustained weight loss (23.4% at 2 years and 16.1% at 10 years) and a 75% relative risk reduction of diabetes compared to controls[77]. Bariatric surgery was also associated with a lower 2 year and 10 year rate of development of type 2 diabetes, cardiovascular disease and reduced number of cardiovascular deaths in obese adults[77,78]. A previous study had demonstrated that after gastric bypass surgery, 78% subjects with previous diabetes and 98% subjects with IGT reverted to normoglycemia[79].

PROS AND CONS FOR TREATMENT OF PREDIABETES

The rationale behind treatment of prediabetes includes, prevention of development of diabetes, prevention of consequences of diabetes and prevention of the consequences of prediabetes itself. Several research studies have shown success of interventions designed for treatment of prediabetes with sustained reduction in incidence of diabetes[20,54,80-82]. The CDQDPS study, with lifestyle intervention and 20 year follow-up showed nearly 50% relative risk reduction in incidence of severe retinopathy, but there was no difference between the intervention and control groups in the risk of developing other microvascular complications, such as neuropathy and nephropathy[83]. The evidence regarding effects of interventions on macrovascular complications is inconsistent. The Malmo Preventive Project with a 12 year follow-up, showed reduce mortality in subjects with IGT after a long-term lifestyle intervention program, with emphasis on dietary counseling and physical activity, but this was not a randomized trial[84]. The Collective evidence of all randomized control trails among prediabetic subjects with lifestyle and drug based interventions in a recent meta-analysis showed that these interventions resulted in reduction in stroke risk but did not result in any risk reduction for all-cause mortality, cardiovascular death or myocardial infarction over a mean follow-up period of 3.8

years[80]. While, the current evidence suggests efficacy of several treatment modalities regarding prevention of progression to diabetes, the long term benefits on microvascular or macrovascular complications remains debatable. There is no evidence to suggest that early intervention is better than late intervention and long term studies looking at cost *vs* benefit and long terms of outcomes related to the point at which glycemic intervention should begin are lacking. Majority of published literature and guidelines support that lifestyle interventions focusing on dietary modification and increased physical activity should be the foundation of therapy for diabetes prevention in patients with prediabetes. Although, lifestyle interventions are safe and have proven efficacy in prevention of diabetes, these programs are not reimbursed by most health care insurance plans. There is increasing evidence to prove the efficacy of pharmacotherapy and support its use in adults with prediabetes. Due to the favorable long term safety profile and observed positive outcomes with metformin, organizations such as ADA have recommended the use of metformin in certain high risk individuals[85] but the end point of pharmacotherapy is yet to be defined. The concept of prediabetes or its treatment has not been systematically studied in children with prediabetes. Long term effect of common medications used for prediabetes on growth and pubertal development in children have not been studied. Moreover in children, due to puberty related insulin resistance, incidence of diabetes may be over all inflated. There is lack of evidence with regards to long term efficacy as well as safety for use of pharmacotherapy in children with prediabetes.

CONCLUSION

In conclusion, there remains a need of systematic evaluation of the health outcomes of prediabetes and benefits if any with its early treatment. It is very important to choose the right outcomes for such a study. Moreover, the criteria used to define prediabetes needs to be refined in accordance to the long term medical outcomes. While, these studies seem essential, the length of duration needed to study the adverse outcomes of prediabetes and low frequency of some of these outcomes may be a limiting factor for such studies. At present there is no concrete evidence to formulate clinical guidelines for treatment of prediabetes. Lifestyle interventions remain an essential part of management of prediabetes. The use of pharmacotherapy should be on an individual case based approach. When pharmacotherapy is used to treat prediabetes, such treatment plan should be initiated with predefined goals and end points by the physician. A cautious approach is warranted for used of pharmacotherapy in children and youth.

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