Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2803–2811

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Health risks and interventions in prediabetes: A review

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ARTICLE INFO

Article history:
Received 28 June 2019
Accepted 23 July 2019

Keywords:
Prediabetes
Risk factors
Complications
Interventions

ABSTRACT

Prediabetes is a condition which appears prior to the development of diabetes in which blood glucose is abnormally high but do not reach the diagnostic threshold of type 2 diabetes mellitus. It is characterized by a cluster of metabolic abnormalities viz. dysglycemia, dyslipidemia, hypertension, physical inactivity, obesity, insulin resistance, procoagulant state, endothelial dysfunction, oxidative stress and inflammation, placing prediabetic subjects to an increased risk for diabetes and its complications. Recent studies demonstrate that complications of diabetes i.e. microvascular and macrovascular complications may manifest in some prediabetic subjects. This article reviews prediabetes-related risk factors and health issues. In addition, this article also highlights the interventions to prevent the development of diabetes in prediabetic subjects.

1. Introduction

Diabetes, one of the world's major health care problems, is associated with an increase in morbidity and mortality and its prevalence is increasing day by day [1]. The greatest increase in the prevalence of diabetes mellitus is reported from low and middle-income countries [2]. The primary reason for this increasing prevalence of type 2 diabetes mellitus in low and middle-income countries is Asia paradox, referring to the rapid socio-economic and demographical changes in the Asian population towards that of a developed economy. This can be seen in its economic growth, urbanization, and nutritional transition [3,4]. According to the pathogenesis and natural history of diabetes, it has a prolonged prediabetic phase, which can exist undetected for many years [5,6]. Prediabetes is considered as borderline diabetes in which blood glucose is abnormally high but do not reach the diagnostic threshold of diabetes mellitus with either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or both IFG and IGT [7]. IFG subjects have high hepatic insulin resistance with almost normal values in skeletal muscle [7,8] and have impaired suppression of hepatic glucose production manifested by hyperglycemia at fast [9]. In contrast, the primary site of insulin resistance in IGT is the muscle with only modest changes in liver insulin sensitivity [7,8,10]. Individuals with IGT have impaired glucose uptake manifested by postprandial hyperglycemia [9]. β-cell dysfunction occurs in both IFG and IGT individuals. IFG people have severely impaired early insulin response during OGTT but their insulin secretion improves during the second phase of the OGTT. In contrast, IGT people present with impaired early and late phase insulin secretion [7,8,11]. The total body glucose disposal gradually worsens from NGT to IFG to IGT and type 2 diabetes mellitus [7]. The American Diabetes Association (ADA) establishes the following value ranges to identify individuals with prediabetes: fasting plasma glucose levels from 100 mg/dl to 125 mg/dl (5.6 mmol/L to 6.9 mmol/L) or 2 h plasma glucose value after 75 gm oral glucose during oral glucose tolerance test (OGTT) 140 mg/dl to 199 mg/dl (7.8 mmol/L to 11.0 mmol/L). Glycated hemoglobin (HbA1c) concentrations varying from 5.7% to 6.4% is further considered as an additional diagnostic criterion for prediabetes [12]. Prediabetes is characterized by a cluster of metabolic abnormalities viz. dysglycemia, dyslipidemia, hypertension, physical inactivity, obesity, insulin resistance, procoagulant state, endothelial dysfunction, oxidative stress and inflammation, placing prediabetic subjects to an increased risk for diabetes and its complications [9,13]. This article reviews the risk factors and health problems associated with prediabetes. In addition, this article also highlights the interventions to prevent the development of

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https://doi.org/10.1016/j.dsx.2019.07.041
1871-4021/

diabetes in prediabetic subjects.

2. Prevalence

In developed and developing countries, glycemic concentrations are increasing rapidly [14] and an increase in glycemia has resulted in an increase in prediabetes prevalence [7]. The prevalence of prediabetes differs across the countries depending on the parameters used for estimation [15]. The IGT population has reached around 352.1 million worldwide, representing 7.3% of the total adult population in 2017. The vast majority about 72.3% of these people live in low and middle-income countries. By 2045, it is estimated that the number of individuals with IGT will rise to 587 million accounting for about 8.3% of the adult population [16]. Fig. 1 shows the prevalence of impaired glucose tolerance (IGT) among different regions of the world for the year 2017 and 2045.

According to phase I report of Indian Council of Medical Research-India Diabetes (ICMR-INDIAB), the prevalence of prediabetes was 77.2 million in the year 2011 in India with 8.3% in Tamilnadu, 12.8% in Maharashtra, 8.1% in Jharkhand and 14.6% in Chandigarh [17]. Again, in 2017, Anjana and Colleagues aimed to estimate the national prevalence of prediabetes in 15 Indian states (Tamil Nadu, Chandigarh, Jharkhand, Maharashtra, Andhra Pradesh, Bihar, Gujarat, Karnataka, Punjab, Assam, Mizoram, Arunachal Pradesh, Tripura, Manipur and Meghalaya) and found that the overall prevalence of prediabetes was 10.3% in all the states. The prediabetes prevalence ranged from 6.0% in Mizoram to 14.7% in Tripura and the prevalence of impaired fasting glucose was usually higher than the prevalence of impaired glucose tolerance [18]. In England, in the year 2011, the prevalence of prediabetes was 35.5% based on HbA1c levels among the adult population [19]. In the year 2010, in Spain, the isolated IFG and isolated IGT were present in 3.4% and 2.9%, respectively, and combined IFG–IGT in 2.2% of the adult population [20] and in the USA, the prevalence was as high as 38% in 2012 using the ADA definition (HbA1c levels or IFG or IGT) [21]. Based on fasting glucose or HbA1c levels, the population-based U.S. National Health and Nutrition Examination Survey (NHANES) suggests that 35% of U.S. adults over 20 years of age and 50% of those over 65 had prediabetes in 2005–2008 [22]. The IFG and IGT prevalences differ between ethnic groups and in older people, both conditions are more common. In addition, IFG is more common among men than women, although the reason for this is not clearly known [23].

3. Pathophysiology of prediabetes

Prediabetes shares similar pathophysiologic mechanisms to that of type 2 diabetes mellitus and the most important factors that can explain the pathophysiology of prediabetes are increased insulin resistance, β-cell dysfunction, and decreased incretin response among others [24].

Prediabetes is associated with increased plasma insulin concentration, known as hyperinsulinemia [25]. This occurs because of insulin resistance, which is characterized by changes in different parts of the insulin signaling pathway, reduced concentration, phosphorylation and activity of insulin receptors (tyrosine kinase), decreased intracellular translocation of glucose transporter 4 (GLUT-4) and also reduced intracellular enzymes activity [26]. Insulin resistance is believed to play a significant role in determining glucose tolerance. Although both IFG and IGT are deemed to be the state of insulin resistance, the site of insulin resistance is distinct. The typical finding in IFG is elevated hepatic insulin resistance, with almost normal skeletal muscle sensitivity. IFG patients have moderate hepatic insulin resistance and impaired early (1–30 min) insulin response exocytosis of insulin from secretory vesicles docked to the membrane during the OGTT [27,28]. Due to the intact late-phase plasma insulin response and normal or near-normal muscle sensitivity, the 2-h plasma glucose returns to the initial FPG level. IGT subjects have moderate to severe insulin resistance in muscle with small changes in liver sensitivity and impaired early and late insulin (60–120 min) response (granule translocation and maturation) during OGTT [27–29]. The increase in insulin

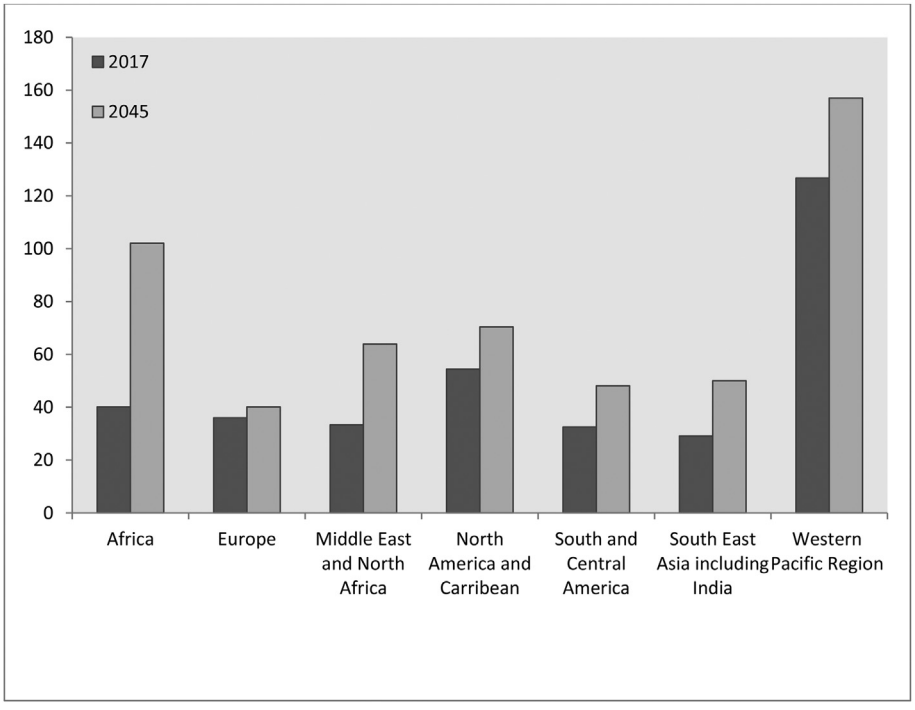

Fig. 1. The number of people with prediabetes (in millions) by region for the year 2017 and 2045 [16].

resistance in prediabetic subjects is followed by a number of metabolic abnormalities, including obesity, high blood pressure and dyslipidemia [26].

In prediabetes, β-cell dysfunction also occurs along with insulin resistance and deteriorates further with subsequent progression to type 2 diabetes mellitus [24]. The sensitivity of β-cell glucose is the ability of the pancreatic β-cell to quickly respond to changes in concentrations of glucose by increasing insulin secretion. As long as the β-cell secretes more insulin to overcome insulin resistance, the tolerance to glucose stays normal and as soon as the β-cell becomes dysfunctional, subjects progress from NGT to prediabetes and then to type 2 diabetes mellitus [30]. There occurs biphasic secretion of pancreatic insulin physiologically [31]. The pancreatic insulin secretion pattern also differs in IFG and IGT. The significance of the first phase of insulin secretion is the inhibition of endogenous hepatic glucose production in the postprandial period, which contributes to the maintenance of glucose concentrations at about 150–160 mg/dl within the first 60 min of the OGTT. The second phase of insulin secretion is responsible for the gradual decrease in blood glucose concentrations until values lower than 140 mg/dl to 120 mg/dl. Individuals with IFG alone show a reduction in the first phase of insulin secretion and a greater increase in glucose levels than normal individuals at 60 and 30 min. Compared to patients with IGT alone, the late response following glucose ingestion in OGTT is normal. Usually the later shows changes in both the first and late phases of secretion. Changes in the second phase (or late phase) of insulin secretion associated with muscle insulin resistance that occurs in IGT alone prevent glucose levels from declining after 60 min and remain elevated at 120 min during OGTT [26]. Previous studies have shown that the subjects with IGT have already lost substantial β-cell function [32,33]. In addition, insulin secretion to insulin resistance ratio (an index of β-cell dysfunction) was reduced in IGT [34] and hence predicts the development of type 2 diabetes mellitus among subjects with prediabetes.

Moreover, impairment in the incretin effect also plays a role in progressive β-cell dysfunction in type 2 diabetes mellitus [28]. The incretin effect is mediated by two different hormones i.e. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) and is believed to be responsible for 70–80% of total insulin release to the oral glucose load [24]. GLP-1 intestinal secretion was revealed to be attenuated after oral glucose ingestion in people with IGT compared with normal glucose tolerance subjects [35]. Similar findings were reported by Rask et al. [36] and Laakso et al. [37].

Other pathophysiological mechanisms that may play an important role in the development of prediabetes include adiposopathy, increased lipolysis, chronic low-grade inflammation and dysregulated hepatic glucose production (HGP) [24].

4. Risk factors associated with prediabetes

The risk factors of prediabetes are the same as for type 2 diabetes mellitus. However, not everyone with prediabetes goes on to develop type 2 diabetes. The risk factors that have been associated with prediabetes are described hereunder:

4.1. Over weight/obesity

In the current scenario, increased consumption of high-calorie food and decreased energy expenditure result in obesity which is interrelated to the risk of developing diabetes and prediabetes as well since prediabetes is the intermediate phase in the natural history of diabetes [38,39]. The excess body fat in overweight/obese people may result in increased fat degradation, which results in the production of large amounts of free fatty acids (FFAs). When the level of FFAs was higher in blood, the ability of liver tissue for insulin-mediated glucose uptake and utilization was lower, resulting in high blood glucose levels [40]. In other words, elevated blood FFAs are one of the major pathogenic causes of obesity caused by insulin resistance [41]. Larger waist circumference was a consistent predictor of prediabetes and insulin resistance with large waist circumference increasing the likelihood of prediabetes by nearly two folds [42]. In a study conducted by Agarwal et al. (2016), BMI and WHR, which are predictors of general and central obesity respectively were found to be elevated in prediabetes [13]. Asians (especially Indians) have been shown to have increased intra-abdominal fat and thicker truncal skin folds which are strongly associated with glucose intolerance [43]. A study by Sahai et al. (2011) in Madhya Pradesh revealed a strong association of anthropometric parameters such as increased BMI and waist to hip ratio with impaired fasting glucose. This research also revealed that the higher waist to hip ratio is the best predictor for prediabetes [44]. Similarly, in Tamilnadu, Balagopal et al. (2008) showed a significant association of higher BMI with IFG [45]. The Chennai Urban Population Study has reported a significant association of abdominal obesity with diabetes risk in prediabetes subjects [46].

4.2. Dyslipidemia

Dyslipidemia, which is characterized by a spectrum of quantitative and qualitative changes in lipids and lipoproteins, increases the risk for prediabetes. A common pattern of lipid abnormalities includes hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C) concentration and a shift towards small dense low-density lipoprotein (LDL) and these can be detected in insulin-resistant prediabetic people several years before the clinical diagnosis of type 2 diabetes [47,48]. An elevated concentration of triglyceride which is a risk factor for developing prediabetes is likely because it could increase the fat deposition in muscle, liver and pancreas and it could damage the function of mitochondria and induce oxidative stress, which in turn could cause insulin resistance and also lead to impaired islet β-cell function [49,50].

4.3. Hypertension

Hypertension was found to be a risk factor of prediabetes [50]. One possible mechanism is that in the circulatory system of patients with hypertension, angiotensin II activity is enhanced. Angiotensin II activates the renin-angiotensin-aldosterone system (RAAS) and affects the function of the pancreatic islets, resulting in islet fibrosis and decreased insulin synthesis and eventually leading to insulin resistance [50,51]. Hypertension can also trigger insulin resistance by altering the delivery of insulin and glucose to skeletal muscle, leading to impairment in the uptake of glucose [52].

Hypertension was the strongest predictor of prediabetes in research undertaken by Nwatu et al. (2016), as they reported a higher prevalence of prediabetes in the community of hypertension [53]. In another study conducted by Ishikawa et al. (2009) reported 51.2% of subjects with prehypertension in prediabetes [54].

4.4. Family history of diabetes (FHD)

Family history of diabetes is a significant risk factor for prediabetes. A positive family history of type 2 diabetes mellitus nearly doubles the risk of diabetes in the offspring. Individuals with FHD are at increased risk of prediabetes since FHD is associated with all characteristic features of diabetes pathophysiology [55]. In people with a family history of diabetes, prediabetes occurs 73.4% more frequently than those without family history [56]. A significant association between pre-diabetes and a positive family history of

diabetes was noted by Iloh et al. (2013). This genetic contribution may be due to the involvement of multiple genes [57]. However, the study showed that a family history of type 2 diabetes was associated with reduced insulin sensitivity and an impaired balance between insulin sensitivity and insulin secretion [58].

Wagner et al. (2013) conducted a meta-analysis of four German studies and found that FHD is associated with a 40% increased risk of having prediabetes [55]. The previous study from Sweden also found a 50% increased risk of prediabetes in subjects with a positive family history of diabetes mellitus [59]. In Karnataka, Zaman et al. (2011) reported 42.42% of prediabetic subjects with FHD. In patients with IGT, this study showed a considerably greater proportion of FHD than the normoglycemic subjects [43]. Veera et al. (2012) carried out a study on prediabetes in young adults at Visakhapatnam and confirmed that if one of the parents has diabetes mellitus and the offspring has hypertriglyceridemia, central adiposity and hypercholesterolemia certainly leads to prediabetes and type 2 diabetes mellitus [60].

4.5. Polycystic ovarian syndrome (PCOS)

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy during the reproductive years, affecting 5–10% of women and women with PCOS are at greater risk of developing glucose intolerance [61]. This may be due to intrinsic insulin receptor defects and post-receptor defects that lead to hyperinsulinemia. Chronic hyperinsulinemia leads to β-cell fatigue and increases the risk of prediabetes [62]. Approximately 30–40% of PCOS women have prediabetes [61]. A study conducted by Velija-Asimi et al. (2016) showed that increased incidence of prediabetes in women with PCOS [63].

4.6. Alcohol consumption

Several studies have shown that alcohol consumption in males, and excess consumption in particular, is associated with the appearance of prediabetes and type 2 diabetes, whereas alcohol consumption in women has a protective effect on the appearance of these issues [64,65]. Alcohol consumption was found as a modifiable risk factor for prediabetes in men in a study conducted by Diaz-Redondo [66].

4.7. Smoking

Smoking is strongly linked to prediabetes [67]. Cigarette smoking has been shown to be able to impair insulin action primarily by reducing peripheral glucose uptake and leading insulin resistance. In addition, smoking is well known to be associated with chronic inflammation, a predictor of the transition from normal glucose tolerance to prediabetes [68,69]. In a population-based cohort in Southern Germany, Kowall et al., conducted a study to assess the impact of passive and active smoking. They found that participants exposed to environmental tobacco smoke (ETS) had an increased diabetes risk in the total sample and in a subgroup of subjects having prediabetes at baseline among never smokers and provides evidence that both passive and active smoking is linked with type 2 diabetes mellitus [70].

4.8. Physical inactivity

One of the documented risk factors for dysglycemia is physical inactivity is. Inadequate physical activity was found to have a significant association with prediabetes. This could be related to the reports that physical inactivity leads to a decrease in insulin effectiveness and poor utilization of glucose and fats in the body cells [57].

4.9. Gender

Various studies reported that there may also be gender differences in the manifestations of prediabetes. Impaired fasting glucose (IFG) tends to predominate in males while impaired glucose tolerance (IGT) tends to predominate in females [71,72]. There is no clear reason for this difference. However, one can speculate that the smaller muscle mass or physical fitness in women would lower insulin-stimulated glucose disposal and account for the highest rate of IGT [73].

4.10. Age

The risk of getting prediabetes increases as age advances [74]. This may be due to a decrease in insulin secretion with advancing age and this decrease may be accelerated by genetic factors [75].

4.11. Diet

In addition to the above risk factors, diet also plays a significant role in the development of prediabetes. In specific, the total dietary fat amount and intake of saturated fat increases the risk of developing impaired glucose regulation while a high intake of dietary fiber and whole grain products decreases the risk [76].

5. Health problems associated with prediabetes

5.1. Diabetes mellitus

Prediabetes progresses to overt diabetes gradually over a period of many years and is characterized by worsening insulin resistance and insulin secretory dysfunction and by gradual increases in fasting and postprandial plasma glucose concentrations [77–79]. Approximately 5–10% of prediabetic subjects progress to diabetes annually [7]. In the Hoorn study, 64.5% of the participants who had both impaired fasting and impaired post-load glucose levels at baseline progressed to diabetes during the 6 years follow up [80]. In a systemic overview and meta-analysis of prospective studies, the annualized incidence rates of progression to diabetes in individuals with isolated IGT (4–6%) or isolated IFG (6–9%) were lower than in those with both IFG and IGT (15–19%) [81]. The incidence of diabetes was reported to be 7% in the group with an HbA1c defined prediabetes and 9% in the IFG group in the Toranomon Hospital Health Management Center Study [82]. 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 [83] (see Fig. 2).

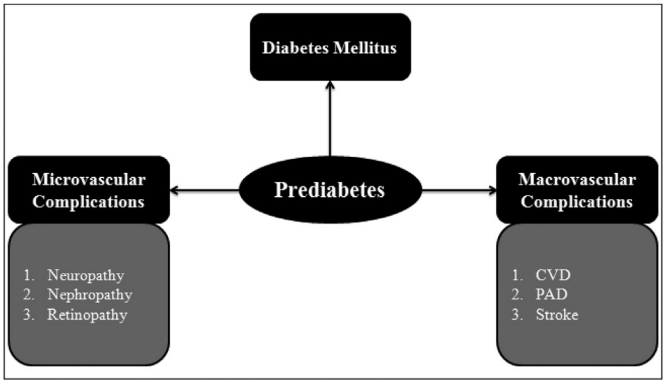

Fig. 2. Complications of prediabetes.

5.2. Microvascular complications

5.2.1. Neuropathy

Neuropathy is a common complication of diabetes occurring over time in more than half of patients with type 2 diabetes mellitus. Nerve conduction studies demonstrate that neuropathy is already present in 10–18% of patients at the time of diabetes diagnosis [84], suggesting that peripheral nerve injury occurs at early stages of the disease and with milder glycemic dysregulation. Approximately 11–25% of individuals with prediabetes show evidence of peripheral neuropathy. Furthermore, prediabetes is associated with autonomic dysfunction, manifesting as reduced heart rate variability and increased prevalence of erectile dysfunction [24]. In the previous studies, peripheral neuropathy had been reported in 11.3% of IFG and 13.0% of IGT patients, which were higher than the prevalence reported in subjects with normal glucose [85]. Conversely, among the patients evaluated for the etiology of idiopathic neuropathy, a number of subjects (27–45%) were diagnosed with prediabetes [86–88]. A recent study demonstrated worsening of small fiber neuropathy in IGT study participants who progressed to T2DM, whereas IGT study participants who reverted to NGT experienced improvement in small fiber neuropathy [89].

5.2.2. Retinopathy

Diabetic retinopathy occurs well before the onset of type 2 diabetes mellitus i.e. in the prediabetic state. In the Diabetes Prevention Program (DPP), 7.9% of subjects had retinopathy among individuals with impaired glucose tolerance [90] which is very much similar to the Gutenberg Health Study in Germany in which 8.1% prevalence of retinopathy was observed among prediabetic subjects [91]. The Australian Diabetes Obesity and Lifestyle (AusDiab) study reported 6.7% of retinopathy among non-diabetic individuals with impaired glucose tolerance and impaired fasting glucose [92]. NANSY-Eye baseline report shows that retinopathy was present in 10% of subjects with IFG and that it was associated with higher blood pressure and higher BMI [93].

5.2.3. Nephropathy

A prospective cohort study involving 1261 middle-aged non-diabetic individuals from the Norwegian general population found that prediabetes was an independent risk factor for glomerular hyperfiltration and increased albuminuria, showing the pathological process of kidney injury caused by increased blood glucose levels starts well before the onset of full-blown diabetes [94]. Similarly, several studies have reported that prediabetic subjects are at increased risk of early nephropathy and chronic kidney disease in prediabetes [95–97]; however, the reason for this is still not clear whether this association is due to the effects of prediabetes itself or increased incidence of diabetes mellitus among prediabetes or the presence of other factors associated with both hyperglycemia and nephropathy [98]. In a systematic review and meta-analysis, Echouffo-Tcheugui et al., concluded that prediabetes is modestly associated with an increase in chronic kidney disease risk; hence, chronic kidney disease screening among people with prediabetes, and aggressive management of prediabetes in those with chronic kidney disease may be warranted [99].

5.3. Macrovascular complications

The macrovascular complications associated with prediabetes are cardiovascular disease, stroke, and peripheral vascular disease. These disorders are established in patients with T2DM, but their initiation and progression are well-recognized to occur during the prediabetic stage. In addition, prediabetes is associated with multiple metabolic abnormalities including obesity, dyslipidemia and hypertension which put prediabetic subjects to an increased risk for macrovascular disease [100–102]. Studies proposed that the increased cardiovascular disease (CVD) risk associated with type 2 diabetes begins well before diagnostic glucose thresholds are reached (the causes of future CVD events begin to develop even in the prediabetic state) [103,104]. The risk of development of CVD in prediabetes increased by 10%–40% compared with individuals of normal glucose regulation [105–107]. An analysis of the 44–55-year-old men from the Paris Prospective Study cohort showed that, compared with normoglycemic subjects, the presence of IGT was associated with a doubling of CVD mortality [108]. In a meta-analysis comprised of 53 cohort studies, patients with prediabetic states were found to be at an increased risk for CVD, coronary heart disease (CHD), and stroke. Patients with IGT had a higher risk compared to those with IFG [109]. Ford et al. included 18 studies from 1997 through 2008, and concluded that people with prediabetes in general have ≈20% increased risk of CVD, irrespective of the type of prediabetes (IFG vs IGT) or the criterion used to define IFG [5]. Compared with NGT subjects, individuals with prediabetes have an increased risk of cerebrovascular diseases, including transient ischemic attack, stroke, and recurrent stroke [110–113]. The prevalence of prediabetes in peripheral artery disease (PAD) is common, accounting about 26%–28%; however, the exact mechanisms remain to be fully elucidated [114–116].

6. Interventions

6.1. Lifestyle interventions

According to NICE (National Institute for Health and Care Excellence) guidelines, prediabetes subjects should firstly receive lifestyle intervention, in the form of intensive lifestyle-change group education programs. These programs should focus on physical activity, weight loss, and nutrition education. It is recommended that individuals undertake 150 min of weekly exercise [117]. Lifestyle intervention involving the modification of dietary and exercise behavior is an efficacious, safe, and cost-effective measure for reducing the risk of type 2 diabetes development in prediabetes [118]. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle-intervention program [119] and for every 1 kg decrease in weight; the risk of developing diabetes in future was reduced by 16% [120]. The Chinese Da Qing IGT and diabetes study showed the beneficial effects of lifestyle intervention on the prevention of diabetes in individuals with IGT [121]. The Finnish Diabetes Prevention Study Group concluded that type 2 diabetes can be prevented by changes in the lifestyle of high-risk subjects and the reduction in the incidence of diabetes was directly associated with changes in lifestyle. The changes in lifestyle not only improve glucose tolerance but also reduce the magnitude of several other cardiovascular risk factors [122]. In a Diabetes Prevention Programme (DPP) randomized study, the lifestyle intervention reduced the incidence of diabetes mellitus by 58% during an average follow up period of 2.8 years [119]. Similarly, the Indian Diabetes Prevention Program (IDPP) reported a 28% reduction in incident T2DM over 30 months in 133 subjects who received a lifestyle modification intervention compared with controls [123]. A meta-analysis of 10 prospective cohort studies showed that moderate-intensity activity for at least 150 min per week reduces the risk of type 2 diabetes mellitus development in prediabetes [124]. Consistent with these findings, the ADA recommends that individuals with pre-diabetes should engage in 150 min of moderate intensity physical activity per week [125]. In a 20 year follow up China Da Qing Diabetes Prevention Study, combined lifestyle intervention groups had a 51% lower incidence of diabetes (hazard rate ratio [HRR] 0·49; 95% CI

0·33–0·73) during the active intervention period of 6 years and a 43% lower incidence (0·57; 0·41–0·81) over the 20 year period [83]. The Diabetes Prevention Program showed improvements in both lipid levels and blood pressure in prediabetic individuals who regressed to NGT during the study period, and the largest improvements were seen in the intensive lifestyle intervention group [126,127]. The Diabetes Prevention Program Outcomes Study reported that reversion to normal glucose regulation, even is transient, was associated with 56% reduced risk of future diabetes [128]. In the year 2012, Hydrie et al., reported that the lifestyle modification involving moderate physical activity and diet modification reduces the risk of diabetes in IGT by 71% during a mean follow up period of 18 months [129]. A randomized controlled trial study found that yoga intervention may be helpful to reduce oxidative stress in prediabetes. In addition, yoga can also be beneficial in the reduction of BMI, waist circumference, systolic blood pressure and fasting glucose [130]. König et al., 2018, investigated the effects of a 12-month interdisciplinary standardized lifestyle program addressing physical activity and changes in dietary and lifestyle behavior in 2227 obese prediabetic participants and reported that multidisciplinary lifestyle interventions could reduce the risk of developing diabetes and the prevalence of a full-blown metabolic syndrome in obese and prediabetic patients [131].

6.2. Pharmacological interventions

In addition to lifestyle modification, several medications have been tested for their efficacy in preventing diabetes among people with prediabetes though the U.S. Food and Drug Administration has not approved any drug specifically for the treatment of prediabetes. Moreover, the medications tested to prevent the development of diabetes in the risk group are same as therapies used to treat established diabetes.

6.2.1. Metformin

If the person is not able to participate in lifestyle-change programs or if he/she has deteriorating fasting plasma glucose or HbA1c results, despite lifestyle intervention, metformin can be prescribed at the clinician's discretion [132]. In the 2.8 years of the Diabetes Prevention Programme (DPP) randomized clinical trial, metformin was found to reduce the incidence of future diabetes in prediabetes by 31% [119] and these patients were also followed for 10 years and at 10 years, the progression of prediabetes to diabetes mellitus was reduced by 18% in the metformin group compared with placebo [133]. Similarly, in Indian Diabetes Prevention Programme (IDPP-1), the incidence of type 2 diabetes mellitus was reduced by 26.4% in metformin group when compared to the control group during a median follow up period of 30 months [123].

6.2.2. Glitazone

Glitazones are a class of drug that reduces insulin resistance by causing increased uptake and utilization of glucose in peripheral organs and reducing gluconeogenesis [132]. The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial evaluated the efficacy of rosiglitazone in preventing the development of T2DM and found that the rosiglitazone reduced incident diabetes by 60% relative to placebo during a median follow up period of 3 years. Moreover, the drug was effective in both subjects with IFG and IGT [134]. The TRIPOD (Troglitazone in Prevention of Diabetes) study conducted in Hispanic women with prior gestational diabetes demonstrated that troglitazone decreased the risk for diabetes by 55% relative to placebo over a median follow up of 30 months [135]. Recently, in a randomized, double-blind placebo-controlled study, pioglitazone was found to reduce the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% during a median follow-up period of 2.4 years. However, it was found to be associated with significant weight gain and edema [136].

6.2.3. Alpha-glucosidase inhibitors

α-Glucosidase inhibitors such as acarbose and voglibose are oral drugs which prolong carbohydrate digestion time and reduce glucose absorption rate to subsequently decrease the postprandial rise in blood glucose [132]. Furthermore, it has been proposed that alpha-glucosidase inhibitors exert a beneficial effect on glucose tolerance by modifying the gut microbiota flora [137].

A multicentre, placebo-controlled randomized trial found a decreased incidence of type 2 diabetes mellitus in IGT subjects treated with acarbose. Furthermore, acarbose significantly increased the reversion of IGT to normal glucose tolerance over time [138].

Similarly, in a randomized, double-blind trial in Japanese individuals with impaired glucose tolerance, voglibose significantly reduced the risk of developing type 2 diabetes in individuals with impaired glucose tolerance and significantly increased the proportion of people who achieved normoglycaemia compared with placebo [139].

6.2.4. Glucagon-like peptide- 1 (GLP-1) analogs and GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) is a hormone, which induces insulin secretion, reduces glucagon concentrations, and delays gastric emptying and hence lowers blood glucose levels. The action of GLP-1 is limited by the rapid degradation by enzyme dipeptidyl peptidase 4(DPP-4), therefore, degradation resistant stable analogs and GLP-1 receptor agonists have been developed [132]. Two such drugs namely liraglutide (analog) and exenatide (receptor agonist) have been studied with context of prediabetes. Liraglutide has been found to reduce prediabetes prevalence after a year by 84–96% [140]. Similarly, results of another study indicated that IGT and IFG regressed to NGT in 77% of subjects who were treated with exenatide. Moreover, these drugs were also found to reduce weight [141].

6.2.5. Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors stabilize the circulating levels of the incretins glucagon-like peptide-1 and gastric inhibitory polypeptide, which improves insulin secretion and reduces glucagon secretion, thereby reducing hyperglycemia [142,143]. A study reported that the DPP-4 inhibitor vildagliptin improves insulin sensitivity and β-cell function, leading to improved postprandial glycemia in subjects with IFG, who are known to have β-cell dysfunction. Thus, vildagliptin may prevent progression of high-risk subjects to diabetes mellitus [144]. Similarly, in another study, vildagliptin, in patients with IGT found that after 12 weeks of treatment, there was a reduction from baseline in prandial glucose excursions and in HbA1c [145]. In Japanese subjects with impaired glucose tolerance, sitagliptin was found to improve glycemic excursion after a meal or after an oral glucose load [143].

7. Conclusion

Lifestyle interventions focusing dietary modifications and physical activities are considered to be the cornerstone for the management of prediabetes and therefore, prediabetic subjects are suggested to adopt a healthy lifestyle, physical exercise, and weight loss in order to prevent progression of prediabetes to type 2 diabetes and its complications. Prediabetic people are also suggested to do yogic exercise since yoga helps to reduce the risk factors

associated with prediabetes. The patients who do not respond to lifestyle interventions may be considered for pharmacological interventions. In addition, education regarding diabetes and its complications should be given to prediabetic subjects so that they adopt a healthy lifestyle.

Conflicts of interest

The authors declare that they have no conflict of interest.

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