



Prediabetes Deserves More Attention: A Review

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Evidence increasingly demonstrates that prediabetes is a toxic state, as well as a risk factor for diabetes, and is associated with pathophysiological changes in several tissues and organs. Unfortunately, use of available evidence-based treatments for prediabetes is low. This review seeks to explain why prediabetes must be viewed and treated as a serious pathological entity in its own right. It offers an overview of the pathophysiology and complications of prediabetes and describes how this condition can be reversed if all treatment avenues are deployed early in its course.

Prediabetes is defined as a state of abnormal glucose homeostasis in which blood glucose levels are elevated above those considered normal, but not high enough to meet the criteria required for a diagnosis of diabetes (1,2). It is characterized by impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Evidence increasingly demonstrates that prediabetes is a toxic state, in addition to being a risk factor for diabetes (3). Emerging evidence suggests that prediabetes is associated with pathophysiological changes in several tissues and organs, which would support its recognition as a distinct pathological entity. The recent inclusion of prediabetes and associated billable conditions in the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* gives credence to this position (1).

The frequency of prediabetes is increasing as the prevalence of obesity rises worldwide (1). The pathophysiologic defects underlying prediabetes include insulin resistance, β -cell dysfunction, increased lipolysis, inflammation, suboptimal incretin effect, and hepatic glucose overproduction (3). These metabolic derangements associated with concomitant obesity cause endothelial vasodilator and fibrinolytic dysfunction, leading to increased risk of macrovascular and microvascular complications (2–6). Prediabetes has also been associated with increased risks of cancer and dementia (4). Recent

studies have demonstrated that patients with prediabetes can suffer from coronary artery disease and diastolic heart failure even before progressing to overt diabetes (5). Macrovascular complications are the greatest contributor to diabetes-related health care expenditures, and prediabetes contributes substantially to these costs (7,8).

Lifestyle interventions, including diet and exercise, are first-line treatments. Medications can also play a role; randomized controlled trials of biguanides (metformin), α -glucosidase inhibitors (acarbose), inhibitors of pancreatic lipase (orlistat), peroxisome proliferator-activated receptor- γ agonists (rosiglitazone and pioglitazone), meglitinides (nateglinide), and glucagon-like peptide 1 receptor agonists (liraglutide) have all shown benefits. Bariatric surgery is another efficacious means of treating prediabetes and type 2 diabetes (9).

Unfortunately, despite the availability of evidence-based treatment options, and especially the pharmacological and surgical means, they are not being fully exploited by clinicians to tackle prediabetes. This underutilization most probably stems from the mindset that prediabetes is just a risk factor and not a serious pathological entity in its own right. Likewise, people with prediabetes are often reluctant to accept antidiabetic prescriptions because they do not have diabetes, aggravating clinicians' own hesitance to initiate drug treatment for prediabetes. The hesitant predisposition of clinicians and patients alike motivated the authors to write this review, which seeks to add to the growing voice aimed at enlightening practitioners and patients worldwide that prediabetes must be viewed and treated as a serious pathological entity, although it is less severe than diabetes.

This review provides insight into the pathophysiology and complications of prediabetes and how they compare with the enormous problems associated with diabetes. By pointing out that prediabetes can be reversed if all treatment avenues are deployed early on in its course

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(9,10), the authors seek to convince practitioners that prediabetes deserves more attention than it is presently being given.

Literature sources included in this review were obtained from searches of databases, including PubMed, PubMed Central, and Google Scholar. Search terms used were “pathophysiology of prediabetes and/or impaired fasting glucose and/or impaired glucose tolerance,” “complications of prediabetes,” “complications of impaired fasting glucose,” and “complications of impaired glucose tolerance.”

Pathophysiology

Hyperglycemia, insulin resistance, inflammation, and metabolic dysfunctions cause endothelial vasodilator and fibrinolytic anomalies, leading to microvascular and macrovascular complications in both prediabetes and diabetes (3). The microvasculature affects insulin sensitivity by determining the delivery of insulin and glucose to skeletal muscle; thus, endothelial dysfunction and extracellular matrix (ECM) remodeling promote the progression from normoglycemia to prediabetes and then to diabetes, suggesting a continuum in a single pathophysiological process (4). Prediabetes and diabetes ensue when compensatory hyperinsulinemia eventually fails to compensate for insulin resistance (1–4).

Endothelial Vasodilator Dysfunction

Endothelial dysfunction can be defined as a loss of vasodilation in response to stress caused by release of an occlusive cuff (flow-mediated dilation) or pharmacological stimuli such as acetylcholine or bradykinin, causing nitric oxide synthase activation (7). Endothelial vasodilator dysfunction precedes the onset of IFG, IGT, and type 2 diabetes, and it occurs early in the pathogenesis of atherosclerosis, which predicts future cardiovascular events (2–6).

Endothelial Fibrinolytic Dysfunction

Endothelial fibrinolytic dysfunction contributes to the risk of cardiovascular disease (CVD) in individuals with insulin resistance, prediabetes, and diabetes. Glucose, adipokines, insulin, and insulin-like growth factor increase the expression of plasminogen activator inhibitor-1, via specificity protein 1 sites (1–4). Plasminogen activator inhibitor-1 is the primary inhibitor of tissue-type plasminogen activator in the endothelium, leading to increased risk of thrombotic events such as stroke and

ischemic heart diseases among people with prediabetes and diabetes (1–4,11).

The following pathophysiological processes all lead to endothelial vasodilator and fibrinolytic dysfunction.

Insulin Resistance

The insulin resistance that precedes prediabetes and type 2 diabetes contributes to endothelial dysfunction. Vascular insulin resistance leads to downregulation of insulin receptor substrate-1 and -2 and decreased phosphorylation of Akt (protein kinase B) and endothelial nitric oxide synthase, whereas the endothelin-1 pathway remains unaffected, with resultant decreased vasodilatory responses in people with prediabetes or diabetes (3,5,11).

Hyperglycemia, Advanced Glycation End Products, and Increased Free Fatty Acids

These factors give rise to oxidative stress, inflammation, and endothelial vasodilator and fibrinolytic dysfunction in prediabetes and diabetes alike. Excess glucose in body cells, including endothelial cells, is metabolized through the polyol pathway to fructose and its metabolites, which are potent glycation agents (3,5). Advanced glycation end products activate various inflammatory pathways, including nuclear factor κ B (4,6). Glycated LDL cholesterol is recognized by scavenger receptors on macrophages and leads to the formation of foam cells (3,4). Furthermore, glycation of complex III proteins enhances mitochondrial superoxide production, causing oxidative stress and endothelial dysfunction (3,11).

Hyperglycemia also activates the protein kinase C and hexosamine pathways, contributing to inflammation, endothelial dysfunction, increased endothelial permeability, and ECM expansion (3).

Adipose tissue, especially that of visceral origin, also influences systemic endothelial function through secretion of inflammatory cytokines such as tumor necrosis factor- α , interleukin-6, leptin, and resistin (3,5,6). The inflammatory processes, oxidative stress, and endothelial dysfunctions caused by prolonged hyperglycemia eventually lead to complications, including CVD, in people with prediabetes or diabetes (7).

Extracellular Matrix, Skeletal Muscle Fibrosis, and Ectopic Fat Deposition

The proinflammatory prediabetic and diabetic state results in increases in skeletal muscle collagens, other ECM proteins, and ECM remodeling. These processes cause endothelial dysfunction, capillary regression, spatial

barriers, and increased ECM component interaction with cell surface receptors (5,7).

Additionally, ECM expansion occurs in the adipose tissues of people with prediabetes or diabetes. This expansion limits adipocyte fat storage, leading to ectopic fat stores in liver and skeletal muscle, lipotoxicity, oxidative stress, and inflammation, with resultant endothelial dysfunction and further insulin resistance (7).

MicroRNAs and Endothelial Dysfunction

Hyperglycemia increases the expression of several microRNAs found in the endothelium such as miR-320, miR-221, miR-503, and miR-125. These microRNAs may promote endothelial dysfunction by inhibiting genes involved in angiogenesis, vascular repair, and inflammatory suppression (1,3,4).

The aforementioned pathophysiological processes are similar in prediabetes and diabetes. It therefore seems that these conditions represent different points along a continuum of the same disease. Whereas prediabetes may be reversible, especially when actively treated early in its course, diabetes is a more severe disease perpetuated by the chronicity and grave depth of these pathophysiological processes, including epigenetic, mitochondrial, and microRNA changes; varying degrees of β -cell exhaustion; and sustained glucotoxicity and lipotoxicity. These processes translate to a higher degree of morbidity, mortality, and complications that are more difficult to reverse among people with diabetes.

Diagnosis

The World Health Organization (WHO) and the American Diabetes Association (ADA) agree on the definition of IGT as a 2-hour post-load plasma glucose of 7.8–11.0 mmol/L (12). However, the WHO defines IFG as a fasting plasma glucose (FPG) of 6.1–6.9 mmol/L, whereas the ADA defines it as an FPG of 5.6–6.9 mmol/L (12). The WHO definition seeks to reduce the frequency of labeling apparently normal people as having prediabetes, but it has the disadvantage of missing some people who actually do have prediabetes. However, the ADA's lower FPG criterion has been argued to be cost-effective, since recent studies have revealed that complications of prediabetes set in even at those levels (13–20).

The ADA also defines prediabetes as an A1C of 5.7–6.4%, and studies have reported metabolic derangements and complications at these levels (13–20). The Canada Clinical Practice Guidelines (CPG) Expert Committee, however, pegged the diagnosis of prediabetes at an A1C of

6.0–6.4% based on a modest consensus that metabolic derangements and complications may begin to occur at such a level (20). The CPG committee reiterated the need for conventional screening once every 3 years for people with normoglycemia and annually for those with prediabetes (Table 1).

The different diagnostic criteria of different professional organizations may be a source of confusion for clinicians. The presence of diabetes risk factors such as obesity, multiparity, and first-degree relative with diabetes, among others, should buttress the diagnosis of prediabetes even at the lower ADA criteria. Considering the argument that complications, especially CVD, have been observed at the ADA FPG cutoff of 5.6 mmol/L and A1C cutoff of 5.7%, it may be wise and cost-effective to rely on the ADA criteria with regard to when to recommend therapeutic lifestyle measures, pharmacological treatment, or even bariatric surgery.

Furthermore, the presence of any symptom or complication evidently attributed to hyperglycemia in a person with prediabetes should mandate immediate commencement of treatment with both therapeutic lifestyle measures and antidiabetic medications. Bariatric surgery should be considered early, too, especially in those who are obese, given the remarkable benefits of such procedures and their documented potential to reverse prediabetes and diabetes (1,7–10).

Complications of Prediabetes

Prediabetes can be a component of the metabolic syndrome, and its associated complications could also arise from other components of the metabolic syndrome such as systemic hypertension, atherogenic dyslipidemia, insulin resistance, and central obesity. Therefore, the studies cited in the sections below were scrutinized to determine whether the researchers adjusted for these other metabolic syndrome components through various statistical methods.

Cardiovascular Complications

Liu et al. (21) recently demonstrated that IFG, IGT, combined glucose intolerance (IFG plus IGT), and newly diagnosed diabetes were all related to a high risk of arterial stiffness in a Chinese community after adjusting for BMI, waist-to-hip ratio, smoking, alcohol intake, systolic blood pressure, diastolic blood pressure, serum triglycerides, total cholesterol, and HDL cholesterol. They further posited that a 2-hour post-load glucose level ≥ 6.14 mmol/L (lower than the current WHO

TABLE 1 Differing Diagnostic Criteria for Prediabetes and Diabetes

Guidelines	FPG, mmol/L		2-Hour Post-Load Plasma Glucose, mmol/L		A1C, %	
	IFG	Diabetes	IGT	Diabetes	Prediabetes	Diabetes
WHO	6.1-6.9	≥7.0	7.8-11.0	≥11.1	5.7-6.4	≥6.5
ADA	5.6-6.9	≥7.0	7.8-11.0	≥11.1	5.7-6.4	≥6.5
CPG	6.1-6.9	≥7.0	7.8-11.0	≥11.1	6.0-6.4	≥6.5

criterion for diagnosing IGT) may increase the risk of arterial stiffness. Hadaegh et al. (14) also demonstrated the association between prediabetes and CVD after controlling for other components of the metabolic syndrome, including systemic hypertension, dyslipidemia, and homeostasis model assessment of insulin resistance (HOMA-IR).

Nasr and Sliem (15) showed that people with prediabetes had myocardial perfusion defects, which represent a pattern of cardiovascular risk. Lee et al. (16) also concluded that increasing FPG in a nondiabetic population was associated with risks of myocardial infarction, stroke, and all-cause mortality. Additionally, Mijajlović et al. (17) and Fonville et al. (18) reported after performing multivariate analysis that prediabetes may play an independent role in the causation of stroke. They concluded that prediabetes might become one of the most important modifiable therapeutic targets in both primary and secondary prevention of stroke.

Although Vistisen et al. (19) showed a high incidence rate of CVD and death among individuals with IFG or IGT, or an A1C of 5.7–5.9%, they suggested that part of the risk posed by prediabetes may be explained by associated CVD risk factors.

Balcioğlu et al. (22) reported cardiac autonomic nervous dysfunction detected by both heart rate variability and heart rate turbulence in people with prediabetes and isolated IFG, after adjusting for LDL cholesterol, total cholesterol, smoking, and systemic hypertension. Similarly, Gudul et al. (23) reported that atrial conduction times and P wave dispersion on surface electrocardiography were longer in people with prediabetes before the development of overt diabetes. They added that the left atrial mechanical functions were impaired secondary to a deterioration in the diastolic functions of the participants. In addition, Rospleszcz et al. (24) and Akhavan-Khaleghi and Hosseinsabet (25) implicated prediabetes as being independently and unfavorably associated with left ventricle wall thickness and deformation.

In a meta-analysis, Huang et al. (26) concluded that IFG, IGT, and prediabetes (by the ADA A1C criterion) are independently associated with an increased risk of composite cardiovascular events, coronary heart disease, stroke, and all-cause mortality. They noted an increased risk in people with FPG as low as 5.6 mmol/L, supporting the stricter ADA criteria.

Several other studies have demonstrated that IFG, IGT, and prediabetes (by the ADA A1C criterion) can be complicated by varying degrees of symptomatic and nonsymptomatic CVD, including coronary heart disease, stroke, and peripheral artery disease. However, most of these studies reported higher risks of CVD in IGT than in IFG, after controlling for total cholesterol, LDL cholesterol, smoking, systolic blood pressure, diastolic blood pressure, some obesity indices, and, in some studies, insulin resistance indices (27–34).

Renal Complications

Kim et al. (35), Tsuda et al. (36), and Živković et al. (37) demonstrated increased glomerular hydrostatic pressure and albuminuria in people with IFG, IGT, and/or prediabetes by the ADA A1C criterion even after adjusting for age, sex, obesity, hypertension, metabolic syndrome, and other risk factors for chronic kidney disease (CKD). Similarly, a systematic review and meta-analysis by Echouffo-Tcheugui et al. (38) showed that prediabetes is modestly associated with an increased risk of CKD. In a similar vein, a case report by Bhatt et al. (39) demonstrated proteinuria and nodular glomerulosclerosis in a middle-aged man with IGT. Several other studies have reported varying degrees of kidney diseases complicating prediabetes after adjustment for other CKD risk factors (40–42).

Ophthalmological Complications

In a cohort of individuals from the Diabetes Prevention Program (DPP) (43), diabetic retinopathy was detected in 12.6 and 7.9% of participants with diabetes and

prediabetes, respectively. This finding shows that, although these complications of diabetes can be found in people with prediabetes, their prevalence is greater among those with diabetes.

Acquired color vision impairment, signs of retinopathy, cataracts, and corneal surface disorders were ophthalmological complications also reported among people with prediabetes by Sokolowska-Oracz et al. (44) in a controlled study. They also demonstrated posterior vitreous detachments and epiretinal membranes by optical coherence tomography among those with prediabetes after adjusting for some components of the metabolic syndrome, including dyslipidemia and systemic hypertension. Additionally, Jończyk-Skórka and Kowalski (45) reported color vision impairment among some people with prediabetes.

In another report, retinal photoreceptors and microvascular dysfunction was demonstrated by Zaleska-Żmijewska et al. (46) using adaptive optics retinal imaging among individuals with prediabetes after adjusting for BMI and cholesterol. Idiopathic blepharoptosis was also observed in some people with prediabetes by Bosco et al. (47) in a controlled study for which exclusion criteria included many causes of blepharoptosis such as myasthenia gravis, neurological disorders, multiple sclerosis, familial causes, vascular diseases, and tumor. Their results revealed that BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and smoking were not associated with an increased risk of blepharoptosis.

Neurological Dysfunctions

Lee et al. (48) demonstrated that the prevalence of peripheral neuropathy was 29, 49, and 50% in people with normoglycemia, prediabetes, and new-onset diabetes, respectively, following adjustment for total cholesterol, LDL cholesterol, triglycerides, systolic blood pressure, central obesity, and smoking. They concluded that the prevalence of peripheral neuropathy in people with prediabetes was higher than in people with normal glucose tolerance and similar to that in those with recently diagnosed diabetes.

Neurovascular dysfunction was also reported among people with prediabetes by Rodrigues et al. (49) in a prospective study after adjusting for age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, HOMA-IR, triglycerides, HDL cholesterol, and apnea-hypopnea index. They emphasized that prediabetes caused autonomic abnormalities, which contributed significantly to vascular dysfunction and muscle

sympathetic nerve alterations due to elevated sympathetic tone. They further concluded that small changes in FPG in participants with the metabolic syndrome, without diabetes or hypertension, was associated with abnormal sympathetic activity and vascular impairment. Specifically, sexual dysfunction (erectile dysfunction, impaired sexual desire, and overall dissatisfaction) and depression in men and women were identified by Krysiak et al. (50,51) as complications of prediabetes. After multivariate analysis, they pointed out that prediabetes substantially caused these complications after adjusting for total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, HOMA-IR, systolic blood pressure, diastolic blood pressure, central obesity, and smoking. This finding was supported by Chen et al. (52) in a study among Chinese men. Dimova et al. (53) also demonstrated a high prevalence of autonomic and sensory dysfunction in early stages of glucose intolerance after adjusting for atherogenic dyslipidemia, insulin resistance, central obesity, systemic hypertension, and smoking.

In a different vein, Kowall et al. (54) showed an association between prediabetes or diabetes and sleep disturbances, irregular nocturnal sleep duration, and poor daytime napping. Similar findings were reported by Andersson et al. (55) and Hung et al. (56). Postherpetic neuralgia and idiopathic restless legs syndrome were demonstrated in separate studies by Bosco et al. (57,58) to occur more frequently among people with IGT. Additionally, Ezerarslan et al. (59) detected sensorineural hearing loss in people with IFG. Peripheral polyneuropathy has also been reported among people with prediabetes in several studies (60–62). These studies considered atherogenic dyslipidemia, insulin resistance, systemic hypertension, central obesity, smoking, and other factors in multivariate analyses and concluded that IFG, IGT, and/or prediabetes A1C levels independently caused or contributed significantly to these complications.

Gastrointestinal Dysfunctions

Nonalcoholic fatty liver disease (NAFLD) is a recognized disorder in people with prediabetes and diabetes alike (63,64). It is a spectrum ranging from fatty liver to nonalcoholic steatohepatitis (NASH), and then to liver cirrhosis (63,64). Hossain et al. (63) and Ortiz-Lopez et al. (64) concluded that prediabetes, insulin resistance, central obesity, and abnormal triglycerides and HDL cholesterol more than total cholesterol and LDL cholesterol contributed independently and significantly to NAFLD and its progression to NASH and liver cirrhosis.

Abnormal intestinal microbiota is another gastrointestinal disorder that is increasingly being reported in people with prediabetes or diabetes. Allin et al. (65) demonstrated intestinal dysbiosis characterized by depletion of the genus *Clostridium* and the mucin-degrading bacterium *Akkermansia muciniphila*. They found this result comparable to observations in inflammatory bowel diseases, suggesting that intestinal dysbiosis may be associated with low-grade inflammation in prediabetes (65). Gut microbiota changes in prediabetes were also reported by Zhang et al. (66), although, they added that inflammation, insulin resistance, obesity, and high triglycerides, in addition to prediabetes, contributed independently to the dysbiosis reported.

Can gut dysbiosis be associated with irritable bowel syndrome in some people with prediabetes, as reported by Gulcan et al. (67)? Future research should provide the answer to this question. Further research will also be needed to explore possible associations between gut dysbiosis in prediabetes or diabetes and increased susceptibility to gastrointestinal infections, recurrent furuncles, and other recurrent infections in people with prediabetes or diabetes.

Other Associated Disorders or Complications

Habitual snoring and obstructive sleep apnea were strongly associated with IFG and IGT in different studies by Wang et al. (68) and Kim et al. (69). Their reports added that insulin resistance, β -cell defects, hypertriglyceridemia, and central obesity also showed some association with these airway disorders. In another vein, Similä et al. (70) reported that tooth loss was strongly associated with prediabetes and diabetes in middle-aged Finnish women after adjusting for insulin resistance indices, obesity indices, and other confounders. Other disorders that have been found among people with prediabetes and diabetes alike included musculoskeletal, hematological, and, micronutrient anomalies. Increased fracture risk was demonstrated by Gagnon et al. (71) among middle-aged and older Australians with IGT in a national, population-based prospective study. This risk is a known complication among people with diabetes and may be more severe and irreversible in them than in those with prediabetes.

Abnormal hematological indices such as high mean platelet volume and platelet distribution width were reported in people with prediabetes or diabetes in a meta-analysis by Zaccardi et al. (72). These abnormal platelet indices may cause increased platelet activation, contributing to CVD, a major complication of prediabetes and

diabetes (72). Serum zinc-to-copper ratio, serum magnesium, vitamin E, and vitamin C levels were significantly reduced in people with IFG, IGT, or diabetes (73–76). Finally, cancers of the stomach/colorectum, liver, pancreas, breast, and endometrium have been significantly associated with prediabetes and even more so with diabetes (77).

Although the complications described here may be present among some people with prediabetes or diabetes, they occur in more severe forms with higher morbidity and mortality in people with diabetes. In addition, some of these complications may be more amenable to treatment and reversal among people with prediabetes than those with diabetes because the pathophysiological vicious cycles upstream to complications are likely to be in their early reversible forms among people with prediabetes. More studies are needed, however, to verify the exact point at which complications become irreversible and whether the cutoffs for prediabetes and diabetes are mere figures or have significant correlation with the reversibility of complications.

Treatment of Prediabetes

Lifestyle intervention is the first-line treatment for prediabetes. Such intervention includes dietary modifications, exercise, avoidance of smoking and alcohol, and other measures (78). However, it is often difficult for people with diabetes to strictly adhere to these lifestyle interventions, even with the best counseling. The DPP research study (79), for instance, showed that lifestyle modification led to greater reduction in the incidence of diabetes compared with metformin use in people with prediabetes (58 vs. 31%). However, it is difficult for some people to strictly adhere to the stringent lifestyle interventions used in the study. Such difficulties should prompt clinicians to consider early pharmacological and/or surgical interventions in addition to lifestyle interventions. Doing so will help to slow or stop the pathophysiological processes upstream to the development of complications and diabetes.

Pharmacological intervention is the second-line treatment. Although, none of the available antidiabetic agents have been approved to treat prediabetes in the United States, ADA recommends metformin, and metformin and some other antidiabetic agents are being used off-label for this purpose. However, many clinicians hardly consider prescribing antidiabetic medications for people with prediabetes. These patients are often reluctant to accept drug prescriptions because they have not been diagnosed with diabetes. These attitudes among clinicians and

TABLE 2 Select Clinical Trials Showing the Efficacy of Antidiabetic Drugs to Treat Prediabetes

Trial	Intervention	Duration	Results
DPP (79)	Lifestyle (7% weight loss and 150 minutes of moderate exercise/week) or metformin	5 years	Reduction in diabetes incidence of 58% with lifestyle modification and 31% with metformin
IDPP (80)	Lifestyle intervention or metformin	3 years	NNT of 6.4 with lifestyle intervention and 6.9 with metformin
STOP-NIDDM (81)	Acarbose	3.3 years	25% reduction in diabetes incidence
ACT NOW (82)	Pioglitazone	2.5 years	72% reduction in diabetes incidence
DREAM (83)	Rosiglitazone	3 years	60% reduction in diabetes incidence
CANOE (84)	Rosiglitazone and metformin	3.9 years	66% relative risk reduction in diabetes incidence and NNT of 4
Dapagliflozin once-daily and exenatide once-weekly dual therapy: a 24-week randomized, placebo-controlled, phase II study (85)	Dapagliflozin and exenatide	24 weeks	50% reversal to normal glucose tolerance
Bariatric surgery (86)	Laparoscopic adjustable gastric banding	4 years	75% reduction in diabetes incidence

NNT, number needed to treat to prevent one case of diabetes.

patients prompted the writing of this article, in which the authors advocate giving more attention to prediabetes.

The DPP (79) and the Indian Diabetes Prevention Program (IDPP) (80) both showed how metformin use in the treatment of prediabetes reduces its progression and complications. Other trials like the STOP-NIDDM (Study to Prevent NIDDM) trial (81) demonstrated a 25% reduction in diabetes incidence with acarbose use over 3.3 years.

Other trials have even shown medications to be more efficacious than the strict lifestyle interventions used in the previously mentioned trials. These include the ACT NOW (Actos Now for Prevention of Diabetes) trial (82), in which pioglitazone use led to a 72% reduction in diabetes incidence over a shorter period of 2.5 years, and the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial (83), which demonstrated a 60% reduction in diabetes incidence over 3 years.

Two antidiabetic agents can also be used in combination in the treatment of prediabetes, as was shown in the CANOE (Canadian Normoglycemia Outcomes Evaluation) trial (84), in which combined use of rosiglitazone and metformin yielded a 66% reduction in diabetes incidence over 3.9 years. Lundkvist et al. (85) also reported immense benefits of dual therapy with dapagliflozin and exenatide, including weight reduction and prevention of prediabetes, with a 50% reversion from prediabetes to normal glucose tolerance among obese nondiabetic people (Table 2).

Based on the authors' experience, some people with prediabetes without dyslipidemia, systemic hypertension, smoking history, or other common comorbid conditions have presented with symptoms such as painful paresthesiae of the feet, blurred vision, insomnia, palpitations, erectile dysfunction, or constipation. For some, these symptoms were reversed after intervention with lifestyle measures and/or medications such as metformin. When lifestyle measures alone could not reverse the hyperglycemia and symptoms, the authors added metformin, with eventual resolution of hyperglycemia and other symptoms. However, a more comprehensive evaluation of some other people with prediabetes and symptoms is ongoing to determine to what extent atherogenic dyslipidemia, obesity, insulin resistance, smoking, systemic hypertension, and other comorbid conditions contribute to these symptoms.

Furthermore, bariatric surgeries, especially in obese people with prediabetes, have shown remarkable potential for reversal of the progression of prediabetes. Wentworth et al. (86) demonstrated a 75% reduction in diabetes incidence after a minimum follow-up period of 4 years among people with prediabetes who underwent laparoscopic adjustable gastric banding.

The evidence of beneficial effects of different treatment strategies for prediabetes underscores the necessity to treat prediabetes as soon as it is diagnosed to avert or reverse associated complications. Treatment should involve early combination of lifestyle intervention and

evidence-based use of suitable antidiabetic agents such as metformin; new-generation α -glucosidase inhibitors with temporary minimal side effects, such as voglibose; pioglitazone; sodium–glucose cotransporter 2 inhibitors such as dapagliflozin; and glucagon-like peptide 1 receptor agonists such as liraglutide.

Conclusion

Prediabetes is a major but silent incubator of future morbidity. The voice for the acknowledgment of its ever-increasing burden must grow louder to be heard by clinicians and patients alike. Carefully chosen pharmacological therapy should be started early in addition to lifestyle modification to circumvent the vicious cycle of pathophysiological processes leading to various complications of prediabetes and to progression to diabetes. Some of these pharmacological agents, as well as bariatric surgery procedures, have shown better efficacy than stringent lifestyle measures in reducing the incidence of diabetes.

Clinician education on this matter must be undertaken to discourage any hesitance to initiate drug therapy in addition to lifestyle measures when necessary in people with prediabetes. In the same vein, patient education and counseling are needed to emphasize the importance of accepting pharmacological treatment or considering surgical procedures to treat prediabetes. Educational campaigns focusing on the high expenditures and reduced quality of life associated with managing the complications of prediabetes and diabetes should be targeted to both people with prediabetes and health care providers. Such efforts can take place in clinics and hospitals, as well as at local, national, and international conferences. Finally, proactive professional organizations such as the ADA should continue to take the lead in publishing evidence-based guidelines regarding lifestyle, pharmacological, and surgical interventions to treat prediabetes.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Y.L. researched data and wrote the manuscript. F.B. reviewed/edited the manuscript. Y.S.K. contributed to the discussion and researched data. Y.L. is the guarantor of this work and, as such, had full access to all the data in the review and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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