Prediabetes: Why Should We Care?

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ABSTRACT: A clear link between cardiovascular disease and prediabetes has emerged over the past few years. Recent studies have shown that patients with prediabetes can suffer from coronary artery disease and diastolic heart failure even before progressing to overt diabetes. With this knowledge, physicians must identify prediabetes and take appropriate measures to optimize glycemic control. The pathophysiological defect seen in prediabetes can be managed with lifestyle modifications; thus, it is essential that physicians have a clear understanding of the current recommendations regarding diet and exercise. This review outlines the complications associated with prediabetes, presents an overview of the available pharmacological and surgical therapies that are effective in treating it, and provides a stepwise, multipronged approach for management.

INTRODUCTION

The 2017 National Diabetes Statistics Report from the U.S. Centers for Disease Control and Prevention estimates that 33.9% of the adult U.S. population has prediabetes based on either fasting glucose or hemoglobin A1c (HbA1c) levels. The prevalence is higher in those aged 65 years and older, at 48.3%. Not surprisingly, only 11.6% of U.S. adults know they have prediabetes.[1]

Diagnosis of prediabetes is based on the presence of impaired fasting glucose, impaired glucose tolerance, and/or elevated HbA1c levels between 5.7% and 6.4%.[2] Impaired glucose tolerance is defined as blood glucose levels of 140 to 199 mg/dL during a 75-gram oral glucose tolerance test (normal < 140 mg/dL), and impaired fasting glucose is defined as blood glucose levels of 100 to 125 mg/dL, although the World Health Organization has a narrower threshold of between 110 and 125 mg/dL.[3] In multiple studies, prediabetes is shown to have a cause-effect relationship to cardiovascular disease and all-cause mortality. In a cohort meta-analysis by Huang et al., prediabetes was associated with an increased risk of coronary heart disease, stroke, and all-cause mortality.[4]

Focusing on lifestyle and medical management of prediabetes, this review highlights the systemic and, in particular, cardiac complications associated with prediabetes, with the goal of providing tools for healthcare providers to treat this patient population and provide secondary preventative measures.

CARDIAC COMPLICATIONS OF PREDIABETES

The prediabetes state is not only a noteworthy risk factor for type 2 diabetes but is also a significant risk factor for macrovascular disease. Although some of the risk may be due to the progression to overt diabetes, an independent risk is still present in individuals who have not yet progressed to diabetes.[5] A meta-analysis of 38 prospective studies in which cardiovascular disease (CVD) or mortality was the end point concluded that increasing glucose levels displayed a linear relationship with CVD risk.[6]

The macrovascular complications from prediabetes typically arise due to atherosclerosis. Because prediabetes and metabolic syndrome often coexist, the risk of developing an atheroma is high. In addition, strong evidence suggests that patients with prediabetes have an increase in fibrinogen and high-sensitivity C-reactive protein (hs-CRP)—both proatherogenic factors—compared with normoglycemic patients.[7,8] This section focuses mainly on the macrovascular complications associated with prediabetes, specifically coronary artery disease and heart failure.

Coronary Artery Disease

While most recognize a direct link between diabetes and coronary artery disease, few physicians and patients acknowledge the potential risk associated with a prediabetes diagnosis. Sen et al. conducted a study on 62 acute coronary syndrome patients who were admitted to a tertiary facility in India to identify the proportion that had prediabetes; they discovered that 48.4% of this patient population had prediabetes and 25% had diabetes.[9]

In a study by the American Diabetes Association (ADA)[10] on the impact of prediabetes on coronary artery atherosclerosis, 67 patients with established coronary artery disease (CAD) underwent angioscopic evaluation of multiple main trunk arteries. Per ADA guidelines, 16 of the patients were classified as nondiabetic, 28 were considered prediabetic, and 23 were diabetic. Yellow plaques identified by angioscopy are commonly considered the primary lesion in acute coronary syndromes, and

the presence of two or more per vessel is considered to be a risk factor for future cardiac events. All groups were assessed for both the number of yellow plaques per vessel and intensity of yellow grade. The number and grade of yellow plaques were higher in the prediabetic patients than in nondiabetics ($P = .02$ and $P = .04$, respectively) but similar in both prediabetic and diabetic patients ($P = .44$ and $P = .21$, respectively). In multivariate logistic regression analysis, both diabetes and prediabetes were independent predictors of multiple yellow plaques.[10] In a larger study done by Scicali et al., the impact of prediabetes on coronary artery calcium (CAC) scores and mean common carotid media thickness (IMT) was compared in prediabetic patients and nondiabetic patients. Of the 272 patients enrolled, both the CAC scores and mean IMT were significantly higher in the prediabetes group ($P < .001$ and $P < .001$, respectively).[11] In conclusion, a prediabetes state could potentially have a similar impact as diabetes on coronary and peripheral atherosclerosis. Larger studies are needed in the prediabetes population to establish a direct link between prediabetes and CAD.

Diastolic Heart Failure

Although studies such as the Framingham Heart Study have established an epidemiologic link between diabetes and heart failure,[12] there is no established pathophysiologic association between prediabetes and cardiac function in humans. In an experimental animal model, Koncsos et al. aimed to better define the relationship between prediabetes and diastolic heart failure by administering a single low dose of streptozotocin to Long Evans rats fed with high-fat chow. This treatment induced prediabetes as characterized by a slight elevation in fasting blood glucose, impaired glucose and insulin tolerance, and an increase in visceral adipose tissue. The cardiac consequence of a metabolic derangement such as prediabetes was assessed in this setting. Measurement of morphological and functional parameters of the hearts, as assessed by echocardiography, determined that left ventricular (LV) mass as well as LV anterior and posterior wall thickness were increased in prediabetes rats. Other cardiac dimensional parameters remained unchanged. The slope of the LV end-diastolic pressure–volume relationship, an early and sensitive indicator of diastolic dysfunction, was elevated in the prediabetes group. Pathological evaluation revealed increased oxidative mitochondrial stress and increased mitofusin-2 (MFN2) levels in vascular smooth muscle. Increased MFN2 is thought to induce apoptotic cell death in rat cardiomyocytes.[13] Of note, in a previous study by Essop et al., cardiac mitochondrial oxidative stress in male Wistar rats was not seen even after 16 weeks, indicating that mitochondrial oxidative stress might not be present in all models and stages of prediabetes.[14] Di Pino et al. studied the effects of prediabetes on diastolic function in 167 patients with HbA1c between 5.7% and 6.4%. In patients with prediabetes, they found a significantly lower peak mitral inflow in early diastole (E wave) to late diastolic atrial filling velocity (A wave) ratio ($P < .05$), a higher left atrium volume (LAV) ($P < .05$), and a higher sphericity index (SI) ($P < .05$) when compared to controls. The E/A ratio, LAV, and SI are all early signs of diastolic dysfunction.[15]

LIFESTYLE MODIFICATIONS

The combination of diet and exercise is arguably the single most important factor that could halt the progression towards type 2 diabetes in patients with prediabetes. Among the first studies to prove this was the Finnish Diabetes Prevention Study (DPS), a controlled randomized trial including 522 overweight subjects with impaired glucose tolerance who were randomized to either an intensive lifestyle intervention group or a standard-of-care control group.[16] The intensive lifestyle intervention group received individualized dietary counseling and circuit-type resistance training and were advised to increase overall physical activity, whereas the control group received general counseling on diet and exercise along with an annual physical exam. The lifestyle intervention arm of the study was designed to be at a high intensity during the first year, followed by a maintenance period, with the goal of reducing both weight and dietary fat intake while increasing physical activity and dietary fiber. Weight reductions were measured after 1 year and at 3 years; the intervention group lost 4.5 kg and 3.5 kg while the control group lost 1.0 and 0.9 kg, respectively. Lipid and glycemic parameters showed more improvement in the intervention group, with a 58% reduction in the risk of developing diabetes compared to the control group. The subjects who were free of diabetes at the end of the intervention were followed up for an additional 3 years, and the incidence of diabetes, physical activity, and dietary intake of fiber and fat was measured. During the total 7-year follow-up period,[17] the study concluded that the incidence of type 2 diabetes was 4.3 versus 7.4 per 100 person-years in the intervention and control group, respectively (log-rank test $P = .0001$), indicating a 36% reduction in relative risk.

Another large study that reproduced similar results was from the Diabetes Prevention Program (DPP), which was similar to the Finnish study in its design but included a group treated with metformin for comparison.[18] A total of 3,234 high-risk adults were recruited; 1,079 participants underwent intensive lifestyle intervention, 924 were treated with metformin, and 932 were treated with a placebo. The lifestyle group achieved two important goals: loss of 7% of their initial body weight and a minimum of 150 min of physical activity per week (at an intensity similar to brisk walking). Diabetes incidence was reduced by 58% in the lifestyle group and by 31% with metformin compared to placebo. Analysis was by intention-to-treat, with

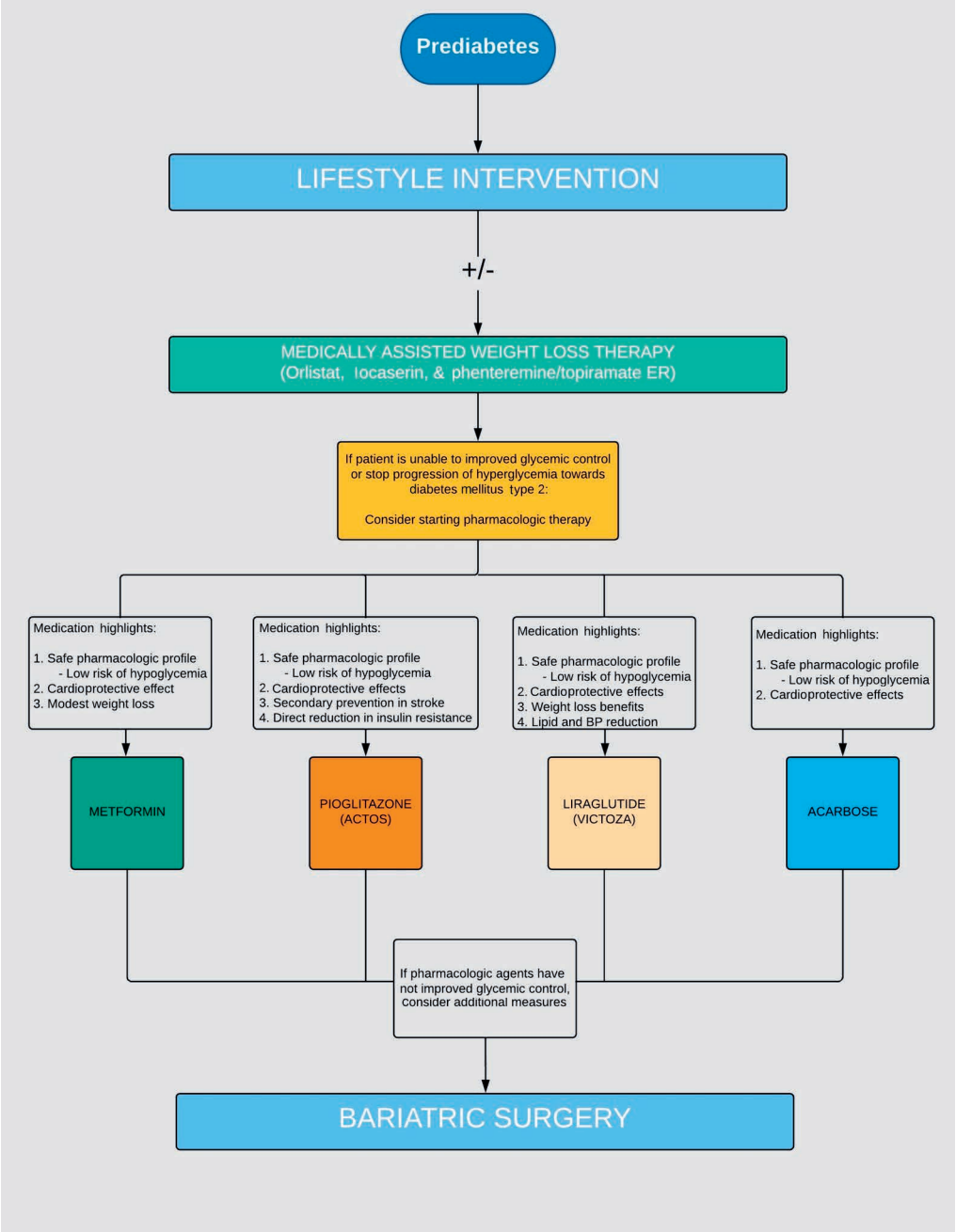

Figure 1.
Lifestyle interventions in prediabetes; adapted from American Association of Clinical Endocrinologists guidelines.[22]

one case of diabetes prevented for every 6.9 people. Further analysis of the lifestyle group showed a 16% reduction in diabetes risk for every kilogram of weight loss.[19] After a 10-year follow-up, the study concluded that the effects of lifestyle modification on diabetes prevention were maintained.

Both the Finnish and DPP studies were successful in demonstrating that lifestyle intervention is a valuable key to managing prediabetes. However, the challenge still remains in implementing these methods in a community setting. Katula et al. applied the methods of the DPP study to the

MEDICATION (BRAND EXAMPLES)	MECHANISM OF ACTION	STUDY OUTCOMES	CARDIOPROTECTIVE FEATURES
Metformin (Glucophage, Glumetza, Fortamet)	Metformin reduces glucose production by inhibiting the mitochondrial respiratory chain in the liver and thus activating AMPK (5′ adenosine monophosphate-activated protein kinase, an enzyme that plays a role in cellular energy homeostasis); this enhances insulin sensitivity and lowers cAMP, which then reduces the expression of gluconeogenic enzymes. AMPK-independent effects of metformin include inhibition of fructose-1,6-bisphosphatase by AMP.[23]	Salpeter et al. (meta-analysis) *4,560 participants* Metformin reduced the incidence of new onset diabetes by 40% (OR 0.6; CI, 0.5-0.8) with an absolute risk reduction of 6% (CI, 4-8) during a mean trial duration of 1.8 years.[24] Ramachandran et al. (study of native Asian Indians) *531 participants* A relative risk reduction in the incidence of T2DM was seen in both the lifestyle (28.5%), and metformin (26.4%) groups compared to control group.[25]	In Svensson et al., investigators studied the association between lowering HbA1c levels and cardiovascular events or death in patients with T2DM on metformin. This study included 24,752 metformin initiators. A mean follow-up of 2.6 years showed a lower risk of cardiovascular events and death when patients achieved an HbA1c of < 6.5% within 6 months of starting metformin.[26] Further research will need to be applied to the prediabetes population, but a potential promising cardioprotective effect could also be attributed with metformin.
Pioglitazone (Actos)	Pioglitazone is a synthetic ligand for peroxisome proliferator-activated receptors (PPARs), which allows it to alter the transcription of genes that influence carbohydrate and lipid metabolism. Through its action at PPAR gamma 1 and 2, pioglitazone enhances insulin sensitivity. Additional benefits include an increase in glucose transporters 1 and 4 and enhanced insulin signaling.[27]	Defronzo et al. (ACT NOW Study) *602 participants* Received either pioglitazone 30 mg once daily (increased to 45 mg/day after 1 month) or placebo. At 2.4 years, the incidence of diabetes was 2.1% with pioglitazone versus 7.6% with placebo.[28]	In the IRIS trail, Actos showed a reduced risk of stroke and MI. When comparing the treatment and control groups, the first event of MI to stroke was 9% vs 11.8%. In addition, T2DM incidence was 3.8% (treatment) vs 7.7% (placebo).[29] This drug appears safe for the prediabetes population as long as they do not have an increased risk for bone fracture and complication from weight gain. Adverse side effects included an increase in bone fractures, weight gain of greater than 4.5 kg, and edema.
Acarbose (Precose)	Acarbose inhibits alpha-glucosidase and is most effective against glucoamylase, followed by sucrase, maltase, and dextranase. It is a diabetic agent that delays carbohydrate digestion and absorption in the intestine.[30]	Chiasson et al. (randomized trial) *1,429 participants* 714 patients received acarbose (100 mg TID) and 715 received placebo. In the arcarbose group, 32% developed diabetes vs 42% in the placebo group (P = .0015, NNT 10). However, the acarbose group experienced increased flatulence and diarrhea, which could account for early treatment discontinuation.[31]	Further analysis of the Chiasson et al. study group showed that the risk of CVD in patients with impaired glucose tolerance was 2.2% in the treatment group vs 4.7% in the control group (0.15% vs 1.75% for MI, respectively). The differences were not as significant in other study areas.[31]
Liraglutide (Victoza)	Liraglutide is an incretin mimetic of the glucagon-like peptide-1 (GLP-1) receptor agonist and has similar biochemical features. The most important aspect of this therapy is that it increases insulin secretion in response to oral ingestion of carbohydrates while also slowing gastric emptying, suppressing glucagon secretion, reducing food intake, and promoting beta-cell proliferation.[32]	SCALE Obesity and Prediabetes trial (randomized controlled trial) *2,254 participants* Prediabetic individuals with a body mass index (BMI) ≥ 30 kg/m^2 or ≥ BMI 27 kg/m^2 with comorbidities were recruited. Although the withdrawal rate was significantly high (47% in liraglutide group, 55% in placebo group), the data obtained at 160 weeks showed a decreased incidence of diabetes in the treatment vs placebo group (2% vs 6%; P < .0001, NNT 25) as well as increased normoglycemia (66% vs 36%; P < .0001, NNT 4), significant weight loss (6.1% vs 1.9%; P < .0001), and close rate of adverse events (15% vs 13%).[33]	The cardioprotective effect of liraglutide has not been fully studied in the prediabetes population. However, the LEADER trial showed significant cardiovascular outcomes in patients with T2DM after a 3.8-year follow-up. In the primary end point of first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, the study showed lower incidence in the treatment group vs control (13.0% vs 14.9%; HR 0.87; 95% CI, 0.78-0.97; P < .001 for noninferiority; P = .01 for superiority).[34] Despite the high withdrawal rate, liraglutide shows promise in the treatment of prediabetes and cardiovascular health and will surely be studied with other agents in this class.

Table 1.
Summary of current medications to treat prediabetes.[23-40] T2DM: type 2 diabetes mellitus; MI: myocardial infarction; CVD: cardiovascular disease

MEDICATION (BRAND EXAMPLES)	MECHANISM OF ACTION	STUDY OUTCOMES	CARDIOPROTECTIVE FEATURES
Orlistat (Alli, Xenical)	Orlistat is a semisynthetic derivative of lipstatin, a potent and selective inhibitor of gastric and pancreatic lipase. By binding to the serine residue of lipase, orlistat inhibits the hydrolysis of triglycerides, thus reducing the absorption of monoacylglycerides and free fatty acids.[35]	Torgerson et al. (randomized prospective trial) *3,305 participants* Participants with BMI ⩾ 30 kg/m^2 and normal or impaired glucose tolerance were randomized to either lifestyle + placebo or lifestyle + orlistat 120 mg 3 times/day. At 4 years, the incidence of T2DM in those receiving orlistat vs placebo was 6.2% vs 9% ($P < .0032$, NNT 36), mean weight loss was 5.8 vs 3 kg ($P < .001$), and progression from normal to impaired glucose tolerance was 27.6% vs 30.5%. The biggest limitation was the high dropout rate of 48% with orlistat and 66% with placebo; however, 99% of randomized patients were included in intention-to-treat analysis.[36]	No studies have been conducted to establish potential cardioprotective features of orlistat.
Phentermine/ Topiramate (Qsymia)	Qsymia is one of the newer agents for treating obesity in the United States. Its properties consist of two known pharmacologic agents used in combination: 1. Phentermine, a centrally acting appetite suppressant that uses sympathomimetic pathway while increasing metabolism, and 2. Topiramate, with a proposed mechanism of neurotransmitter-mediated appetite suppression and enhanced satiety.[37]	Guo et al. (randomized controlled trials) *3,040 participants* The authors pooled data from three RCTs (CONQUER, SEQUEL, and EQUIP). Patients who were overweight or obese without diabetes received 7.5 mg/46 mg vs 15 mg/92 mg of phentermine/topiramate vs placebo once daily for > 1 year. Patients were risk-stratified based on Cardiometabolic Disease Staging score. The 1-year risk of incidence of diabetes in the treatment vs placebo groups was 0.67% vs 1.51% for those at low risk, 2.37% vs 4.67% for those at moderate risk, and 6.29% vs 10.43% for those at high risk.[38]	No studies have been conducted to establish potential cardioprotective features of phentermine/topiramate. Teratogenic potentials and elevations in heart rate are possible concerns.
Lorcaserin (Belviq)	Lorcaserin is a small-molecule agonist of the 5-HT$_{2C}$ receptor designed to promote weight loss in obese/overweight patients as an adjunct to a reduced-calorie diet and increased physical activity. It acts on the 5-HT$_{2C}$ receptors in the central nervous system, mainly the hypothalamus, to suppress appetite.[39]	Nesto et al. (post hoc analysis) *6,136 participants* The authors performed a post hoc analysis from two phase 3 studies (Bloom and Blossom) with the goal of monitoring weight and glycemic parameters for 52 weeks in the subpopulation of obese or overweight prediabetic patients. The percentage who progressed to T2DM in the lorcaserin vs placebo group was 3.2% vs 5.0% ($P = .032$) based on HbA1c but was insignificant based on fasting blood glucose.[40] In addition, a greater percentage of lorcaserin- vs placebo-treated patients reverted to euglycemia based on both HbA1c (40% vs 29.5%, $P < .001$) and FPG (52.4% vs 46.5%, $P = .047$)	No studies have been conducted to establish potential cardioprotective features of lorcaserin.

Table 1. Continued

local community via key modifications to enhance efficiency and feasibility.[20] Community healthcare workers with well-controlled diabetes and a history of a healthy lifestyle were recruited to deliver a group-based lifestyle weight loss (LWL) intervention through a partnership with a community-based diabetes educational program. The study recruited 301 obese volunteers who were prediabetic on at least two occasions. The LWL intervention had two valuable goals for their participants: calorie intake between 1,200 and 1,800 kcal per day, and ≥ 180 min of physical activity per week. This approach is in agreement with parameters set by the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society of Clinical Nutrition.[21] Participants were present at 67.7% of all group intervention sessions. On an adjusted average of the 6- and 12-month means, LWL intervention participants had a net weight loss of 6.0% of their body weight and 5.0 cm in waist circumference compared to standard of care patients. There was also a 4.3 mg/dL decrease in fasting glucose in the LWL intervention participants versus a decrease of 0.4 mg/dL in the standard of care patients ($P < .001$).

PHARMACOLOGICAL AGENTS

There are currently four medications for treating the prediabetes subpopulation, including metformin, pioglitazone, acarbose, and liraglutide. In addition, the American Association of Clinical Endocrinologists (AACE) has also proposed three weight-loss therapies—including orlistat, lorcaserin, and phentermine/topiramate ER—to manage obesity with the goal of halting the progression of insulin resistance and type 2 diabetes (Figure 1).[22] No data is available for naltrexone/bupropion. Table 1 provides an extensive review of the currently available pharmacological agents.[23-40]

BARIATRIC SURGERY

In 2011, the American College of Surgeons Bariatric Surgery Center Network (ACS-BSCN) recognized bariatric surgery as a potential intervention for type 2 diabetes and prediabetes in addition to assisting in weight loss in morbidly obese patients. De la Cruz-Muñoz and colleagues performed a retrospective analysis of 1,602 adults who underwent bariatric surgery; they were categorized into those with diagnosed type 2 diabetes, those with prediabetes, those with high fasting plasma glucose (FPG), and those with normal FPG. At 1- and 3-year follow-up post bariatric surgery, all four groups had normal FPG, but the prediabetes group had more significant weight loss (47 kg) than the diabetes population.[41] Procedures such as the Roux-en-Y gastric bypass and the biliopancreatic diversion have been shown to be the most effective for patients with diabetes.[42] Normalization of plasma glucose concentrations, HbA1c, and insulin levels were seen in 80% to 100% of patients within days post-surgery prior to any weight loss. The above findings could be attributed to reduced food intake, malabsorption of nutrients, and alterations in gastrointestinal anatomy that incite changes in the incretin system.

Among obese patients (body mass index > 40) who are candidates for bariatric surgery, prediabetes patients should be prioritized because they are at higher risk of diabetes and complications that can be prevented with surgery and the subsequent weight loss. This is supported by a post hoc analysis of 4,032 participants from the Swedish Obese Subjects study, half of whom had bariatric surgery and the other half receiving usual care. After 15 years of follow-up, patients in the diabetes, prediabetes, and normoglycemic groups who underwent bariatric surgery had a reduced incidence of macrovascular complications. Interestingly, the largest risk reduction for macrovascular complications was seen in the prediabetes group.[43]

CONCLUSION

The link between prediabetes and cardiovascular disease has been clearly established, and physicians should be aware of the implications for their patients. At this time, major organizations such as the AACE have publish written statements on the importance of diagnosing and treating the prediabetes population. Following these steps will help ensure that future complications in this subpopulation will not take a toll on our healthcare system.

The first step in managing patients with prediabetes is to encourage strict lifestyle modifications consisting of ≥ 180 min of physical activity per week and a calorie intake of 1,200 to 1,800 kcal per day. Providers can also refer their patients to ancillary providers, such as dieticians or weight management specialists, who can help them achieve their goals. In addition to lifestyle management, anti-obesity agents such as orlistat, lorcaserin, and phentermine/topiramate should be considered for obese patients with prediabetes.

Healthcare providers can also consider pharmacologic agents (metformin, pioglitazone, liraglutide, or acarbose) for management of prediabetes. Each of these drugs has a safe pharmacologic profile with regard to hypoglycemia. Metformin has a good track record of being a safe, tolerable drug with benefits such as modest weight loss and a potential cardioprotective effect. Pioglitazone (e.g., Actos) is another viable option due to its ability to increase insulin sensitivity and its known advantage in secondary prevention among stroke/myocardial infarction patients; however, it is also known to cause side effects such as weight gain and

bone fractures in the osteoporotic population. If weight loss is a desired effect, providers can consider liraglutide, a weight-loss agent approved by the U.S. Food and Drug Administration that has been shown to improve glycemic control and HbA1c levels.

If medical management fails to achieve glycemic control, advanced measures such as bariatric surgery can be used with the goal of reversing prediabetes and helping obese patients lose weight. All surgical procedures are complex processes that require mental preparedness on the part of the patient and an in-depth understanding of how it will impact their lifestyle; thus, surgery should be reserved for those who are resistant to other forms of treatment. Providers should not be discouraged from sending patients who meet surgical criteria to bariatric surgical centers since studies have shown that surgery can control prediabetes and improve both lipid profiles and blood pressure.

In short, providers can help patients with prediabetes through multiple means and should use the above tools in their arsenal. Providers should also feel comfortable referring patients to an endocrinologist when the clinical picture is complex enough to require multidisciplinary care.

KEY POINTS

- Prediabetes is a growing concern as it affects roughly 33.9% of U.S. adults, with the majority of this population left untreated.
- Complications of prediabetes include macrovascular effects such as myocardial infraction, stroke, and peripheral vascular disease as well as microvascular changes such as retinopathy, neuropathy, and nephropathy.
- Healthcare providers should start screening for prediabetes and initiate treatment as soon as possible, starting with lifestyle interventions and progressing to pharmacologic therapies.
- Health providers should consider a multidisciplinary approach by involving a certified diabetes educator and/or nutritionist and recruiting additional support from an endocrinologist or bariatric surgeon as needed.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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