Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)
Issue (39),2020
ISSN: 2617-9563
www.mecsj.com/

Pre-Diabetes and its Management

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Abstract

Prediabetes is a condition with higher than normal blood sugar levels but not classified as diabetes. Prediabetes carries a higher risk of future development of type 2 diabetes, cardiovascular disease and risk of mortality. The incidence of prediabetes is increasing world-wide and physicians and health care providers need to understand and identify the associated risks. Appropriate measures must be taken to optimise the glycaemic control and the measure include lifestyle changes, exercise, weight loss, pharmacological agents as well as surgical options. This short literature review outlines the risks associated with prediabetes and presents an overview of the available pharmacological and surgical options in managing the same.

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نبذة مختصرة

مقدمات السكري هي حالة ترتفع فيها مستويات السكر في الدم عن المعدل الطبيعي ولكنها غير مصنفة على أنها مرض السكري. تحمل مقدمات السكري مخاطر أعلى للتطور المستقبلي لمرض السكري من النوع 2 وأمراض القلب والأوعية الدموية وخطر الوفاة. يتزايد معدل الإصابة بمقدمات السكري في جميع أنحاء العالم ويحتاج الأطباء ومقدمو الرعاية الصحية إلى فهم وتحديد المخاطر المرتبطة بها. يجب اتخاذ التدابير المناسبة لتحسين التحكم في نسبة السكر في الدم ، ويشمل الإجراء تغييرات في نمط الحياة ، وممارسة الرياضة ، وفقدان الوزن ، والعوامل الدوائية ، فضلاً عن الخيارات الجراحية تحدد مراجعة الأدبيات القصيرة هذه المخاطر المرتبطة بمقدمات السكري وتقدم نظرة عامة على الخيارات الدوائية والجراحية المتاحة في إدارة ذلك.

Keywords: Prediabetes, Management of prediabetes, High risk Diabetes, Diabetes prevention, Impaired glucose tolerance, Impaired fasting glucose

Introduction

Prediabetes is a condition in which blood sugar levels are elevated than normal but not elevated enough to be diagnosed as diabetes mellitus. Around 88 million American adults which means 1 in 3 adults have prediabetes, out of which around 84% don't know that they have prediabetes. Prediabetes increases the future risk of developing type 2 diabetes (T2DM), heart disease and stroke (CDC, 2020). Prediabetes means higher than usual blood sugar levels, not high enough to be classified as T2DM but the long-term effects of T2DM on body organs, especially on heart, kidneys, nerves and blood vessels may have already started. Having a healthy life style, health eating habits, regular physical activity as a daily routine and weight loss can prevent the progression of prediabetes towards T2DM and can help bring the sugar levels back to normal (*Prediabetes - Symptoms and Causes*, n.d. 2020).

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www.mecsj.com/

Prediabetes is usually silent and asymptomatic but can present with symptoms of hyperglycemia which may include polyuria, polydipsia, blurred vision and tiredness. The diagnosis of prediabetes can be made with fasting blood sugar (FBS) levels, oral glucose tolerance test (OGTT) and HbA1c levels. FBS < 100 mg/dl is considered as normal, FBS 100 - 125mg/dl is considered as Prediabetes and FBS ≥ 126 mg/dl is considered as diabetes mellitus. For OGTT, 2 hours post sugary drink, the blood sugar level < 140 mg/dl is considered normal. Blood sugar level 140 – 199 mg/dl is Prediabetes and level ≥ 200 mg/dl or higher is diabetes mellitus. HbA1c < 5.7% is normal, 5.7 – 6.4 % Pre-diabetes and > 6.5 % is diabetes mellitus (*Prediabetes (Borderline Diabetes)*, n.d. 2013) (Edwards & Cusi, 2016). American Diabetes Association (ADA) has similar diagnostic criteria (*Diagnosis | ADA*, n.d. 2013). A summary of all three diagnosing criteria is given in Figures -1 & 2.

Measure	Normal	Prediabetes*	Diabetes
FPG (mg/dl)	< 100	100–125 (IFG)	≥ 126
2-hour plasma glucose 75-g OGTT (mg/dl)	< 140	140–199 (IGT)	≥ 200
A1C (%)	< 5.7	5.7–6.4	≥ 6.5

**For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.*

Figure 1- Diagnostic criteria for Prediabetes and Diabetes Mellitus (Rich et al., 2013)

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ISSN: 2617-9563
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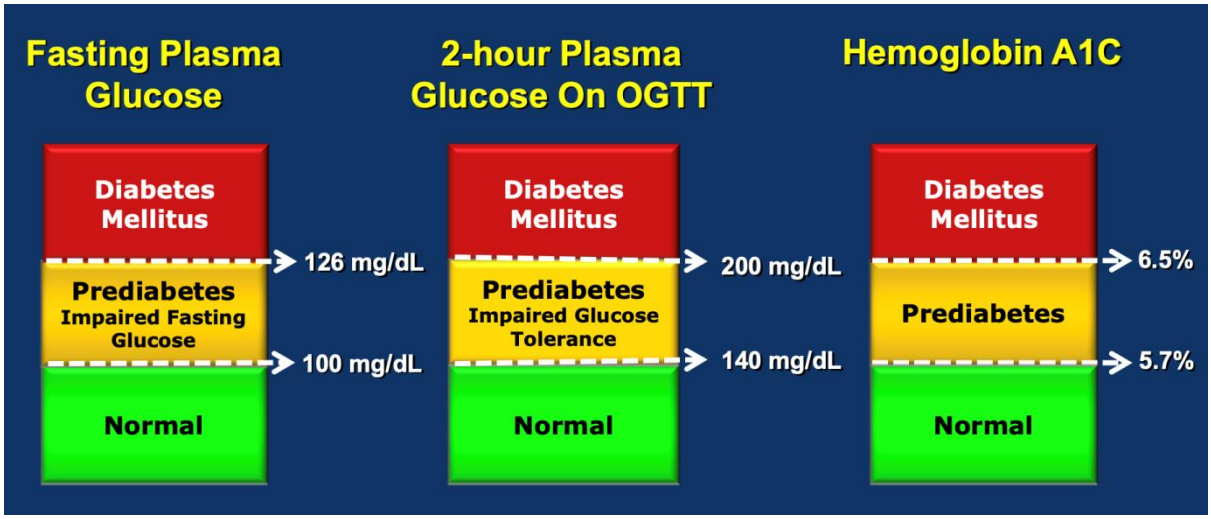

Figure 2- Diagnostic criteria for Prediabetes and Diabetes Mellitus as per American Diabetes Association (*Prediabetes.Pdf*, n.d.)

People with prediabetes are at increased risk of stroke and cardiovascular diseases including myocardial infarction and death from cardiovascular cause and their overall risk factor profile should be reviewed for appropriate and timely management which includes management of dyslipidaemia, dysglycemia, obesity, hypertension, insulin resistance and physical inactivity (Lee et al., 2012) (DeFronzo & Abdul-Ghani, 2011). Around 10% people with prediabetes develop T2DM annually, although the conversion rate is different for different populations. As per a meta-analysis published in 2004, the annual incidence rate of conversion to T2DM from prediabetes was 6-9% for impaired fasting glucose (IFG) patients , 4-6% for those with impaired glucose tolerance (IGT) test and 15-19% for combined IFG and IGT (Tabák et al., 2012) (Forouhi et al., 2007)(Nathan et al., 2007).

Prediabetes not only increases the risk of future T2DM but also is a significant risk factor for macrovascular complications. As per a meta-analysis of 38 prospective studies, the risk of cardiovascular disease and mortality was significantly higher in people with increased glucose levels and showed a linear relationship with cardiovascular disease risk (Figure-3). Prediabetics have more myocardial perfusion defects and cardiovascular risks (Nasr & Sliem, 2010)(Levitan et al., 2004).

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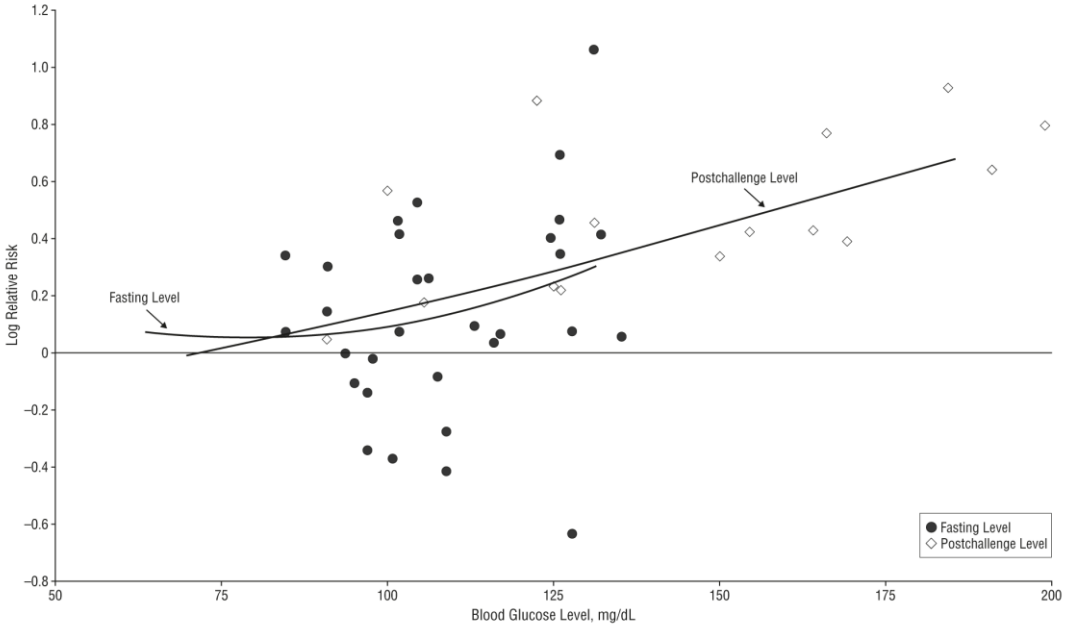

Figure 3 - Dose-response relationship of cardiovascular disease with fasting and post-challenge blood glucose levels. To convert glucose to millimoles per liter, multiply by 0.0555 (Levitan et al., 2004).

Literature Review

It is important to treat prediabetes given its associated risks of morbidity and mortality. The combination of diet, exercise and weight loss is the most important factor that can help in stopping the progression of prediabetes to T2DM. This has been shown in Finnish Diabetes Prevention Study (DPS) which was a randomised controlled trail (RCT) including 522 overweight people with prediabetes randomised to to either an intensive lifestyle intervention or a standard of care control group. During the total 7 year of follow up period, the incidence of T2DM was 4.3 vs 7.4 per 100 person-years in intensive intervention group compared to standard of care group respectively (*The Finnish Diabetes Prevention Study (DPS) | Diabetes Care*, n.d.)(Lindström et al., 2006). Another large study that showed similar results to DPS was Diabetes Prevention Program (DPP) and included 3,234 high risk adults with prediabetes. Out of these 1079 people were enrolled under intensive lifestyle intervention, 924 treated with metformin and 932 treated with placebo. In intervention group the diabetes

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www.mecsj.com/

incidence was reduced by 58% and by 31% in metformin group as compared to placebo group (Diabetes Prevention Program (DPP) Research Group, 2002)(Hamman et al., 2006).

Regarding the pharmacological management of prediabetes, there are currently four medications being used and include metformin, acarbose, pioglitazone and liraglutide. In addition to these the American Association of Clinical Endocrinologists (AACE) have proposed the therapies which help in weight loss which include orlistat, lorcaserin and others (Figure-4) (Garber et al., 2018). A meta-analysis of 31 randomised controlled trials with 4570 participants looked at the benefits of metformin at the new onset diabetes incidence and also on metabolic parameters. A data base search of trials over 40 years showed that metformin reduced BMI, FBS, fasting insulin, triglycerides, low density lipoproteins, and insulin resistance as compared to placebo and no treatment groups. Also, new onset of diabetes incidence was reduced by 40% and an absolute risk reduction of 6% during a mean trial period of 1.8 years (Salpeter et al., 2008).

An analysis of multiple randomised controlled trials with 4186 participants investigated if pioglitazone had any effects in preventing or delaying the onset of T2DM in people with prediabetes. The studies compared pioglitazone with diet, exercise, placebo or no intervention at all. Six studies compared pioglitazone with placebo showed a reduction or delay in onset of T2DM. Total 75 people per 1000 treated with pioglitazone developed T2DM vs 188 out of

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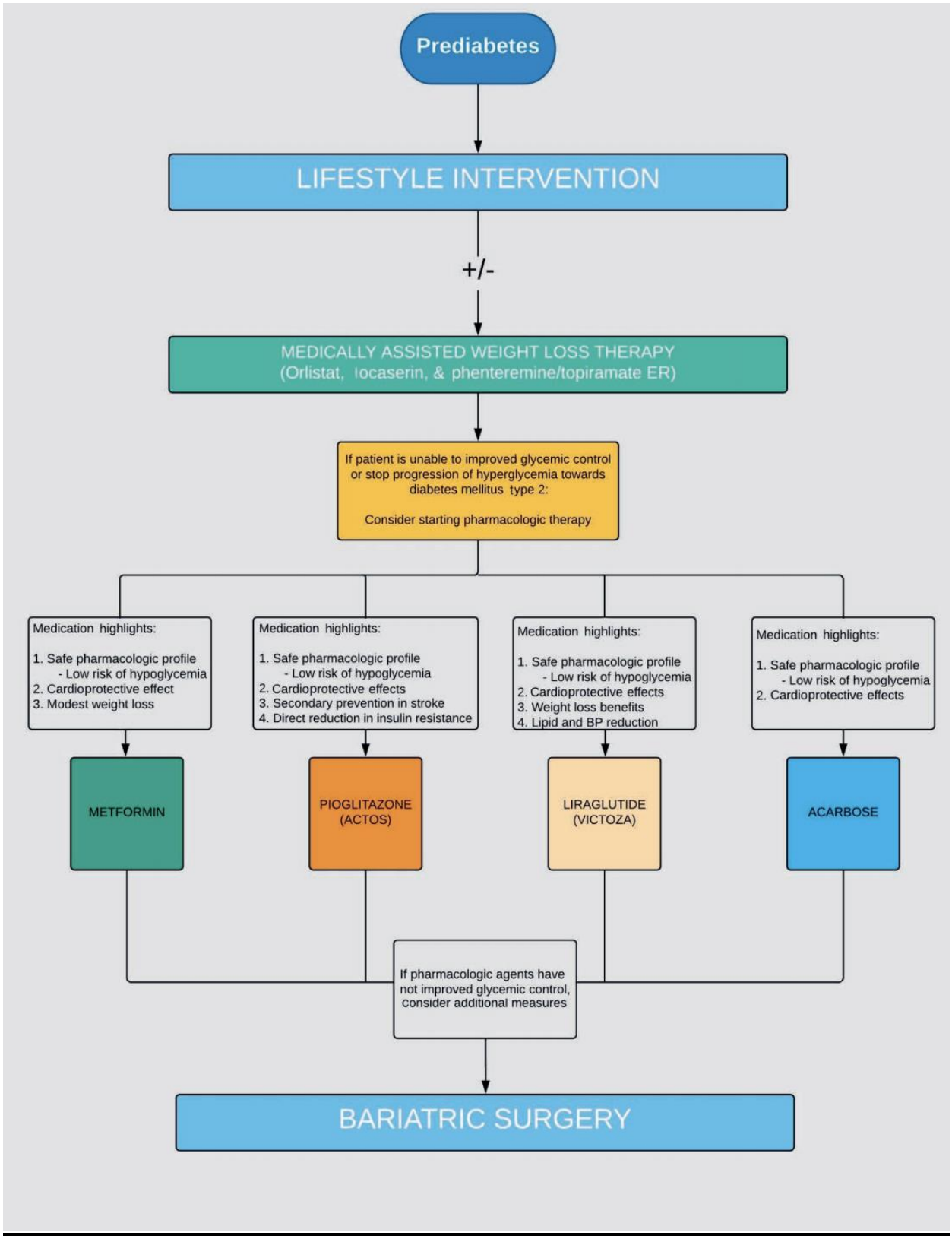

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)
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Figure 4 – Management of prediabetes; adapted from American Association of Clinical Endocrinologists guidelines (Garber et al., 2018)

1000 people treated with placebo. Another 23 studies compared pioglitazone with no intervention also showed a reduction or delay in onset of T2DM. Total 193 out of 1000 people developed T2DM in no intervention group vs 60 per 1000 people in pioglitazone group. Pioglitazone delayed or reduced the incidence of development of T2DM in people with prediabetes (Ipsen et al., 2020).

A multi-centre placebo controlled randomised trial compared acarbose 100mg to placebo three times a day. 714 patients with impaired glucose tolerance were allocated to acarbose group and 715 to placebo group. 32% patients (n=221) randomised to acarbose group and 42% patients (n=285) to placebo group developed diabetes. Interestingly, acarbose reversed the impaired glucose tolerance to normal glucose tolerance ($p<0.0001$) and the placebo group had an increased conversion of prediabetes to diabetes at the end of 3 months (Chiasson et al., 2002).

In a multi-centre randomised double blinded placebo-controlled trial, people with prediabetes and a BMI of 30 kg/m^2 or a BMI of attest 27 kg/m^2 with comorbidities were allocated to once a day liraglutide 3.0mg subcutaneous (n=1505) vs placebo (n=749). After 160 weeks of follow up period, 2% (n=26) individuals in liraglutide group were diagnosed with diabetes vs 6% (n=46) in placebo group. Liraglutide treatment group showed benefits in terms of diabetes risk reduction in adults with prediabetes (le Roux et al., 2017).

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)
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Table 1 – An extensive review of current pharmacological treatment available for prediabetes (Garber et al., 2018)

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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.

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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/m² 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.

The American College of Surgeons Bariatric Surgery Centre Network (ACS-BSCN) in 2011 recognised bariatric surgery as an important intervention for prediabetes as well as for T2DM in people with morbid obesity. A retrospective analysis of 1602 adults who have had bariatric surgery were categorised in people with prediabetes, T2DM, high FBS and normal FBS. At 1 and 3 year follow up period, all four groups fasting plasma glucose was normal but the group with prediabetes had more significant weight loss of around 47kg than other groups. Normalisation of HbA1c, insulin levels and plasma glucose levels were seen in 80-100% of

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patients within few days post-surgery, even before any weight loss (de la Cruz-Muñoz et al., 2011)(Keidar, 2011).

People with high body mass index (BMI) > 40 who are good candidates for bariatric surgery, those with prediabetes should be prioritised for surgery given their higher risk for T2DM and other cardiovascular complications and risk of mortality (Zand et al., 2018). This was also supported by a Swedish study involving 4032 obese individuals. Half of them received usual care and half underwent bariatric surgery. After a follow up of 15 years the bariatric surgery group had a lower incidence of macrovascular complications and interestingly the largest risk reduction of macrovascular complications was seen in the prediabetes group (Carlsson et al., 2017).

Conclusion

Prediabetes has a strong association with future risk of cardiovascular disease, mortality and risk of T2DM. Prediabetes carries a great future risk, and the physicians should be aware of its implications on their patients. The first and most important step in managing prediabetes is encouraging and promoting strict lifestyle changes which include diet control, restricted calorie intake, regular physical activity and weight management. Health care providers can also consider the pharmacological management of patients with prediabetes and currently four medications are being used in the management of prediabetes. These include metformin, pioglitazone, acarbose and liraglutide. Each of these pharmacological agents have a safe profile in terms of long-term benefits and hypoglycaemia. In addition to these agents, few anti-obesity medications have also been advocated in the management of obese patients with prediabetes and include orlistat, lorcaserin and phentermine/topiramate. In case if medical management fails to achieve the desired goal, the surgical option of bariatric surgery can also be used in patients with prediabetes.

Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)
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ISSN: 2617-9563
www.mecsj.com/

In summary, the health care providers can help their patients with prediabetes at an early stage through multiple options which include life style changes, pharmacological options as well as surgical methods as explained above.

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Multi-Knowledge Electronic Comprehensive Journal For Education And Science Publications (MECSJ)
Issue (39),2020
ISSN: 2617-9563
www.mecsj.com/

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