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Metformin's Role in the Prevention of Type 2 Diabetes in Individuals Diagnosed with Prediabetes: A Systematic Literature Review

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NURS 695: Alternate Plan Paper

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Abstract

The United States is facing a growing epidemic of unchecked and untreated individuals with prediabetes. While lifestyle interventions have remained the gold standard of treatment, has this been enough? A literature review was carried out to identify metformin's role in treatment and management of prediabetes as well as perceived barriers to its prescribing. A total of 24 articles met inclusion criteria. Main findings include (a) metformin is effective in reducing the incidence of diabetes, though not as effective as lifestyle interventions; (b) certain populations did benefit more from metformin usage then other populations; (c) there was more treatment compliance with metformin; (d) metformin was shown to be effective in reducing microvascular complications often associated with diabetes; (e) while metformin was effective in reducing diabetes incidence, it has no effect on returning prediabetes to normal glucose ranges; (f) metformin was shown to be safe and tolerable; and (g) even when metformin was shown to be effective, it was still under prescribed and underutilized due to a knowledge gap and perceived barriers by primary care providers. These findings have important practice and policy implications, including increasing patient and provider awareness of prediabetes and its complications, developing guidelines regarding screening, diagnosing, and treatment/management of prediabetes, closing the knowledge gap and perceived barriers of primary care providers, and developing prevention programs that can be widely implemented. Further research is needed regarding the long-term implications that metformin has regarding prediabetes treatment and long-term patient outcomes.

Keywords: prediabetes, pre-diabetes, lifestyle modification, medications, pharmacological intervention, metformin, management, treatment, gestational diabetes, weight loss, pioglitazone, insulin

Metformin's Role in the Prevention of T2DM in Individual's Diagnosed with Prediabetes: A Systematic Literature Review

According to the Centers for Disease Control and Prevention (2020), 88 million American adults have prediabetes, which equivalates to 1 out of 3 adults. Over 80percent of those 88 million American adults do not know they have it (Centers for Disease Control and Prevention [CDC], 2020). Prediabetes increases an individual's risk of developing Type 2 Diabetes Mellitus (T2DM), heart disease, and stroke (CDC, 2020). The following factors place an individual at an increased risk for prediabetes: overweight, 45 years of age or older, parent or sibling with T2DM, physically inactive, history of gestational diabetes, and/or polycystic ovary syndrome (CDC, 2020). Lifestyle changes such as increasing physical activity and dietary modifications are the first route to preventing prediabetes from escalating into T2DM. What about the individuals who continue to have high glucose levels? In cases where an individual has prediabetes and are considered to be at a high risk for T2DM, recent guidelines recommend considering use of metformin, especially for patients who are under 60 years old, have a body mass index (BMI) over 35 kg/m2, or have a history of gestational diabetes (JAMA, 2017). The question remains what role metformin plays in not only treating prediabetes, but in preventing T2DM or at least slowing the progression. As the 7th leading cause of death in the United States, diabetes is a major condition seen in clinical practice. Therefore, finding a safe and effective way to prevent or slow the progression of prediabetes, would be a major game-changer for our patient's health (ADA, n.d.)! This systematic literature review aims to examine the research evidence pertaining to the use of metformin in prediabetes for the prevention of T2DM. Recommendations for clinical practice and future research will be synthesized.

Prediabetes Background

Prediabetes occurs when serum blood glucose levels are higher than normal, though not high enough to be diagnosed as diabetes (American Diabetes Association [ADA], n.d.). Prediabetes can be diagnosed with the same tests for T2DM, with different diagnostic criteria. To diagnosis prediabetes, an individual has to have one of the following: (a) glycosylated hemoglobin (A1C) level between 5.7 percent - 6.4 percent; (b) fasting plasma glucose (FPG) level between 100 mg/dl – 125 mg/dl; or (c) oral glucose tolerance test (OGTT) level between 140 mg/dl – 199 mg/dl (ADA, n.d.).

According to the National Institute of Diabetes and Digestive and Kidney Diseases (2017), there is an estimated 30.3 million adults in the United States alone who have diabetes (9.4 percent of the U.S population). Of those 30.3 million adults, 23.1 million have been diagnosed, while 7.2 million are undiagnosed. The statistics regarding prediabetes are even more staggering. An estimated 84.1 million adults in the United States have prediabetes. A total of 23.1 million adults ages 65 or older have prediabetes and more men than women have prediabetes (National Institute of Diabetes and Digestive and Kidney Diseases, 2017). The combined total of individuals with T2DM and prediabetes, equals 114.4 million adults in the United States alone, equating to 43.3 percent of the adult population (National Institute of Diabetes and Kidney Diseases, 2017). In 2017, $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity, was spent due to diagnosed diabetes (National Institute of Diabetes and Digestive and Kidney Diseases, 2017).

Prediabetes increases an individual's risk of developing T2DM, heart disease, and stroke (CDC, 2019). The increased risk for cardiovascular disease in prediabetes is multifactorial, with etiologies including insulin resistance, hyperglycemia, dyslipidemia, hypertension, systemic inflammation, and oxidative stress (Hsueh, Orloski, & Wyne, 2010). When prediabetes leads to

diabetes, it affects the entire body, with individuals often developing major complications such as nephropathy, retinopathy, and peripheral neuropathy. Researchers suggest that diabetes doubles the risk of depression, and that risk increases as more diabetes-related health problems develop (CDC, 2018).

Known risk factors place an individual at an increased risk for prediabetes and T2DM. Known risk factors include, being overweight, age 45 years or older, first degree relative with T2DM, member of a high risk population (African American, Hispanic/Latino, American Indian, Alaska Native, Asian American, Pacific Islander), physical inactivity, history of gestational diabetes, or giving birth to an infant over 10 pounds, hypertension, low high density lipoprotein (HDL) cholesterol level, high triglycerides (TG) level, atherosclerotic cardiovascular disease, conditions associated with insulin resistance (acanthosis nigricans, non-alcoholic steatohepatitis, polycystic ovarian syndrome), and treatment with atypical antipsychotics or glucocorticoids (CDC, 2018; National Institute of Diabetes and Digestive and Kidney Diseases, n.d.).

Prediabetes Management and Current Use of Metformin

Currently, screening for prediabetes is vague, often mimicking screenings for T2DM. The American Academy of Clinical Endocrinologists (AACE) recommends that individuals who meet any of the clinical risk criteria, noted above, should be screened for prediabetes or T2DM (AACE, n.d.). If results are normal, repeat testing at least every three years, but if an individual has two or more risk factors, annual screening should be considered (AACE, n.d.). Primary treatment goal for prediabetes is to normalize glucose and prevent the progression to diabetes and microvascular complications (AACE, n.d.). Therapeutic lifestyle management through a healthy diet, physical activity, and weight loss is the first choice in management for prediabetes. Therapeutic lifestyle management entails patient self-monitoring, realistic and stepwise goal

setting, stimulus control, cognitive strategies, social support, and appropriate reinforcement (AACE, n.d.). Medical nutrition therapy consists of consistency in day-to-day carbohydrate intake, limitation of sucrose-containing or high-glycemic index foods, adequate protein intake, and weight management (AACE, n.d.). Physical activity and weight loss entails individuals being evaluated initially for contraindications and/or limitation to increased physical activity, an exercise prescription should be developed for each patient based on his or her goals and limitations, and any new physical activity should be started slowly and built up gradually (AACE, n.d). In addition to therapeutic lifestyle management there are pharmacological approaches to glucose management in prediabetes when diet, weight loss, and physical activity have not been enough. Pharmacological approaches include, acarbose, thiazolidinediones, insulin glargine, glucagon-like peptide-1 (GLP-1) receptor agonists and metformin. Metformin is usually the first line option when adding a pharmacological agent as it has been shown to have beneficial effects on metabolic syndrome components, including mild to moderate weight loss, lipid profile improvements, and improved fibrinolysis (AACE, n.d.). However, due to inconsistent and vague guidelines regarding screenings and treatment, metformin has been considered underutilized and under prescribed. This systematic review delves into the research regarding metformin's effectiveness compared to lifestyle modifications, safety, tolerability, reduction in microvascular complications and understand the barriers to prescribing.

Clinical Question

Based on the above phenomena of interest, the following clinical question was developed in PICO format to guide a systematic review of the literature: *For adults with Prediabetes (P), does the use of metformin (I) reduce the future risk of developing T2DM Mellitus and vascular complications (O) when compared to the usual practice of lifestyle modification alone (C)?*

Importance for Primary Care Providers

Nurse practitioners frequently work as primary care providers and will see patients frequently who have one or more risk factors for prediabetes and T2DM. A lack of adequate knowledge regarding how to screen, manage and treat prediabetes can contribute to longstanding future complications for the patient and family as well as unnecessary spending and cost for our health care system. When prediabetes is left untreated and unchecked, it has the ability to progress to T2DM, which can lead to microvascular complications such as hypertension, hyperlipidemia, heart disease, stroke, kidney disease, nerve damage, vision problems (possibly loss of vision), and amputations (Mayo Clinic, 2020). Lifestyle management (diet, physical activity and weight loss) is at the core of treatment for prediabetes and T2DM, but what about individuals where lifestyle management isn't enough or barriers such as age and other medical conditions prevent lifestyle management? The AACE guidelines suggest metformin therapy for prevention of T2DM should be considered in those with prediabetes, especially for those with BMI over 35 kg/m2, those ages under 60 years, and women with prior gestational diabetes (AACE, n.d.). Unfortunately, providers are underutilizing metformin as a treatment option for prediabetes whether that is from a lack of knowledge, inconsistent and vague guidelines, or doubt regarding metformin effectiveness, efficacy and/or safety is unclear. Nurse Practitioners and other primary care providers need to bridge the knowledge gap regarding metformin's use in treatment and management of prediabetes to provide clear cut guidelines regarding screening, treatment and management of prediabetes so we can all work to improve the overall health and well-being of diabetes patients with competence and confidence.

Methods

A systematic literature review was performed to explore the current literature as it pertains to the clinical question listed in the previous section. Six databases were chosen to provide a wide range of sources and information including CINAHL Plus with Full Test (CINAHL), Academic Search Premier, MEDLINE (PubMed), SAGE Journals, Google Scholar (GS), and Nursing and Allied Health Database. Table 1 provides rationales for choosing the six databases, as well as a list of search restrictions and date ranges for each database. The keywords prediabetes, pre-diabetes, lifestyle modification, medications, pharmacological intervention, metformin, prediabetes management, pre-diabetes management, prediabetes treatment, pre-diabetes treatment, gestational diabetes, weight loss, pioglitazone, and insulin were searched individually and/or in combination with other keywords in all six databases (see Table 2 in Appendix for specific keyword combination searches). Of note, the terms gestational diabetes, weight loss, pioglitazone, and insulin were excluded terms, meaning they were used to specify that the articles were not to include these terms to help narrow down article selection.

The number of articles obtained in every keyword search or combination in each database were recorded, and searches with 15 or fewer articles were chosen for a review (see Table 2 in Appendix, articles for further review are bolded and marked with an asterisk). Of the articles that were chosen for a brief review, if they eluded a relevance to the identified clinical question or provided important and relevant information to the overall phenomenon these were marked for a more in-depth review (see Table 2 in Appendix). There were 72 articles identified, after eliminating duplicate articles, this review yielded 54 articles to be reviewed for inclusion or exclusion in the literature review. After extensively reviewing all 54 articles for relevance of the identified clinical question, 25 articles met the inclusion criteria.

The 25 articles that met inclusion criteria directly addressed (a) the pharmacodynamics of metformin; (b) whether metformin alone is superior to lifestyle modifications in preventing or delaying the progression from prediabetes to T2DM; (c) whether metformin combined with lifestyle modifications is superior to lifestyle modifications alone in preventing or delaying the progression from prediabetes to T2DM; (d) the safety, tolerability, and cost-effectiveness of metformin; (e) metformin's role in the reduction of microvascular complications that often coincide with T2DM; (f) barriers to screening/diagnosing prediabetes and barriers to prescribing metformin; and (g) specific population where metformin may reign superior to lifestyle modification alone. The 29 articles that met exclusion criteria directly addressed (a) lifestyle modification alone (no inclusion of metformin or pharmacological interventions), (b) an incorrect target population (i.e., pediatrics and adolescents only), (c) incorrect disease progression (i.e., volunteers/patients/participants already diagnosed with T2DM), and (d) language barrier, such as those available only in Spanish (see Table 3 in Appendix for specific detail regarding the rational for exclusion and inclusion of each article).

The 25 articles chose for the literature review were read in entirety and analyzed for identification of study purpose, population/size/setting, level of evidence, variables/instruments, findings, and implications for practice. The Hierarchy of Evidence (Melynk & Fineout-Overholt, 2015) was used to identify the strength of the research evidence according to levels. The highest level of evidence obtained were two level I studies, which were systematic reviews of metal-analyses or randomized control trials. There were nine level II studies included, which were all randomized control trials. Two level III articles were identified, one being a retrospective cohort study and the other an observational study. There were four level IV studies included, with a mix of cross-sectional analysis and scoping review of literature. Level V had seven articles included,

all of which were expert opinion (see Table 4 in Appendix for further detail on level of evidence and data abstraction of included articles).

The search methods used for this systematic literature review included a variety of databases and wide range of keywords, which yielded a variety of high-level evidence articles that applied to the clinical question. The search methods yielded a high number of articles which provided the ability to be detailed in the exclusion/inclusion criteria to obtain the highest quality and level of evidence data out there for this specific phenomenon. Other databases, such as Cochrane could have been included and may have provided more systematic reviews. These methods yielded a strong body of evidence with nearly half of the studies at a level I or II.

Literature Review

Pharmacodynamics of Metformin

Metformin is the world's most prescribed anti-diabetic drug and is effective in delaying/preventing T2DM in people at high risk, by lowering body weight, fat mass, and circulating insulin levels through mechanisms that aren't completely understood (Coll et al., 2019). Metformin's pharmacological mechanisms of action is that it decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization (FDA, 2006). However, even though these mechanisms of action of metformin have been identified, they do not sufficiently explain the beneficial weight loss promoting effects (Coll et al., 2019). Recent studies have seen an association between metformin and circulating levels of GDF-15. GDF-15 is a peptide hormone produced by cells responding to a wide range of stressors and acts through a receptor complex solely expressed in the hindbrain, where it suppresses appetite and thereby food intake (Coll et

al., 2019). It was proposed through this association that metformin's effect to lower body weight as well as other effects in prediabetes involves the elevation of circulating levels of GDF-15 (Coll et al., 2019). In a randomized placebo-controlled trial of metformin, GDF-15 was measured in participants without diabetes over a period of 18 months (Coll et al., 2019). Over that period, participants receiving metformin lost significantly more weight compared to placebo and correlated with higher levels of GDF-15 (Coll et al., 2019). It was found that weight loss was positively correlated to the levels of plasma GDF-15 (Coll et al., 2019). In this same study, wild-type mice were given oral metformin and were shown to have increased circulating GDF-15 with GDF-15 expression increasing predominately in the distal intestine and kidney (Coll et al., 2019). When provided with a high fat diet and administered metformin, metformin prevented weight gain, but not in mice lacking GDF-15 or its receptor glial-cell-line-derived neurotrophic factor family receptor alpha like (GFRAL) (Coll et al., 2019). Essentially, metformin worked at preventing weight gain only in mice that had the peptide hormone GDF-15.

Metformin was also found to have effects on energy intake, energy expenditure, insulin sensitization, and insulin tolerance that all required GDF-15 (Coll et al., 2019). Metformin is the only glucose-lowering medication or therapy that has been found to acutely increase serum GDF-15 levels, especially in patients with insulin resistance or T2DM (Coll et al., 2019). Knowing that GDF-15 signals through a specific receptor complex through the hindbrain to reduce body weight and that metformin has the ability to increase GDF-15 is a major development in the prevention or delaying of T2DM in prediabetic patients because weight loss is one of the primary goals of prediabetic and diabetic treatment. These findings open avenues into more research as to the role metformin plays in diabetes and beyond. According to Day et al. (2019):

> There are currently over 1,500 registered clinical trials to test the effects of metformin in different diseases, including cancers, cardiovascular disease and even ageing. Mice overexpressing GDF15 have enhanced lifespan and are protected from atherosclerotic cardiovascular disease. These phenotypes are remarkably similar to those induced by metformin, which also reduces cardiovascular disease and potentially improves lifespan. Therefore, the possibility that GDF15 has a causal role in multiple beneficial effects of metformin treatment warrants further investigation (p. 1206).

These findings allow insight into why and how metformin prevents or delays T2DM in prediabetic individuals. This knowledge has potential to inform providers who treat diabetic patients on the best and most effective treatment options available.

Metformin Versus Lifestyle Modifications

Currently the gold standard and most practiced approach to treatment of prediabetes and delaying progression to T2DM is lifestyle modifications, including weight loss, physical activity, and healthy diet. It is not until the individual and disease progress to T2DM that pharmacological interventions such as metformin are used. Research has shown that metformin is effective in treating and sustaining T2DM. Can metformin be just as effective as lifestyle modifications in the treatment of prediabetes, whether that be in combination or solely?

The Diabetes Prevention Program Research Group (2002) conducted one of the biggest studies that compared lifestyle-modifications to metformin and their ability to reduce the incidence of diabetes. There were 3,234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations (prediabetes) that were randomly placed into a placebo, metformin, or lifestyle-modification program (Diabetes Prevention Program Research Group,

2002). The control group was given nothing, metformin group was prescribed metformin 850 mg twice daily and the lifestyle-modification group was given a goal of attaining a 7 percent weight loss and participating in at least 150 minutes of physical activity per week (Diabetes Prevention Program Research Group, 2002). After an average 2.8 year follow-up the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 persons in the placebo, metformin, and lifestyle groups which equated to a reduced incidence by 58 percent in the lifestyle group and 31 percent in the metformin group when compared to the placebo group (Diabetes Prevention Program Research Group, 2002). To prevent one individual from being diagnosed with diabetes in a three-year period, 6.9 persons would have to participate in the lifestyle intervention program while 13.9 would have to receive metformin (Diabetes Prevention Program Research Group, 2002). It was shown that lifestyle modifications and metformin both reduced the incidence of diabetes, however, lifestyle modifications were more effective in the side by side comparison (Diabetes Prevention Program Research Group, 2002). An interesting finding that came out of this study was regarding compliance to the two interventions. Fifty-percent of the individuals in the lifestyle-intervention group achieved their goal weight loss by the end of the 24 week period and thirty-eight percent had that goal weight loss at the most recent visit which was over a year later (Diabetes Prevention Program Research Group, 2002). Individuals who met the physical activity goal of 150 minutes seven times a week was seventy-four percent at 24 weeks and fifty-eight percent at the most recent visit (Diabetes Prevention Program Research Group, 2002). For the individuals taking the placebo and metformin pills, ninety-seven and eight four percent respectively were compliant (Diabetes Prevention Program Research Group, 2002). It is evident that compliance with taking a daily medication was far superior then lifestyle modifications such as health eating and physical activity and can play a key role in the success of the treatment.

In a similar study to The Diabetes Prevention Program, 3,041 adults with hyperglycemia were randomly selected into lifestyle, metformin, or placebo groups. The dependent variables in this study were weight loss at 6 and 12 months; FPG at 6 months; A1C at 6 months, and post-load glucose at 12 months with the main outcome being time to diabetes diagnosis (Maruthur et al., 2013). In six months, 140 individuals developed diabetes in the lifestyle group, 206 in the metformin group, and 258 in the placebo group (Maruther et al., 2013). In all groups, at attainment of optimal 6-month FPG and A1C and 12-month post-load glucose predicted a greater than sixty percent lower risk of diabetes (Maruther et al., 2013). It was found that there was certain variable that could predict decreased diabetes risk depending on what group an individual was assigned. For the lifestyle group, variables such as weight loss and FPG were better predictors of decreased diabetes risk. In the metformin group, early reduction in glycemia, looking at the variables of FPG, A1C and post-load glucose were stronger predictors of future diabetes risk than weight loss was (Maruther et al., 2013). This information could guide providers in management decisions based on what treatment their patient is receiving. If their patient is participating in lifestyle intervention, then looking at variables such as weight loss and FPG may be more important when understanding if their treatment is effective and their risk of progressing to T2DM.

In a trail similar to the previous two, 103 participants were divided into three groups, standard care, intensive lifestyle modification, intensive lifestyle modification and metformin (Kulkarni et al., 2018). In this trial they variables looked at were weight, fasting blood sugar, A1C, high-sensitivity C-reactive protein (hsCRP) (risk factor for atherosclerosis), and carotid intima-media thickness (CIMT) after six months (Kulkarni et al., 2018). After six months, there was a reduction in weight and fasting blood sugar in all three groups and A1C in the intensive

lifestyle modification (ILSM)+Metformin group (Kulkarni et al., 2018). Over six months the difference in hsCRP within the three groups were -0.12 (standard care), -0.58 (ILSM), and -.11 (ILSM+Met) (Kulkarni et al., 2018). Regarding CIMT, there was no difference between the three groups at six months (Kulkarni et al., 2018). Interesting enough, in the standard care group there was a significant reduction in the waist-hip ratio, LDL cholesterol, and triglycerides, which was not seen in the other two groups (Kulkarni et al., 2018). Metformin and exercise have shown to reduce hsCRP and other inflammatory biomarkers in prediabetes and diabetes which reduces CVD risk (Kulkarni et al., 2018). This trial did not look solely at metformin compared to lifestyle interventions, instead looked at the combination of the two. This data suggests that metformin has the ability to reduce relative risk and may have the extra benefit of reducing A1C in combination with ILSM or solely.

In a hallmark study, the UK Prospective Diabetes Study Group (1998) confirmed this finding with their study that compared metformin with the conventional group (insulin or sulphonyl urea therapy) and found that the metformin group had a A1C of 7.4percent compared to 8.0percent in the conventional group (UK Prospective Diabetes Study Group, 1998). It was also found that metformin, compared to conventional therapy, had risk reductions of 32percent for any diabetes-related endpoint, 42percent for diabetes-related death, and 36percent for all-cause mortality (UK Prospective Diabetes Study Group, 1998). Based off these findings and the fact that metformin decreases the risk of diabetes related endpoints, is associated with less weight gain (actually aides weight loss), and has fewer hypoglycemic attacks then other pharmacological interventions, it was suggested that metformin be the first-line therapy (UK Prospective Diabetes Study Group, 1998). Sheng et al., (2019) further supports that the progression of diabetes could be delayed to varying degrees by lifestyle and pharmacological

interventions except for angiotensin-converting enzyme inhibitors, statins, sulfonylureas and vitamin D. “In adults with pre-diabetes, firm evidence supports the notion that lifestyle modifications and metformin reduces the incidence of diabetes with an average of 20percent relative risk reduction, while statins increase the relative risk 20percent” (Sheng et al., 2019, p. 1). Regarding lifestyle modifications, long-term strategies that involve three factors, nutrition, exercise, and weight loss, contribute to an abundance of positive results such as reducing BMI, body weight, waist and hip circumference, systolic and diastolic pressure, fasting, and 2-h postprandial blood glucose, total cholesterol and by increasing HDL (Sheng et al., 2019).

There have been a number of clinical trials that demonstrated the effectiveness of lifestyle and/or pharmacological therapy at preventing or delaying the progression to T2DM in prediabetic patients, but none have looked at the other side of the spectrum and how effective interventions are at returning prediabetic patients to normal glucose ranges (Perrault et al., 2009). Perrault et al., (2009), examined the effect of basal biologic factors, weight change, and prevention strategies such as intensive lifestyle intervention or metformin on the incidence of regression from prediabetes to normal glucose range. There were two major findings in this study. The first finding was that insulin secretion, and other biologic processes that are retained with younger age are key in restoring prediabetics to normal glucose ranges (Perrault et al., 2009). The other finding was that through weight loss and intensive lifestyle interventions normal glucose ranges can be restored in prediabetic patients, meaning metformin, while effective in preventing progression to T2DM, it is not effective in restoring normal glucose ranges (Perrault et al., 2009). Weight loss was shown to be the most important aspect of intensive lifestyle interventions as with every 1 kg loss there was an associated 16 percent reduction in diabetes risk (Perrault et al., 2009). However, other aspects of intensive lifestyle

interventions such as healthy eating and exercise also restored normal glucose ranges, though not as effective as weight loss. There was one nonmodifiable predictor that could play a major role in prediabetes management and that was age. Younger individuals had a greater associated with regression to normal glucose ranges then older individuals, meaning intensive lifestyle interventions may be more effective in the younger population and not as effective in the older and therefore other strategies may come in play for prediabetes treatment as an individual ages (Perrault et al., 2009).

It has been shown that lifestyle interventions reduce the relative risk of diabetes in individuals with prediabetes but what happens when lifestyle interventions are no longer as effective in improving glycaemia? There have only been a few studies that looked at pharmacological effectiveness in individuals who were deemed non responders to lifestyle interventions (Ibrahim et al., 2018). These studies found that metformin treatment was associated with a thirty-one percent risk reduction for diabetes compared to placebo (Ibrahim et al., 2018). They also found that other pharmacological interventions such as orlistat, pioglitazone, and liraglutide had relative risk reduction for diabetes by thirty-seven, seventy-two, and sixty-six percent respectively (Ibrahim et al., 2018). The major barriers with other pharmacological interventions other than metformin is cost and side effects. When you consider the non-responders to lifestyle interventions; young age at diagnosis of diabetes, relatively lower BMI, high rates of insulin resistance and lower thresholds for the risk factors of diabetes and compare metformin with lifestyle interventions that effectives becomes almost identical (Ramachandra et al., 2006). In a study that looked at native Asian Indians who are considered to be high risk for progression to diabetes, the effects of lifestyle modification, metformin, and lifestyle medication with metformin were compared (Ramachandra et al., 2006). They found that the relative risk

reduction to diabetes was 28.5 percent with the lifestyle modification group, 26.4 percent with the metformin group, and 28.2 percent with the lifestyle modification and metformin group (Ramachandra et al., 2006). To prevent 1 case of diabetes, you would have to treat 6.4 persons with lifestyle modifications, 6.9 with metformin, and 6.5 with lifestyle modification and metformin (Ramachandra et al., 2006). In individuals who are considered high risk and uniquely present with prediabetes where BMI and weight are not major factors, metformin can play a role in prevention progression to T2DM.

Individuals with A1C of 5.7-6.4 percent, impaired glucose tolerance, and/or impaired fasting glycemia should all be counseled on lifestyle modifications with the goal of 7 percent weight loss and moderate physical activity 150 minutes per week (Standards of Medical Care in Diabetes, 2012). Metformin should be the only drug considered for pharmacological intervention as other drugs have issues with cost, side effects and lack of research (Standards of Medical Care in Diabetes, 2012). Even though metformin was less effective than lifestyle interventions in certain studies, there may be cost saving over a 10-year period and metformin has shown to be effective; (a) in individuals with a BMI of at least 35 kg/m2, (b) in women with a history of gestational diabetes where metformin and lifestyle interventions led to a 50 percent reduction in risk of diabetes (Standards of Medical Care in Diabetes, 2012). It is reasonable to consider metformin usage in these individuals (Standards of Medical Care in Diabetes, 2012).

In summary, research shows that lifestyle modifications were most effective in preventing or delaying the progression of prediabetes to T2DM, however, there were certain scenarios where metformin can play a significant role and be equally as effective.

Safety and Tolerability

One barrier to prescribing and administration of metformin for treatment of prediabetes is the safety and tolerability of metformin. Common reactions of metformin are as follows: diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, anorexia, headache, metallic taste, and rash (Epocrates, n.d.). Serious reactions can include lactic acidosis, anemia, and hepatotoxicity (Epocrtes, n.d.).

In a study conducted by the Diabetes Prevention Program Research Group found that gastrointestinal (GI) symptoms were more common among metformin compared with placebo participants, averaging 28 percent and 16 percent respectively (Diabetes Prevention Program Coordinating Center, 2012). Metformin participants also reported "study medication-related" GI symptoms more frequently than the placebo group (9.5percent vs. 1.1percent) (Diabetes Prevention Program Coordinating Center, 2012). GI symptoms included diarrhea, flatulence, nausea, and vomiting (Diabetes Prevention Program Research Group, 2002). GI symptoms did decline throughout the study and by year 6, rates of GI symptoms were similar in the metformin and placebo group (Diabetes Prevention Program Coordinating Center, 2012). Symptoms did vary by race/ethnicity and sex (data not provided regarding which race/ethnicity or sex reported higher rates of symptoms), however, overtime symptom rates became similar by demographic group (Diabetes Prevention Program Coordinating Center, 2012). Reports of nonserious adverse events such for hypoglycemia and anemia were uncommon, and no differences were reported between groups (Diabetes Prevention Program Coordinating Center, 2012). There were seven metformin and eight placebo participants that reported hypoglycemia while fifty metformin and thirty-eight placebo participants reported anemia (Diabetes Prevention Program Coordinating Center, 2012). Serious adverse events were even rarer with three reports for anemia (two

metformin, one placebo) and zero for lactic acidosis (Diabetes Prevention Program Coordinating Center, 2012).

During the Diabetes Prevention Program study, hemoglobin (Hgb) and hematocrit (Hct) levels were closely followed and it was found that average Hgb and Hct levels were the same at baseline and over time were slightly lower in the metformin compared to the placebo group (Diabetes Prevention Program Coordinating Center, 2012). Again, Hgb and Hct levels varied by race/ethnicity and sex, but overtime became similar (Diabetes Prevention Program Coordinating Center, 2012). Percent of participants with low Hgb was not significantly different between metformin and placebo group (11.2 percent vs. 7.6 percent) but were more different regarding low Hct (12.6 percent vs. 8.4 percent). Hgb and Hct changes occurred during the first year with stabilization shortly after (Diabetes Prevention Program Coordinating Center, 2012). Overall, metformin participants did have slightly higher rates of GI symptoms and nonserious adverse events, but these improved with time and did not ultimately affect their compliance and adherence to the medication regimen.

When comparing metformin and lifestyle modification, GI symptoms was highest in the metformin group, but musculoskeletal (MSK) symptoms was highest in the lifestyle-intervention group (Diabetes Prevention Program Research Group, 2002). MSK symptoms included myalgia, arthritis, and arthralgia. In this study, rates of other adverse events, hospitalization, and mortality were comparable (Diabetes Prevention Program Research Group, 2002). It was concluded that metformin and lifestyle interventions were safe in addition to being effective (Diabetes Prevention Program Research Group, 2002). It is important to understand that with any treatment option for prediabetes, there are side effects and risks, however, these regress as the longer the

patient is on the medication and therefore weighing benefits, risks, and side effects is extremely important.

Reduction in Macrovascular Complications

Individuals with diabetes mellitus and prediabetes are at an increased risk for macrovascular complications, including coronary artery disease, atherosclerosis, and cardiovascular disease.

Coronary heart disease (CHD) risk is doubled in T2DM mellitus and is the top cause of morbidity and mortality in T2DM (Goldberg et al., 2017). A 1 percent increase in HbA1C was associated with a 21 percent increased risk of CHD events and a 37 percent increase in retinopathy or nephropathy (Newman et al., 2017). Interventions targeting dyslipidemia, hypertension, and hyperglycemia have reduced CHD in the general population, however, diabetes-related CHD risk remains, signifying there may be limitations to benefits of interventions targeted at CHD in diabetics (Goldberg et al., 2017). To reduce CHD preventative approaches, need to be addressed and initiated as early as possible, including diabetes prevention itself (Goldberg et al., 2017).

In a study conducted with the Diabetes Prevention Program Research Group, subclinical atherosclerosis was assessed in individuals with coronary artery calcium (CAC) (Goldberg et al., 2017). CAC measurements are a noninvasive tool that reflects total coronary atherosclerotic burden, helping predict CHD (Goldberg et al., 2017). Research found that in men but NOT in women, CAC severity and presence were lower in the metformin compared with the control group (Goldberg et al., 2017). When comparing the metformin and lifestyle group, CAC severity and presence were similar (Goldberg et al., 2017). Race/ethnicity and age did play a role in the

CAC severity and presence, with lower CAC being found in younger men (Goldberg et al., 2017). No CAC differences were identified between the two groups (Goldberg et al., 2017). Metformin reduced early stages of plaque development in men and CHD events compared with diet and sulfonylurea placebo groups, suggesting that metformin may be beneficial in preventing coronary atherosclerosis in prediabetic patients (Goldberg et al., 2017). In a recent treatment program using metformin in subjects with HIV infection and metabolic syndrome, it was found that metformin reduced CAC progression compared to a placebo group (Goldberg et al., 2017).

Of note, there was a gender difference in the effect of metformin on CAC that was observed in this study but has not been observed in other studies. In women, CAC severity was lower, making it harder to study the effect of metformin (Goldberg et al., 2017). More than half of the women in the study had measurable CAC levels yet metformin did not have an effect on CAC presence (Goldberg et al., 2017). In this study, 36 percent of women were premenopausal, and it is known that atherogenesis proceeds more slowly in premenopausal women, contributing to the lack of effect of metformin in women (Goldberg et al., 2017).

There was no reduction in the prevalence of clinically significant CAC in men that had high CAC levels compared with placebo group, meaning the effects of metformin were more paramount with lower levels of CAC (Goldberg et al., 2017). Lower CAC scores are associated with a significant increase in CHD event rate, implying that metformin has a greater effect when the individual has smaller and recently calcifying plaques rather than well-established lesions which would support the evidence that metformin has a greater effect on CAC severity in younger men (Goldberg et al., 2017). This could mean that metformin has less clinical efficacy in older men, but more testing would have to be conducted before this could be determined.

Of importance, lower CAC in the metformin group was noted regardless of whether diabetes mellitus had developed (Goldberg et al., 2017). There has been question whether metformin was effective in reducing vascular complications before the development of T2DM regardless of its ability to delay diabetes development and its use in prediabetes. Based on the information presented above, the sooner metformin is started before or after diabetes diagnosis the more of a beneficial effect it has on early stages of atherosclerosis in men, though more research is needed regarding its effect in women (Goldberg et al., 2017).

Even though macrovascular complications such as CAD is the leading cause of mortality and morbidity for patients with T2DM, there is a lack of research or evidence regarding metformin's role and ability to reduce those macrovascular complications. Metformin has been proven to reduce weight gain, improve glycemic control, and reduce insulin requirements, which all may have a direct benefit on reducing CHD and macrovascular complications.

Barriers to Metformin Prescribing

Metformin has been shown through research that it can be an effective new therapy for the treatment of prediabetes and progression to T2DM, yet Metformin continues to be under prescribed and underutilized in this population. The reasons as to why metformin use remains low are not entirely clear, however, research has set its sights on the front lines, trying to understand the barriers providers face when prescribing metformin for treatment of prediabetes.

In a study that estimated the rates of prevalence, diagnosis, and treatment of impaired FPG (IFG) and impaired glucose tolerance (IGT) found that approximately 34.6 percent of the United States population met the criteria for prediabetes diagnosis and that life-style modification and metformin reduced the incidence of T2DM by 58 percent and 38 percent

respectively in just 3 years (Karve & Hayward, 2010). Yet, only 3.4 percent of the 34.6 percent of the individuals meeting prediabetes criteria reported that their physicians diagnosed them with prediabetes (Karve & Hayward, 2010). None of those individuals reported receiving metformin (Karve & Hayward, 2010). In a study that examined metformin prescription for diabetes prevention and patient characteristics that may affect metformin prescription, reported better results, suggesting that 3.7 percent of insured, working-age adults with prediabetes, were prescribed metformin over a three-year period (Moin et al., 2015). It was found that the prevalence of metformin prescription was higher among patients with a history of gestational diabetes or a BMI < 35 kg/m2, but that was still only at 7.8 percent (Moin et al., 2015). Meaning less than 1 of 12 high-risk patients, who met criteria based off national guidelines, received metformin (Moin et al., 2015). This extremely low rate is concerning given the significant benefits metformin potentially can offer patients.

There are theories as to the extremely low metformin prescription rate such as physicians do not emphasize the importance of prediabetes to their patients, physicians do not adequately screen for and diagnose prediabetes, physicians do not recommend lifestyle modification to prediabetic patients any more intensively than normoglycemia subjects, physicians are unaware of metformin's benefits or they are aware of the benefits, but find them unconvincing (Karve & Hayward, 2010). Tseng (2017), found that six percent of providers were able to correctly identify all the risk factors that should trigger screening. On average, providers were able to identify 8 out of the 11 risk factors with the most commonly identified risk factors being family history, overweight, history of gestational diabetes, dyslipidemia, hypertension, and history of heart disease (Tseng et al., 2017). The least-commonly identified risk factors were Hispanic and Asian ethnicity (Tseng et al., 2017). A total of 17 percent of providers were able to identify the

laboratory parameters for diagnosing prediabetes based on both FPG and A1C (Tseng et al., 2017). Family medicine and medicine-pediatric providers were able to correctly identify the parameters more often than internal medicine providers (Tseng et al., 2017). When patients were diagnosed with prediabetes, 90 percent of providers did report close follow-up with them, often seeing their patients with 6 months of diagnosis (Tseng et al., 2017). As far as a management approach, one-quarter of providers selected the correct value regarding the minimum amount of weight loss recommended and nearly 30 percent answered they did not know (Tseng et al, 2017). Less than half of the providers selected the right answer regarding the recommended minimum amount of physical activity and when asked to identify the best recommended initial management approach only 11 percent selected a referral to a behavioral weight loss program, while 96 percent selected educating patient on diet and physical activity (Tseng et al., 2017).

Providers agreed that diagnosing prediabetes is important regarding their patients' health and that lifestyle modification minimizes that progression, but providers disagreed that metformin could do the same (Tseng et al., 2017). Lack of motivation, patient's physical limitations in doing activity, and lack of weight or nutrition resources were all selected as barriers to lifestyle modifications and providers feel as though they need more time for counseling, more educational resources for patients, improved nutrition resources, and access to weight loss programs to improve prediabetes management (Tseng et al., 2017). Providers feel as though patient's avoidance of medications, pharmacological side effects, and anticipated poor adherence are barriers to metformin use in prediabetes, NOT medication cost or lack of FDA approval for metformin use in prediabetes (Tseng et al., 2017).

These findings highlight concern about translation of decade-old evidence support the use of metformin in treatment of prediabetes and diabetes prevention (Moin et al., 2015). The lack of

translation of a safe, evidence-based therapy for a highly prevalent epidemic is a public health nightmare (Moin et al., 2015). While lifestyle modification can be cost-effective, metformin has the potential to be cost saving (Moin et al., 2015). Ideally, all patients who meet diagnostic criteria would be diagnosed with prediabetes and all of them would pursue lifestyle interventions. Research is showing that this is simply not true. Minimally, patients should be educated about the potential benefits of metformin and should be offered this option as preventative treatment (Moin et al., 2015). However, before anything can be done, providers need to be educated regarding risk factors, screening, diagnosis, management, and treatment of prediabetes. According to Tseng (2017):

> PCPs had substantial gaps in knowledge about prediabetes that need to be addressed for interventions, such as the CDC prediabetes screening and prevention campaign, to be successful. Educating providers on screening guidelines, diagnostic criteria and management options will be the important first step to filling these gaps. The role of professional societies in improving knowledge and addressing attitudes cannot be underestimated. Systems changes to support provider behavior are also important. Despite substantial evidence for the effectiveness of DPPs, they remain underutilized. Reasons for this are likely complex and warrant further investigation. Expanding insurance coverage and the availability of these high quality, comprehensive programs are essential. With these changes, PCPs are optimally positioned to take a lead in curbing the diabetes epidemic (p. 1177).

Special Population Needs

Primary treatment goal for prediabetes is to normalize glucose and prevent the progression to diabetes and microvascular complications (AACE, n.d.). Therapeutic lifestyle

management through medical nutrition therapy (MNT), physical activity, and weight loss is the first choice in management for prediabetes. However, there are special populations that may benefit more from the addition of metformin due to their unique barriers that do not allow lifestyle interventions to be as effective.

In a study conducted by the Diabetes Prevention Program Research Group (2002), lifestyle intervention alone was least effective in older participants due to their physical limitations, which means there needs to be a consideration regarding whether a patient can participate effectively in lifestyle interventions to make a difference. It was suggested that older patients my need to have metformin added to their treatment regimen early on due to their physical limitations (Diabetes Prevention Program Research Group, 2002). There are populations that have physical, cognitive or both barriers that can significantly limit their ability to participate in physical activity or follow a strict regimented diet plan. With these specific and unique populations, metformin may be a more appropriate first line therapy then lifestyle interventions.

Another finding was that metformin was less effective in persons with a lower BMI or a lower FPG concentration, meaning the effectiveness of metformin may increase with FPG concentration and how advanced the individual is in their diabetes (Diabetes Prevention Program Research Group, 2002). Now, this does not mean that an individual has to have a high BMI or high FPG concentration for metformin to be effective, it means that metformin tends to be more effective when the more advanced the disease is. This is an important point because metformin does have an added cost and therefore the patient may not get their bang for their buck if they are borderline prediabetic. If a patient has a relatively low BMI and low FPG concentration but still considered prediabetic, the more cost-effective treatment may be lifestyle modifications. In

contrast, if an individual has a high BMI and high FPG concentration and is considered prediabetic, metformin may be the more cost-effective treatment.

There is also evidence that metformin should be strongly considered for patients who are younger than 60 years of age, those with a BMI over 35 kg/m2, or those with a history of gestational diabetes (Moin, 2015). Nathan (2007) elaborates on that point more by stating patients with elevated IFG and IGT and any of the following: under 60 years of age, BMI over 35 kg/m2, family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL cholesterol, hypertension, A1C greater than 6.0 percent should be treated with lifestyle modifications and/or metformin. When prescribing to any individual it is important to keep in mind that while metformin has been proven to be safe to take, precautions should be taken in patients with renal or hepatic insufficiency.

Ethnicities, such as Asian Indians, Asian American, African American, Alaska Native, American Indian, Hispanic/Latino, Native Hawaiian, or Pacific Island that have a very high progression rate of IGT to diabetes, meaning they are at a high risk of progressing to T2DM if diagnosed with prediabetes. Individuals who are from these ethnicities may benefit from early intervention with metformin due to being considered high risk of progressing to T2DM solely due to their ethnicity (Ramahandran, 2006).

In summary, while lifestyle interventions such as weight loss, exercise, and dietary modifications are considered first line treatment for prediabetes, there are unique circumstances and populations where barriers to lifestyle interventions present themselves. In these populations, metformin should be considered in addition to or first line treatment for prediabetes. However, weight loss, exercise, and dietary modifications should always be addressed and individualized.

Discussion

According to the Centers for Disease Control and Prevention (2019), 84 million American adults have prediabetes. Prediabetes increases an individual's risk of developing T2DM, heart disease, and stroke (CDC, 2019). Lifestyle changes such as weight loss, increasing physical activity and dietary modifications are the first route to preventing prediabetes from escalating into diabetes type 2 or at least delaying the progression. While lifestyle changes have been the gold standard for quite some time, there is still a T2DM epidemic occurring and therefore providers and society are looking for other avenues to help fight the epidemic. When lifestyle modifications fail to provide us with the necessary results and individuals continue to have high glucose levels, where do we turn? In cases where an individual has prediabetes and are considered to be at a high risk for T2DM, recent guidelines recommend considering use of metformin, especially for patients who are under 60 years old, have a BMI over 35 kg/m2, or have a history of gestational diabetes (JAMA, 2017). Metformin used historically for patients with active T2DM can play a role in preventing prediabetes from progressing to T2DM and developing complications.

As you can see, there are a lot of factors that play a role in the screening, diagnosing, and treatment/management of prediabetes to prevent or delay progression to T2DM. The question that was to be answered through this systematic review of literature was: *For adults with Prediabetes, does the use of metformin reduce the future risk of developing T2DM Mellitus and vascular complications when compared to the usual practice of lifestyle modification alone?* Through the literature review, the answer to this question is not black and white. While there is no denying that lifestyle interventions such as weight loss, physical activity, and healthy eating are effective in the treatment/management of prediabetes, metformin does play a role. Yes,

metformin does reduce the risk of developing T2DM compared to the usual practice of lifestyle modification, but is more effective in certain populations such as individuals with physical limitations where physical exercise is not as easy, individuals who are considered high and individuals who do not fit the typical "diabetes mold" (young age of onset of diabetes, a relatively lower BMI, with high rates of insulin resistance and lower thresholds for the risk factors for diabetes). In these individuals, lifestyle modification should still be considered the gold standard, though metformin should be considered as an additional option for treatment. Although diet and physical activity are effective, the sole reliance on such will not be enough, especially for patients who are high risk (Cefula, 2016). Pharmacological interventions, such as metformin, are going to need to be implemented and we cannot rely solely that diet and physical activity will be enough (Cefula, 2016). With the fast-paced life that many adults are living and the constant stress from work and raising a family, adults do not have the time, money, or ambition to commit to the recommended lifestyle modifications. Even though lifestyle modifications are considered the gold standard, they may not be realistic for all. In an ideal world, our diabetic patient would eat healthy and participate in moderate to strenuous activity 150 minutes a week, but many fail to make sufficient or sustained lifestyle changes. Improved success may be achieved by designing a treatment plan that fits into everyday life and is sustainable.

It is important to understand patients outside of the office and examine their everyday lives. For patients with significant time commitments and restraints that make lifestyle changes challenging, metformin may provide them with prevention strategies to avoiding the progression into T2DM. This does not mean stop educating prediabetic patients on lifestyle interventions such as weight loss, exercise, and dietary modifications. Rather, seek to understand that patients

are humans who have lives beyond the doctor's office and in an ideal world they would eat right and exercise the right amount, but that is not the reality. Instead, meet your patient where they are at and do not set them up for failure and be a bystander as they progress into T2DM when you knew from the beginning that lifestyle interventions were going to be hard for them. It is important to educate regarding lifestyle interventions and allow your patients to try that, but it is also important to help them gain control of their health and metformin may provide that for them.

Implications for Future Practice

Recommendations for Clinical Practice

Metformin is under prescribed and underutilized. The lack of awareness of how serious prediabetes is and the associated risks (micro and macrovascular complications) is scary and puts our patients and population at high risk. There is speculation that since metformin is not approved by the U.S. FDA for prediabetes, providers are hesitant to prescribe it, but research is showing the opposite. There is a knowledge gap at the front lines that we need to combat. We cannot simply wait for the U.S. FDA to approve metformin for the treatment of prediabetes, we are in an epidemic right now and if we wait, it will be too late. Although the reasons are not entirely clear, providers lack of knowledge creates a barrier to broader implementation. Closing the knowledge gap for providers regarding screening, diagnosing, and treatment/management of prediabetes has to be at the forefront. Clearer guidelines regarding when to screen patients and who is considered at high risk need to be developed. If metformin is shown to be effective in the treatment of prediabetes, guidelines have to reflect this (Wang et al., 2013). Universal screening is needed. "Noninvasive risk scores should be used in all countries, but they should be locally validated in all ethnic populations focusing on cultural differences around the world" (Ibrahim et

al., 2018, pg. 8). Currently metformin is not approved by the U.S. FDA for prediabetes and therefore may be creating hesitancy to prescribe it "off label" (Moin et al., 2015). High priority needs to be placed on the management of prediabetes. Media campaigns to increase awareness of prediabetes and its consequences if left untreated could be a start to increasing public awareness.

Other strategies to increase awareness and promote informed decision making include, clinical decision-making tools and physician directed and performance-based incentive programs (Moin et al., 2015). Cefalu et al., (2016) states that an early step in advancing preventative strategies for diabetes medical community is to reach an agreement on how to implement programs on a global level. Developing clear guidelines that help providers identify individuals at high risk, when to screen, diagnostic criteria, and treatment/management are necessary. These guidelines also need to pay special attention to pharmacological interventions and acknowledge their benefits in treatment of prediabetes (Cefalu et al., 2016). Understanding an individual's perspectives and preferences is essential to managing prediabetes, but also understanding the providers' perspectives and preferences will provide us with insight as to where the barriers lie and if there is a disconnect between provider and patient.

Recommendations for Research

More research needs to be conducted regarding provider perceived barriers to pharmacological treatment, including metformin and patient perceived barriers to pharmacological treatment and lifestyle interventions. There needs to be an understanding of potential barriers to wider adoption of this safe, tolerable, evidence-based, and cost-effective prediabetes therapy (Moin et al., 2015). More research regarding compliance of pharmacological and lifestyle interventions and how compliance factors in regarding treatment success. Metformin is not the only pharmacological intervention and therefore future research may

include other medications if they prove to be effective, have a good safety profile, are tolerable, and are of relatively low cost (Nathan et al., 2007). Questions regarding benefits of metformin and lifestyle modifications need to be answered. Continuing to follow-up on study participants and analyzing secondary outcomes can help us gain insights into whether glucose concentrations can be maintained at levels below diagnostic criteria and the long-term outcomes (Diabetes Prevention Program Research Group, 2002). There is insufficient evidence regarding the cost-effectiveness of treatment strategies for prediabetes and therefore, research is needed on the long-term cost savings for starting metformin early in prediabetic care. Research, thus far regarding prediabetes has included small sample sizes, relatively healthy prediabetes, and short follow-ups which provides us with only a fraction of information as prediabetes and T2DM can often be lifelong disease and therefore continued research with longer follow-up with adequate sample size could help reassess effects and understand long term effects of interventions (Kulkarni et al., 2018).

Conclusion

Prediabetes has reached epidemic proportions with no signs of slowing. Prediabetes places individuals at an increased risk for T2DM and the associated micro and macrovascular complications. Currently, lifestyle interventions, such as weight loss, physical activity, and healthy diet are the gold standard of prediabetes and T2DM. However, pharmacological interventions have been gaining attention for their efficacy in the treatment of T2DM. This logically leads to questions regarding their role in prediabetes treatment and the prevention or delaying of T2DM. Research has found that lifestyle interventions and metformin are effective in decreasing the incidence of T2DM, although lifestyle interventions have remained most effective. However, most of the research has encompassed small sample sizes with relatively

healthy participants, in unrealistic situations. Our health care system needs to shift from being reactive to proactive. It is clear that we cannot continue to rely solely on lifestyle interventions to control this epidemic. Instead, deploying the evidence surrounding metformin use, in combination with lifestyle interventions can strengthen efforts toward combating the epidemic.

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Appendix

Table 1

Database Search Description

Database (or Search Engine)	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
1. CINAHL Plus with Full Text (CINAHL)	Full text, Peer Reviewed, English Language	Previous 10 years: 2009-2019	All aspects of nursing and allied health
2. Academic Search Premier	Full text, Scholarly (Peer Reviewed) Journals	Previous 10 years: 2009-2019	Citations, abstracts to articles as well as full text of articles from almost every academic subject
3. MEDLINE (PubMed)	Free full text, clinical trial, review, systematic reviews	Previous 10 years: 2009-2019	Citations, abstracts, and full text about medicine, nursing, dentistry, veterinary medicine, health care system, and preclinical sciences
4. SAGE Journals	Content with Full Access	Previous 10 years: 2009-2019	Communication Studies, Criminology, Education, Health Sciences & Nursing, Management & Organization Studies, Materials Science, Non-Profit Leadership, Political Science, Psychology, Sociology, and Urban Studies & Planning.
5. Google Scholar (GS)	Full Text, English Language, Words in the Title of the Article	Previous 10 years: 2009-2019	Peer-reviewed papers, theses, books, abstracts and technical reports from all broad areas of research
6. Nursing and Allied Health Database	Full Text, Peer Reviewed, English Language, Adults	Previous 10 years: 2009-2019	Citations, abstracts, articles about all aspects of nursing and allied health

Table 2

Data Abstraction Process

Date of Search	Key Words	Hits in CINAHL	Hits in Academic Search Premier	Hits in MEDLINE (PubMed)	Hits in SAGE	Hits in Google Scholar	Hits in Nursing and Allied Health Database
10-2-19	Prediabetes	645	1,013	7,047	1,369	4,040	4,141
	Pre-diabetes	463	822	22,402	14,898	1,420	2,570
10-7-19	Prediabetes & lifestyle modification	18	40	229	506	7	124
	Pre-diabetes & lifestyle modification	9	29	232	2195	9	88
	Pre-diabetes & medications	18	37	11713	6668	0	230
	Pre-diabetes & pharmacological intervention	None	**3***	955	2132	0	43
10-15-19	Prediabetes & medications	35	54	4965	772	**1***	318
	Prediabetes & pharmacological intervention	**2***	**6***	394	271	0	53
	Prediabetes & Metformin	23	44	290	280	50	126
	Pre-diabetes & Metformin	14	32	525	694	**9***	83
	Metformin AND prediabetes management OR pre-diabetes management AND Lifestyle Modification	**5***	17	89	49	0	135
10-20-15	Metformin AND Prediabetes Management OR Pre-diabetes Management AND	**4***	**9***	167	0	0	116

	Pharmacological Intervention						
	metformin AND prediabetes treatment OR pre-diabetes treatment AND pharmacological intervention NOT gestational diabetes NOT weight loss NOT lifestyle modifications	18	39	282	0	0	97
	Prediabetes AND Metformin AND Pharmacological intervention	0	0	19	119	0	26
	Pre-diabetes AND Metformin AND Pharmacological Intervention	0	**1***	41	232	0	20
	Pre-diabetes AND Metformin AND Pharmacological Intervention NOT Pioglitazone	0	0	38	0	0	**14***
	Pre-diabetes AND Metformin AND Pharmacological Intervention NOT Pioglitazone NOT insulin	0	0	**7***	0	0	20
	Metformin AND Prediabetes or pre-diabetes AND pharmacological intervention – TITLE	**3***	**4***	0	0	0	**3***

***BOLD** = articles reviewed for match with systematic review inclusion criteria

Table 3

Characteristics of Literature Included and Excluded

Reference	Included/Excluded	Rationale
Alnasrallah, B., Pilmore, H., & Manley, P. (2017). Protocol for a pilot randomized controlled trial of metformin in pre-diabetes after kidney transplantation: The transplantation and diabetes study. *BMJ Open, 7*(8), 1-6. https://doi.org/10.1136/bmjopen-2017-016813	Excluded	Focuses on diabetes mellitus after kidney transplantation
American Diabetes Association. (2012). Standards of medical care in diabetes-2012. *Diabetes Care, 35*, S11-63. https://doi.org/10.2337/dc12-s011	Included	Standard of medical care for pre-diabetes
Arunkumar, D. (2018). The effect of metformin on biochemical parameters in pre and post menopause women with type 2 diabetes mellitus. *Institute of Science Technology and Advanced Studies*. http://hdl.handle.net/10603/224777	Excluded	Focuses on effects of metformin on biochemical parameters in women with T2DM
Bruce, K. D. (2014). Maternal and in utero determinants of type 2 diabetes risk in the young. *Current Diabetes Reports*, *14*(1), 446. https://doi.org/10.1007/s11892-013-0446-0	Excluded	Focuses on the young population
Calanna, S., Scicali, R., Di Pino, A., Knop, F., Piro, S., Rabuazzo, A., & Purrello, F. (2014). Alpha- and beta-cell abnormalities in haemoglobin A1c-defined prediabetes and type 2 diabetes. *Acta Diabetologica*, *51*(4), 567–575. https://doi.org/10.1007/s00592-014-0555-5	Excluded	Reviewed new recommendations for diagnosing prediabetes and T2DM that may constitute new targets for pharmacological interventions. Did not look at pharmacological interventions.
Cefalu, W., Buse, J., Tuomilehto, J., Fleming, G., Ferrannini, E., Gerstein, H., Bennett, P., Ramachandran, A., Raz, I., Rosenstock, J., & Kahn, S. (2016). Update and next steps for real-world translation of interventions for type 2 diabetes prevention: Reflections from a diabetes care editors expert forum. *Diabetes Care, 39*(7), 1186-1201. https://doi.org/10.2337/dc16-0873	Included	Overall view of interventions for T2DM prevention
Chowdhury, K. K., Legare, D. J., & Lautt, W. W. (2013). Lifestyle impact on meal-induced insulin sensitization in health and prediabetes: A focus on diet, antioxidants, and exercise	Excluded	Reviews pharmacological and nonpharmacological interventions, although not does focus on metformin

interventions. *Canadian Journal of Physiology & Pharmacology*, *91*(2), 91–100. https://doi.org/10.1139/cjpp-2012-0228		
Coll, A., Chen, M., Taskar, P., Rimmington, D., Patel, S., Tadross, J., Cimino, I., Yang, M., Welsh, P., Virtue, S., Goldspink, D., Miedzybrodzka, E., Tung, Y., Rodriguez-Cuenca, S., Tomaz, R., Harding, H., Melvin, A., Yeo, G., Preiss, D., … Savage, D. (2019). GDF15 and the beneficial actions of metformin in pre-diabetes. *Cold Spring Harbor Laboratory*. https://doi.org/10.1101/677831	Included	Benefits of metformin in pre-diabetes
Coppell, K. J., Abel, S. L., Freer, T., Gray, A., Sharp, K., Norton, J. K., Spedding, T., Ward, L., & Whitehead, L. C. (2017). The effectiveness of a primary care nursing-led dietary intervention for prediabetes: a mixed methods pilot study. *BMC Family Practice*, *18*, 1–13. https://doi.org/10.1186/s12875-017-0671-8	Excluded	Does not focus on metformin or any pharmacological intervention, instead focusing solely on dietary intervention
Day, E. A., Ford, R. J., Smith, B. K., Mohammadi-Shemirani, P., Morrow, M., Gutgesell, R., Lu, R., Raphenya, A., Kabiri, M., McArthur, A., McInnes, N., Hess, S., Pare, G., Gerstein, H., & Steinberg, G. (2019). Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. *Nature Metabolism*, *1***,** 1202–1208. https://doi.org/10.1038/s42255-019-0146-4	Included	Pharmacodynamics of metformin
Diabetes Prevention Program Research Group. (2012). Long-term safety, tolerability, and weight loss associated with metformin in the diabetes prevention program outcomes study. *Diabetes Care*, *35*(4), 731-737. https://doi.org/10.2337/dc11-1299	Included	Safety, tolerability, and weight loss of metformin and its role in diabetes prevention
Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine*, *346*(6), 393-403. https://doi.org/10.1056/NEJMoa012512	Included	Comparison of lifestyle modification and metformin preventing T2DM
Ferrara, A., Peng, T., & Kim, C. (2009). Trends in postpartum diabetes screening and subsequent diabetes and impaired fasting glucose among women with histories of gestational diabetes mellitus: A report from the translating research into action for	Excluded	Examine trends in postpartum glucose screening for women with gestational diabetes mellitus (GDM), predictors of screening, trends in postpartum impaired fasting glucose (IFG) and diabetes, and diabetes and pre-diabetes

diabetes (TRIAD) study. *Diabetes Care*, *32*(2), 269-74. https://doi.org/10.2337/dc08-1184		
Fujii, R., Junqueira, M., Restrepo, M., & Turatti, L. (2015). Metformin and intensive lifestyle intervention for pre-diabetes – systematic review of efficacy. *Value in Health*, *18*(3), 55-56. https://doi.org/10.1016/j.jval.2015.03.326	Included	Reviews metformin and lifestyle intervention for pre-diabetes treatment
Garnett, S. P., Baur, L. A., Noakes, M., Steinbeck, K., Woodhead, H. J., Burrell, S., Chisholm, K., Broderick, C. R., Parker, R., De, S., Shrinivasan, S., Hopley, L., Hendrie, G., Ambler, G. R., Kohn, M. R., & Cowell, C. T. (2010). Researching effective strategies to improve insulin sensitivity in children and teenagers – RESIST: A randomized control trial investigating the effects of two different diets on insulin sensitivity in young people with insulin resistance and/or pre-diabetes. *BMC Public Health*, *10*(1), 575–584. https://doi.org/10.1186/1471-2458-10-575	Excluded	Children and teenagers with insulin resistance and/or pre-diabetes, not adults
Goldberg, R. B., Aroda, V. R., Bluemke, D. A., Barrett-Connor, E., Budoff, M., Crandall, J. P., Dabelea, D., Horton, E. S., Mather, K. J., Orchard, T. J., Schade, D., Watson, K., & Temprosa, M. (2017). Effect of long-term metformin and lifestyle in the diabetes prevention program and its outcome study on coronary artery calcium. *Circulation*, *136*(1), 52–64. https://doi.org/10.1161/CIRCULATIONAHA.116.025483	Included	RCT comparing metformin treatment or an individual behavioral lifestyle intervention program with placebo in preventing or delaying incident diabetes mellitus
Hausner, H., Derving, K. J., Holst, A. G., Jacobsen, J. B., Wagner, F. D., Golor, G., & Anderson, T. W. (2017). Effect of semaglutide on the pharmacokinetics of metformin, warfarin, atorvastatin, and digoxin in healthy subjects. *Clinical Pharmacokinetics*, *56*(11), 1391-1401. https://doi.org/10.1007/s40262-017-0532-6	Excluded	No focus on prediabetes and prevention of T2DM
Ibrahim, M., Tuomilehto, J., Aschner, P., Beseler, L., Cahn, A., Eckel, R. H., Fischl, A. H., Guthrie, G., Hill, J. O., Kumwenda, M., Leslie, R. D., Olson, D. E., Pozzilli, P., Weber, S. L., & Umpierrez, G. E. (2018). Global status of diabetes prevention and prospects for action: A consensus statement. *Diabetes/Metabolism Research & Reviews*, *34*(6), 1. https://doi.org/10.1002/dmrr.3021	Included	Discusses pharmacological prevention as well as lifestyle modification in preventing or delaying T2DM

Karve, A., & Hayward, R. A. (2010). Prevalence, diagnosis, and treatment of impaired fasting glucose and impaired glucose tolerance in nondiabetic U.S. adults. *Diabetes Care*, *33*(11), 2355-9. https://doi.org/10.2337/dc09-957	Included	Estimate prevalence, diagnosis, and treatment of prediabetes
Kovač, J., Šutuš Temovski, T., Rozmarič, T., Horvat, S., Beltram, J., Trebušak Podkrajšek, K., & Kotnik, P. (2017). DEPTOR promoter genetic variants and insulin resistance in obese children and adolescents. *Pediatric Diabetes*, *18*(2), 152–158. https://doi.org/10.1111/pedi.12371	Excluded	Focuses on children and adolescents only
Kulkarni, S., Xavier, D., George, B., Umesh, S., Fathima, S., & Bantwal, G. (2018). Effect of intensive lifestyle modification & metformin on cardiovascular risk in prediabetes: A pilot randomized control trial. *Indian Journal of Medical Research*, *148*(6), 705-712. https://doi.org/10.4103/ijmr.IJMR_1201_17	Included	Effect of exercise and metformin in CVD with pre-diabetic patients
Liu, W. Y., Lu, D. J., Du, X. M., Sun, J. Q., Ge, J., Wang, R. W., … Xia, Z. C. (2014). Effect of aerobic exercise and low carbohydrate diet on pre-diabetic non-alcoholic fatty liver disease in postmenopausal women and middle-aged men--the role of gut microbiota composition: study protocol for the AELC randomized controlled trial. *BMC Public Health*, *14*(1), 48. https://doi.org/10.1186/1471-2458-14-48	Excluded	Does not focus on metformin or any pharmacological intervention, instead focusing solely on aerobic exercise and low carbohydrate diet
Manco, M., Panunzi, S., Macfarlane, D. P., Golay, A., Melander, Olle., Konrad, T., & Mingrone, G. (2010). One-hour plasma glucose identifies insulin resistance and beta]-cell dysfunction in individuals with normal glucose tolerance: Cross-sectional data from the relationship between insulin sensitivity and cardiovascular risk (RISC) study. *Diabetes Care*, *33*(9), 2090-7. https://doi.org/10.2337/dc09-2261	Excluded	Characterize metabolic phenotype of healthy volunteers with high 1-h excursion of plasma glucose
Mangurian, C., Newcomer, J. W., Modlin, C., & Schillinger, D. (2016). Diabetes and cardiovascular care among people with severe mental illness: A literature review. *Journal of General Internal Medicine*, *31*(9), 1083-1091. https://doi.org/10.1007/s11606-016-3712-4	Excluded	No focus on metformin or pharmacological intervention

Maruthur, N. M., Ma, Y., Delahanty, L. M., Nelson, J. A., Aroda, V., White, N. H., Marrero, D., Brancati, F. L., & Clark, J. M. (2013). Early response to preventive strategies in the Diabetes Prevention Program. *Journal of General Internal Medicine*, *28*(12), 1629–1636. https://doi.org/10.1007/s11606-013-2548-4	Included	Lifestyle, metformin, or placebo and their effect on time to diabetes diagnosis
Mata Cases, M., Artola, S., Escalada, J., Ezkurra Loyola, P., Ferrer García, J. C., Antonio Fornos, J., & Rica, I. (2014). Consenso sobre la detección y el manejo de la prediabetes. Grupo de trabajo de consensos y guías clínicas de la Sociedad Española de Diabetes. *Farmacéuticos Comunitarios*, *6*(4), 26–39. https://doi.org/10.1016/j.semerg.2014.12.001	Excluded	Available only in Spanish
Mattei, J., Malik, V., Wedick, N. M., Campos, H., Spiegelman, D., Willett, W., & Hu, F. B. (2012). A symposium and workshop report from the global nutrition and epidemiologic transition initiative: Nutrition transition and the global burden of type 2 diabetes. *The British Journal of Nutrition*, *108*(7), 1325-35. https://doi.org/10.1017/S0007114512003200	Excluded	Dietary interventions not pharmacological
Metra, M., & Teerlink, J. R. (2017). Heart failure. *The Lancet*, *390*(10106), 1981-1995. https://doi.org/10.1016/S0140-6736(17)31071-1	Excluded	Heart failure is sole focus
Moin, T., Li, J., Duru, O. K., Ettner, S., Turk, N., Keckhafer, A., Ho, S., & Mangione, C. M. (2015). Metformin prescription for insured adults with prediabetes from 2010 to 2012: A retrospective cohort study. *Annals of Internal Medicine*, *162*(8), 542–548. https://doi.org/10.7326/M14-1773	Included	Translation of evidence surround metformin
Nathan, D. M., Davidson, M. B., DeFronzo, R. A., Heine, R. J., Henry, R. R., Pratley, R., & Zinman, B. (2007). Impaired fasting glucose and impaired glucose tolerance: Implications for care. *Diabetes Care*, *30*(3), 753–759. https://doi.org/10.2337/dc07-9920	Included	When metformin is appropriate for treatment of T2DM
Newman, J. D., Schwartzbard, A. Z., Weintraub, H. S., Goldberg, I. J., & Berger, J. S. (2017). Primary prevention of cardiovascular disease in diabetes mellitus. *Journal of the American College of*	Included	Role metformin plays in primary prevention of cardiovascular disease in pre-diabetes

Cardiology, *70*(7), 883-893. https://doi.org/10.1016/j.jacc.2017.07.001		
Nguyen, B., & Clements, J. (2017) Obesity management among patients with type 2 diabetes and prediabetes: a focus on lifestyle modifications and evidence of anti-obesity medications. *Expert Review of Endocrinology & Metabolism*, 12(5), 303-313. https://doi.org/10.1080/17446651.2017.1367285	Excluded	Reviews locaserin, phentramine with topiramate, buproprion with naltrexone, and liraglutide, but not metformin.
Perreault, L., Kahn, Steven E., Christophi, C., Knowler, W., & Hamman, R. (2009). Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. *Diabetes Care*, *32*(9), 1583-8. https://doi.org/10.2337/dc09-0523	Included	Reduced incidence of diabetes with intensive lifestyle modification or metformin
Quinn, C. C., Shardell, M. D., Terrin, M. L., Barr, E. A., Ballew, S. H., & Gruber-Baldini, A. (2011). Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. *Diabetes Care*, *34*(9), 1934-42. https://doi.org/10.2337/dc11-0366	Excluded	Mobile application coaching and effect on reduction of glycated hemoglobin levels
Ramachandran A., Snehalatha C., Mary S., Mukesh B., Bhaskar A.D., Vijay V. (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*, *49*(2), 289–297. https://doi.org/10.1007/s00125-005-0097-z	Included	Comparison of lifestyle modification and metformin preventing T2DM
Retnakaran, R., Qi, Y., Sermer, M., Connelly, P. W., Hanley, A. J. G., & Zinman, B. (2010). Beta-cell function declines within the first year postpartum in women with recent glucose intolerance in pregnancy. *Diabetes Care*, *33*(8), 1798-804. https://doi.org/10.2337/dc-10-0351	Excluded	Whether metabolic changes that occur in the 1st year postpartum vary in relation to gestational glucose tolerance status
Rhee, M., Herrick, K., Ziemer, D., Vaccarino, V., Weintraub, W., Narayan, K., Kolm, P., Twombly, J., & Phillips, L. (2010). Many Americans have pre-diabetes and should be considered for metformin therapy. *Diabetes Care*, *33*(1), 49-54. https://doi.org/10.2337/dc09-0341	Included	Determines the proportion of the American population who would merit metformin treatment

Roberts, S., Barry, E., Craig, D., Airoldi, M., Bevan, G., & Greenhalgh, T. (2017). Preventing type 2 diabetes: Systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. *BMJ Open, 7*(11), 1-18. https://doi.org/10.1136/bmjopen-2017-017184	Included	Explore cost-effectiveness of lifestyle interventions and metformin in preventing or delaying T2DM, both alone and in combination
Robertson, C. (2012). The role of the nurse practitioner in the diagnosis and early management of type 2 diabetes. *Journal of the American Academy of Nurse Practitioners*, *24*, 225–233. https://doi.org/10.1111/j.1745-7599.2012.00719.x	Included	Nurse practitioner role in treating prediabetes. Focuses on metformin and lifestyle modification. Gives tips for treating prediabetes
Rodriguez-Gutierrez, R., & Montori, V. M. (2015). Metformin prescription for insured adults with prediabetes from 2010 to 2012. *Annals of Internal Medicine*, *163*(6), 482–483. https://doi.org/10.7326/M14-1773	Excluded	Summary of Moin et al. research
Sheng, Z., Cao, J. Y., Pang, Y. C., Xu, H. C., Chen, J. W., Wang, R., Zhang, C. S., Wang, L. X., & Dong, J. (2019). Effects of lifestyle modification and anti-diabetic medicine on prediabetes progress: A systematic review and meta-analysis. *Frontiers in Endocrinology, 10*(455), 1-15. https://doi.org/10.3389/fendo.2019.00455	Included	Systematic Review and Meta-Analysis on lifestyle modifications and metformin's role in pre-diabetes
Sinha, A., Bhattacharjee, K., Sinha, P., Verma, A., & Halder, A. (2016). Effect of metformin on serum thyrotropin (thyroid stimulating hormone) levels in hypothyroid patients on stable and adequate levothyroxine doses with diabetes and pre-diabetes. *Journal of Endocrinology and Diabetes, 3*(6), 1-5. https://dx.doi.org/10.15226/2374-6890/3/6/00166	Excluded	Focuses on the effect of metformin on serum thyrotropin levels in hypothyroid patients with pre-diabetes. Doesn't discuss metformin regarding pre-diabetes control.
Siskind, D., Friend, N., Russell, A., McGarth, J. J., Lim, C., Patterson, S., Flaws, D., Stedman, T., Moudgil, V., Sardinha, S., Suetani, S., Kisely, S., Winckel, K., & Baker, A. (2018). CoMET: A protocol for a randomized controlled trial of co-commencement of metformin as an adjustive treatment to attenuate weight gain and metabolic syndrome in patients with schizophrenia newly commenced on clozapine. *BMJ Open, 8*(3). https://doi.org/10.1136/bmjopen-2017-021000	Excluded	No focus on prediabetes and prevention of T2DM

Souto, S., Souto, E., Braga, D., & Medina, J. (2011). Prevention and current onset delay approaches of type 2 diabetes mellitus (T2DM). *European Journal of Clinical Pharmacology*, *67*(7), 653–661. https://doi.org/10.1007/s00228-011-1038-z	Included	Reviews metformin's role in preventing or delaying the onset of T2DM
Srivastava, G., Fox, C. K., Kelly, A. S., Jastreboff, A. M., Browne, A. F., Browne, N. T., & Apovian, C. M. (2019). Clinical considerations regarding the use of obesity pharmacotherapy in adolescents with obesity. *Obesity*, *27*(2), 190–204. https://doi.org/10.1002/oby.22385	Excluded	Focuses on the adolescent population
Sutherland, L. L., Weiler, D. M., Bond, L., Simonson, S., & Reis, J. (2012). Northwest latinos' health promotion lifestyle profiles according to diabetes risk status. *Journal of Immigrant and Minority Health, 14*(6), 999-1005. https://doi.org/10.1007/s10903-012-9641-3	Excluded	Physical assessment for risk status of T2DM
Tian, J., Jin, D., Bao, Q., Ding, Q., Zhang, H., Gao, Z., & Tong, X. (2019). Evidence and potential mechanisms of traditional Chinese medicine for the treatment of type 2 diabetes: A systematic review and meta-analysis. *Diabetes, Obesity & Metabolism*, *21*(8), 1801–1816. https://10.1111/dom.13760	Excluded	Focuses on traditional Chinese medicine
Tseng, E., Greer, R., O'Rourke, P., Yeh, H.-C., McGuire, M., Clark, J., & Maruthur, N. M. (2017). Survey of primary care providers' knowledge of screening for, diagnosing and managing prediabetes. *Journal of General Internal Medicine*, *32*(11), 1172–1178. https://doi.org/10.1007/s11606-017-4103-1	Included	Identifies barriers that PCPs have when screening for, diagnosing and managing prediabetes
UK Prospective Diabetes Study Group. (1998). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet*, *352*(9131), 854-865. https://doi.org/10.1016/S0140-6736(98)07037-8	Included	Metformin role in treatment of newly diagnosed patients with T2DM
Wang, T., Eguale, T. & Tamblyn, R. (2013). Guidelines adherence in the treatment of patients with newly diagnosed type 2 diabetes: A historical cohort comparing the use of metformin in Quebec pre and post-Canadian Diabetes Association guidelines. *BMC Health*	Included	Comparing use of metformin pre and post guideline change in Canada

Services Research, *13***,** 442. https://doi.org/10.1186/1472-6963-13-442		
Weigensberg, M. J., & Goran, M. I. (2009). Type 2 diabetes in children and adolescents. *The Lancet*, *373*(9677), 1743-4. https://doi.org/10.1016/S0140-6736(09)60961-2	Excluded	Children and adolescents, not adult.
Li, X., Lian, F., Guo, D., Fan, L., Tang, J., Peng, J., & Tong, X. (2013). The rs1142345 in TPMT affects the therapeutic effect of traditional hypoglycemic herbs in prediabetes. *Evidence-Based Complementary & Alternative Medicine*, 1–8. https://doi.org/10.1155/2013/327629	Excluded	Focuses on effect of traditional herbs not metformin on prediabetes treatment
Zeitler, P., Arslanian, S., Fu, J., Pinhas, H. O., Reinehr, T., Tandon, N., Urakami, T., Wong, J., & Maahs, D. M. (2018). ISPAD clinical practice consensus guidelines 2018: Type 2 diabetes mellitus in youth. *Pediatric Diabetes*, *19*, 28–46. https://doi.org/10.1111/pedi.12719	Excluded	T2DM in youth, not adults
Zhang, L., Zhang, Z., Zhang, Y., Hu, G., & Chen, L. (2014). Evaluation of Finnish diabetes risk score in screening undiagnosed diabetes and prediabetes among U.S. adults by gender and race: NHANES 1999-2010. *PLoS One*, *9*(5). https://doi.org/10.1371/journal.pone.0097865	Excluded	Evaluation of Finnish Diabetes Risk Score, no pharmacological interventions were discussed

Table 4

Literature Review Tables of All Studies Included

Reference	**Study Purpose**	**Pop(p)/Size(n)/Setting(s)**	**Level of Evidence/ Design**	**Variables/Instruments**	**Findings**	**Implications**
American Diabetes Association. (2012). Standards of medical care in diabetes-2012. *Diabetes Care*, *35*, S11-63.	Recommendations for medical care of diabetes	N/A	Expert Opinion Level VII	N/A	individuals who have prediabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar	

https://doi.org/10.2337/dc12-s011					with the components of diabetes MNT Weight loss is recommended for all overweight or obese individuals At the time of T2DM diagnosis initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated In newly diagnosed T2DM patients with markedly symptomatic and/or elevated blood glucose levels or A1C consider insulin therapy, with or with-out additional agents, from the outset If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3–6 months add a second oral agent, a GLP-1 receptor agonist, or insulin	
Cefalu, W., Buse, J., Tuomilehto, J., Fleming, G., Ferrannini, E., Gerstein, H., Bennett, P., Ramachandran, A., Raz, I., Rosenstock, J., & Kahn, S. (2016). Update and next steps for real-world translation of interventions for type 2 diabetes prevention: Reflections from a	Summary of seminal prevention trials Discussion of considerations for selecting appropriate populations for intervention and diagnostics Outline knowledge gaps	N/A	Expert Opinion Level VII	N/A	Preventive pharmacology has been proposed as a adjunct to lifestyle modification due to cost, reimbursement, and shortage of lifestyle coaches Metformin the only drug that has been studied long term and shown to be effective TZD have serious adverse events documented	Early step in advancing preventive strategies for the diabetes medical community is to reach an agreement on how to approach programs that can be implemented on a global level. How do we design and implement diabetic prevention programs for prediabetes that are general enough to be implemented anywhere and in any setting Although diet and physical activity are effective, the sole reliance on such will

diabetes care editors expert forum. *Diabetes Care, 39*(7), 1186-1201. https://doi.org/10.2337/dc16-0873	Explore new avenue for securing regulatory approval of a prevention-related indication for metformin Specific considerations for pharmacological interventions to delay onset of T2DM				Newer obesity and diabetes medications such as orlistat and glucagon-like peptide 1 receptor agonists, have potential to be effective but are costly, some are injectable, and all require further studies. Making metformin at the moment, the best option for widespread use due to its proven effectiveness, long-term safety and cost-effectiveness. Metformin use has been minimal due to GI side effects and lack of perceived benefit, even though studies have shown to be beneficial After 3 years, diabetes risk was reduced by 28.5, 26.4, and 28.2percent in the lifestyle, metformin, and combination groups In the follow-up DPP Outcomes Study, cumulative diabetes incidence rates still differed significantly 10 years (34 and 18percent for lifestyle and metformin compared with placebo, respectively) and 15 years (27 and 17percent, respectively) after initial randomization into the DPP	not be enough, especially for patients who are high risk. Pharmacological interventions are going to need to be implemented and we can't rely solely that diet and physical activity will be enough Attention needs to be given to pharmacological interventions and acknowledge their benefits in treatment of prediabetes FDA approval for a new indication of metformin as prevention for T2DM would be a start
Coll, A., Chen, M., Taskar, P., Rimmington, D., Patel, S., Tadross, J., Cimino, I., Yang, M.,	Understand the connection between metformin and	n = 173 adults	Randomized, double-blinded, placebo-	Randomized 1:1 to 850mg metformin or matched placebo	Those who were allocated metformin lost significant weight and their levels of GDF15 were persistently	For metformin to work properly it needs to increase the circulating levels of GDF15. The ability of metformin to aid

Welsh, P., Virtue, S., Goldspink, D., Miedzybrodzka, E., Tung, Y., Rodriguez-Cuenca, S., Tomaz, R., Harding, H., Melvin, A., Yeo, G., Preiss, D., … Savage, D. (2019). GDF15 and the beneficial actions of metformin in pre-diabetes. *Cold Spring Harbor Laboratory*. https://doi.org/10.1101/677831	circulating levels of GDF15		controlled trial Level II	twice daily with meals. Attended six monthly visits after overnight fasts and before taking their morning dose of metformin. Blood samples collected.	elevated compared to placebo. 9	in weight loss is beneficial to its overall effectiveness.
Day, E. A., Ford, R. J., Smith, B. K., Mohammadi-Shemirani, P., Morrow, M., Gutgesell, R., Lu, R., Raphenya, A., Kabiri, M., McArthur, A., McInnes, N., Hess, S., Pare, G., Gerstein, H., & Steinberg, G. (2019). Metformin-induced increases in GDF15 are important for suppressing appetite and promoting weight loss. *Nature Metabolism, 1*, 1202–1208. https://doi.org/10.1038/s42255-019-0146-4	Determine if metformin increases the secretion of a hepatocyte-derived endocrine factor that communicates with the central nervous system	n = 16	Randomized control trial Level II	NA	Metformin induces expression and secretion of growth differentiating factor 15 (GDF15).	An increase in serum GDF15 associated with weight loss in patients with T2DM who take metformin.
Diabetes Prevention Program Coordinating Center. (2012). Long-term safety, tolerability, and weight loss associated with metformin in the diabetes prevention program outcomes study.	Examine long-term safety and tolerability along with weight loss and change in waist circumference	n = 3,234 participants	Randomized double-blind clinical trial Level II	1,073 randomly assigned to metformin arm and 1,082 to the placebo arm Participants were ≥ 25 years of	Gastrointestinal symptoms more common in metformin than placebo participants but these symptoms declined overtime Hemoglobin and hematocrit levels slightly lower in	

Diabetes Care, *35*(4), 731-737. https://doi.org/10.2337/dc11-1299				age, had a BMI ≥ 24 kg/m2, elevated fasting glucose, and impaired glucose tolerance 2 h after a 75-g oral glucose load Excluded for prior diagnosis of diabetes or conditions or medication that would impair ability to participate or affect weight loss Metformin or matching placebo initiated at 850 mg once daily and increased by 1 month to 850 mg BID unless GI symptoms warranted longer titration period Standard lifestyle recommendations, and written information on healthy eating/weight, and physical	metformin then placebo participants but this was only observed in first year and no further changes occurred Body weight and waist circumference decreased in metformin then placebo participants (2.06 vs 0.02, 2.13 vs 0.79) During unblinded part of trial, weight loss was significant in the metformin versus placebo group which was related to the degree of continuing metformin adherence Metformin reduced the development of diabetes by 31percent over an average of 2.8 years	

				activity provided annually Weight measured twice yearly and waist circumference annually		
Diabetes Prevention Program Research Group. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine, 346*(6), 393-403. https://doi.org/10.1056/NEJMoa012512	Modifying factors that place an individual at risk for diabetes through lifestyle-intervention program or administration of metformin will prevent or delay development of diabetes	n = 3,234	Randomized Control Trial Level II	Intervention 1 – standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily Intervention 2 – standard lifestyle recommendations plus placebo twice daily Intervention 3 – intensive program of lifestyle modification (achieve and maintain a weight reduction of at least 7 percent of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk	Average follow-up was 2.8 years Incidence of diabetes was as follows; intervention 1 (7.8), intervention 2 (11.0), and intervention 3 (4.8) per 100 persons Lifestyle intervention reduced incidence of diabetes by 58percent in intervention 3 and 31percent in intervention 1 Lifestyle modification more effective than metformin To prevent one case of diabetes 6.9 persons would have to participate in lifestyle-intervention program and 13.9 would have to receive metformin	Lifestyle modification and metformin are effective at preventing or delaying diabetes no matter gender, race or ethnicity. Lifestyle modification compared to metformin was more effective at preventing or delaying diabetes, although both were effective Lifestyle intervention was LEAST effective in older participants and therefore need to consider whether a patient can participate effectively in lifestyle interventions to make a difference. Older patients may need to have the metformin component added due to their physical limitations Metformin was less effective in persons with a lower base-line body mass Index or a lower fasting plasma glucose concentration than in those with higher values for these variables – the effectiveness of metformin may increase with fasting glucose concentration and how advanced diabetes is Rate of gastrointestinal symptoms was highest in the metformin group and the rate of musculoskeletal symptoms was highest in the lifestyle-intervention group

				walking, for at least 150 minutes per week) Primary outcome was diabetes based off annual oral glucose-tolerance test or semiannual fasting plasma glucose test Self-reported levels of leisure physical activity were assessed annually with the Modifiable Activity Questionnaire The physical-activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent of that activity (MET) and summed for all activities performed, with the		– understand the whole picture where one intervention may be more appropriate (such as if a patient already has musculoskeletal issues or symptoms, will lifestyle only intervention by effective?) benefits would depend on whether glucose concentrations could be maintained at levels below those that are diagnostic of diabetes and whether the maintenance of these lower levels improved the long-term outcome – questions that need to be answered for future research

				result expressed as the average MET-hours per week for the previous year		
Fujii, R., Junqueira, M., Restrepo, M., & Turatti, L. (2015). Metformin and intensive lifestyle intervention for pre-diabetes – systematic review of efficacy. *Value in Health*, *18*(3), 55-56. https://doi.org/10.1016/j.jval.2015.03.326	Evaluate efficacy and safety of metformin versus intensive lifestyle intervention for the treatment of prediabetes	n = 11	Systematic Review of RCTs Level I	Databases included PubMed/MEDLINE, Cochrane Library, LILACS, and CRD.	Intensive lifestyle intervention and metformin reduced incidence of T2DM but didn't demonstrate that combination of both did so. Intensive lifestyle intervention and metformin reduced incidence of T2DM, but lifestyle was more effective	Intensive lifestyle intervention and metformin can provide significant results. Treatment choice should balance benefits and adverse effects while integrating patient's personal values and feasibility of each intervention.
Goldberg, R. B., Aroda, V. R., Bluemke, D. A., Barrett-Connor, E., Budoff, M., Crandall, J. P., Dabelea, D., Horton, E. S., Mather, K. J., Orchard, T. J., Schade, D., Watson, K., & Temprosa, M. (2017). Effect of long-term metformin and lifestyle in the diabetes prevention program and its outcome study on coronary artery calcium. *Circulation*, *136*(1), 52–64. https://doi.org/10.1161/CIRCULATIONAHA.116.025483	How diabetes prevention interventions (lifestyle modification and metformin) reduced coronary heart disease risk	n = 3234 subjects with prediabetes	Randomized control trial Level II	Diabetes Prevention Program Diabetes Prevention Program Outcome Study Subclinical atherosclerosis assessed with coronary artery calcium measurements	No CAC differences between lifestyle and placebo groups in either sex. CAC severity and presence lower among men in the metformin versus placebo groups, but no effect seen in women.	Metformin may protect against coronary atherosclerosis in prediabetes among men
Ibrahim, M., Tuomilehto, J., Aschner, P., Beseler, L., Cahn, A., Eckel, R. H., Fischl, A. H., Guthrie, G., Hill, J. O., Kumwenda, M., Leslie, R. D., Olson,	Primary prevention of T2DM achievable through implementation of early and sustainable measures, including	N/A	Commentary/Expert Opinion Level VII	N/A	Lifestyle interventions (healthy diet, physical activity, and weight control) are needed for prevention of diabetes.	Mobile phones help facilitate communication between health professionals and general population

D. E., Pozzilli, P., Weber, S. L., & Umpierrez, G. E. (2018). Global status of diabetes prevention and prospects for action: A consensus statement. *Diabetes/Metabolism Research & Reviews, 34*(6), 1. https://doi.org/10.1002/dmrr.3021	nutrition education, weight loss, physical activity, and medications.				Risk scores need to be assessed. Inclusion criteria should be based on combination of risk factors and available resources.	Noninvasive risk scores should be used but validated locally for cultural differences in all ethnic populations Lifestyle interventions reduce progression, however there are studies that show benefits of pharmacological prevention as well.
Karve, A., & Hayward, R. A. (2010). Prevalence, diagnosis, and treatment of impaired fasting glucose and impaired glucose tolerance in nondiabetic U.S. adults. *Diabetes Care, 33*(11), 2355-9. https://doi.org/10.2337/dc09-1957	Estimate rates of prevalence, diagnosis, and treatment of impaired fasting glucose and impaired glucose tolerance	n = 1,547	Cross-sectional survey Level V	The National Health and Nutrition Examination Survey (NHANES) Multivariate regression analysis used to identify predictors of diagnosis and treatment	34.6percent had prediabetes. 4.8percent reported receiving a formal diagnosis. None received oral antihyperglycemics and exercise was recommended for 31.7percent while 33.5percent were recommended diet modification. 19.4percent had IFG, 5.4percent had IGT, 9.8percent had both	Knowing that interventions greatly reduce progression from IFG/IFT to T2DM, individuals are still underdiagnosed and undertreated. PCPs may be unaware of evidence, unconvinced by evidence or unclear regarding criteria. Education to PCPs needs to occur
Kulkarni, S., Xavier, D., George, B., Umesh, S., Fathima, S., & Bantwal, G. (2018). Effect of intensive lifestyle modification & metformin on cardiovascular risk in prediabetes: A pilot randomized control trial. *Indian Journal of Medical Research, 148*(6), 705-712. https://doi.org/10.4103/ijmr.IJMR_1201_17	Research the effects of exercise and metformin on high-sensitivity C-reactive protein (hsCRP) and carotid intima-media thickness (CIMT) which are markers for atherosclerosis and CVD in prediabetes patients, as these are often complications of T2DM	n = 103	Randomized Control Trial Level II	103 participants were randomized. 33 were assigned to the standard arm (STD), 35 to the intensive lifestyle modification arm (ILSM), and 35 to the intensive lifestyle modification plus metformin	At six months there was a reduction in weight and fasting blood sugar in all three arms Reduction in A1C only in the intensive lifestyle treatment and metformin arm Difference in hsCRP for STD was -.12, ILSM was -.58, and ILSM + Met was -.11 over six months At six months there was no difference between the three	Weight reduction and FBS reduction occurred in all three arms, meaning lifestyle modification and metformin play active roles in treatment of prediabetes There was no difference seen in hsCRP and CIMT in intensive lifestyle modification and metformin arms, which is contrary to other studies, but this could be due the inclusion of patients who were normoglycaemic and recently turned dysclycaemic within the previous year (meaning they were relatively new prediabetes)

				arm (ILSM + Met) Followed up at 6 months Radiologist used a high-resolution B-mode carotid artery ultrasound to measure intima-media thickness of the posterior walls of bilateral common carotid arteries at two different sites hsCRP was measured using an immunoturbidimetric assay Metformin (500 mg) tablets were provided from a single batch. Tablets were repackaged in similar packs with appropriate labelling and instructions.	arms for hsCRP, CIMT (right), CIMT (left)	Trial was only conducted over a 6-month period which is a short duration to analyze changes – usually require at least a year Wasn't a significant difference in hsCRP levels across three arms, which is similar to other studies outcomes, but interventions with metformin and exercise have shown to reduce hsCRP and other inflammatory biomarkers in prediabetes which reduces CVD – again this could be seen if trial spanned over a year rather than 6 months Longer follow up with adequate sample size could help re-assess the effects of these interventions in the future and to confirm findings
Maruthur, N. M., Ma, Y., Delahanty, L. M., Nelson, J. A., Aroda, V., White, N. H., Marrero, D., Brancati, F. L., & Clark,	Quantify relationship between early measures of weight and glucose and subsequent diabetes	n = 3,041 adults n = 1,018 to	Randomized controlled trial	Independent variable included weight loss at 6 & 12 months, fasting glucose	After 6 months, 604 participants developed diabetes Lifestyle = 140 Metformin = 206	Lifestyle intervention predicts lower diabetes risk for weight and glucose at 6 and 12 months

J. M. (2013). Early response to preventive strategies in the Diabetes Prevention Program. *Journal of General Internal Medicine, 28*(12), 1629–1636. https://doi.org/10.1007/s11606-013-2548-4	in patients undergoing diabetes prevention interventions	lifestyle group n = 1,036 to metformin group n = 987 to placebo group	Level II	and hemoglobin A1c at 6 months, and post-load glucose at 12 months. Outcome = time to diabetes diagnosis	Placebo = 258 If patients obtained optimal 6-month FG & A1C and 12-month post-load glucose they had > 60percent lower diabetes risk	When patient is taking metformin, early reduction in glycemia has a stronger correlation to diabetes risk then weight loss
Moin, T., Li, J., Duru, O. K., Ettner, S., Turk, N., Keckhafer, A., Ho, S., & Mangione, C. M. (2015). Metformin prescription for insured adults with prediabetes from 2010 to 2012: A retrospective cohort study. *Annals of Internal Medicine, 162*(8), 542–548. https://doi.org/10.7326/M14-1773	Examine metformin prescription for diabetes prevention and patient characteristics that may affect metformin prescription	n = 17,352	Retrospective Cohort Study Level IV	Examined data from 2010 to 2012 form United Healthcare, nation's largest private insurer. Academic team members analyzed all data independently and retained sole authority over all publication-related decisions throughout the study All analyses done using SAS and STATA.	3.7percent of patients with prediabetes were prescribed metformin Women were almost two times more likely to be prescribed metformin Obese patients were almost two times more likely to be prescribed metformin Patients with 2 or more comorbid conditions were 1.5 times more likely to be prescribed metformin	Metformin rarely prescribed for diabetes prevention Need to understand potential barriers to safe, tolerable, evidence-based, and cost-effective prediabetes therapy Even with evidence that metformin is beneficial in prediabetes treatment, it is still not being translated into practice Underuse of highly effective prevention strategy Lack of translation of a safe, evidence-based therapy for a highly prevalent condition is problematic At the very minimum, patients should be educated regarding the potential benefits of metformin and ideally offered this option as prevention For patient with significant time commitments and restraints that make lifestyle changes challenging, metformin may provide them with prevention strategies

						The reasons for low metformin use are not entirely clear, and future studies should examine an array of patient-, provider-, and organization-level factors that may contribute to underuse Barriers – lack of knowledge about evidence from providers, "off label" use – not approved by FDA for prediabetes, higher priority placed on other medical needs, reluctance to "medicalize" prediabetes, lack of awareness of prediabetes by patients The evidence for metformin use is strongest for patients younger than 60 years, those with a BMI greater than 35 kg/m2, or those with a history of gestational diabetes Potential strategies to increase awareness and promote informed decision making among this at-risk population could include clinical decision-making tools, physician directed and performance-based incentive programs, or media campaigns to increase public awareness of prediabetes and its consequences if left untreated.
Nathan, D. M., Davidson, M. B., DeFronzo, R. A., Heine, R. J., Henry, R. R., Pratley, R., & Zinman, B. (2007). Impaired fasting glucose and impaired glucose tolerance: Implications for care. *Diabetes Care, 30*(3), 753–759.	What are IFG and IGT, and what is their natural history? What is known about the pathogenesis of IFG and IGT? How do we define the natural history of	N/A	Expert Opinion Level VII	N/A	Metformin effective although half as effective as lifestyle modification, but is inexpensive and has virtually no long-term side effects Acarbose is as effective as metformin, but many cannot tolerate its GI side effects and is costly	Metformin is the safest and cost-effective anti-diabetic medication as of today, however, if other medications become more cost-effective metformin may not be the best option. With that being said, metformin has the least amount of side effects and therefore may always be the leading anti-diabetic medication based solely off of side effects

https://doi.org/10.2337/dc07-9920	IFG/IGT, and can we alter it? Do interventions that prevent the progression from IFG/IGT to diabetes also prevent the development/worsening of diabetes-related microvascular complications, cardio metabolic risk factors, or CVD events? Are there adequate data to prevent or delay diabetes in IFT/IGT at this time? Who should be screening and with what methods and frequency to prevent/delay the adverse consequence of IFG/IGT?				Orlistat also has been shown to be effective but is poorly tolerated, however, now that it is an OTC drug, it is less costly Rosiglitazone was as effective in dallying/preventing diabetes as lifestyle modification but is costly and associated with a sevenfold increase in heart failure	Patients with elevated IFG or IGT with no other risk factors should be treated through lifestyle modification (5-10percent weight loss and moderate intensity physical activity – 30 min/day Patients with elevated IFG and IGT and any of the following: < 60 years of age, BMI ≥ 35 kg/m2, family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL cholesterol, hypertension, A1C > 6.0percent should be treated with lifestyle modifications and/or metformin Lifestyle modifications should always be addressed and used as a foundation; however, metformin has been proven effective to help prevent or delay the progression to T2DM Future recommendations may include other medications if they prove to be effective, have a good safety profile, are tolerable, and are of relatively low cost.
Newman, J. D., Schwartzbard, A. Z., Weintraub, H. S., Goldberg, I. J., & Berger, J. S. (2017). Primary prevention of cardiovascular disease in diabetes mellitus. *Journal of the American College of Cardiology*, *70*(7), 883-893.	Cardiovascular disease is major risk factor of T2DM and most common cause of death. Need to expand the use of therapies proven to reduce CVD in diabetic patients	N/A	Expert Opinion Level VII	N/A	Metformin generally considered first line therapy for glycemic control Other pharmacological strategies such as SGLT2, GLP-1 analogues have also shown to reduce vascular risk Further research is needed to determine if these agents are superior or additive in the CVD	CVD risk reduction is critical Statins, aspirin, glucose-lowering therapies, and BP reduction should all be considered along with intensive lifestyle management Uniform medical therapies impact morbidity and mortality of diabetic patients

https://doi.org/10.1016/j.jacc.2017.07.001					risk reduction with the use of metformin	
Perreault, L., Kahn, Steven E., Christophi, C., Knowler, W., & Hamman, R. (2009). Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. *Diabetes Care*, *32*(9), 1583-8. https://doi.org/10.2337/dc09-0523	Regression from prediabetes to normal glucose regulation was associated with reduced incidence of diabetes, examined whether regression also reduced risk for microvascular disease	N/A	Observational Study Level III	N/A	For models adjusted for age, sex, race, ethnicity, baseline A1C, and treatment odds, a regression to normal glucose regulation also lead to a lower prevalence of microvascular disease. When models included average A1C during follow-up or diabetes status at the end of follow-up, the association between regression to normal glucose regulation and lower prevalence of microvascular disease, no longer existed With regression to normal glucose regulation there was also a lower prevalence of nephropathy and retinopathy. As A1C increased so did MVD, nephropathy, and retinopathy	Diabetes can be prevented or delayed in people with prediabetes Complications can also be prevented in prediabetics when early intervention is aimed at reducing body weight, lipids, blood pressure, and/or plasma glucose Regression to NGR is associated with lower prevalence of MVD, nephropathy, and retinopathy Limiting cumulative glycemic exposure is central in prediabetes care, whether they develop diabetes or not Highlights different relationships between the microvascular disease subtypes and glycemia over time Timing for glucose-lowering intervention(s) may well need to change as tools are developed to determine individual risk for MVD and its subtypes
Ramachandran A., Snehalatha C., Mary S., Mukesh B., Bhaskar A.D., Vijay V. (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired	Progression to diabetes could be influenced by interventions in native Asian Indians with IGT who were younger, leaner, and more insulin resistant than multiethnic Americans, Finnish and Chinese	n = 531 subjects (421 men and 110 women)	Randomized Control Trial Level II	Group 1 was the control (n = 136) Group 2 given advice on lifestyle modification (n = 133) Group 3 was treated with	Median follow-up period was 30 months 3-year cumulative incidences of diabetes were as follows; group 1 (55.0percent), group 2 (39.3percent), group 3 (40.5percent), and group 4 (39.5percent)	Can prevent diabetes in native Asian Indian subjects with IGT using lifestyle modification Metformin also effective but in smaller doses (500 mg/day), which could be contributed to lower BMI of Asian Indians No additional benefit seen by combining lifestyle modification and metformin

glucose tolerance (IDPP-1). *Diabetologia*, *49*(2), 289–297. https://doi.org/10.1007/s00125-005-0097-z				metformin (n = 133) Group 4 given advice on lifestyle modification and prescribed metformin (n = 129) Primary outcome was defined as development of T2DM	Relative risk reduction for group 2 (28.5percent), group 3 (26.4percent), and group 4 (28.2percent) Number needed to treat to prevent one case of diabetes for group 2 (6.4), group 3 (6.9), and group 4 (6.5)	Asian Indians have a very high progression rate of IGT to diabetes and therefore are considered high risk based off ethnicity LSM was more effective than metformin in all races, including the ethnic minority population, and the effect of metformin was lower in the thinner individuals Mechanisms responsible for the beneficial effects of interventions, independent of weight change, need to be analyzed It has also demonstrated the effectiveness that lifestyle modification involving moderate, but consistent, physical activity and diet modification help to prevent diabetes even in the Asian Indians, who have a high risk of developing diabetes
Rhee, M., Herrick, K., Ziemer, D., Vaccarino, V., Weintraub, W., Narayan, K., Kolm, P., Twombly, J., & Phillips, L. (2010). Many Americans have pre-diabetes and should be considered for metformin therapy. *Diabetes Care*, *33*(1), 49-54. https://doi.org/10.2337/dc09-0341	Determine proportion of Americans who would merit metformin treatment, according to ADA to prevent or delay development of diabetes	n = 4.706 subjects who were non-Hispanic white and black, without known diabetes	Cross-Sectional Analysis Level IV	Screening for Impaired Glucose Tolerance (SIGT) Third National Health and Nutrition Examination Survey (NHANES III) National Health and Nutrition Examination Survey (NHANES)	Isolated patients into three groups, IFG, IGT, and IFG and IGT. In SIGT, NHANES III, and NHANES, criteria for metformin consideration were met in 99, 96, 96percent with IFG and IGT, 31, 29, and 28percent with IFT, and 53, 57, and 62percent with IGT.	More than 96percent of individuals with both IFG and IGT are likely to meet criteria. Providers should perform oral glucose tolerance tests to find concomitant IGT in all patients with IFG. Roughly 1/12 adults meet criteria that may justify consideration of metformin treatment

				Criteria for consideration of metformin included the presence of both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), with ≥1 additional diabetes risk factor: age <60 years, BMI ≥ 35 kg/m 2, family history of diabetes, elevated triglycerides, reduced HDL cholesterol, hypertension, or A1C >6.0percent.		
Roberts, S., Barry, E., Craig, D., Airoldi, M., Bevan, G., & Greenhalgh, T. (2017). Preventing type 2 diabetes: Systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. *BMJ Open*, *7*(11), 1-18. https://doi.org/10.1136/bmjopen-2017-017184	Explore cost-effectiveness of lifestyle intervention and metformin, alone and in combination	27 studies included all evaluated lifestyle interventions while 12 also included metformin	Systematic Review Level II Not all were RCT	Database searches included Embase, Medline, PreMedline, and NHS EED. The International Society for Pharmaco-ecomonics and Outcomes Research's Questionnaire to	Lifestyle programs and metformin appeared cost effective, but economic estimated varied. Intervention only programs more cost effective than programs that included screenings. Longer the period evaluated, more cost-effective. Insufficient evidence to determine whether lifestyle programs are more cost effective then metformin or	Preventing diabetes is complex and can be expensive. Although evidence is insufficient regarding what direction is most cost-effective, it is important to consider the advantages and disadvantages for your patient that is unique to them. Are you going to be spending more money in the beginning (lifestyle interventions and metformin cost) but ultimately saving cost by preventing patients delay to T2DM and complications associated with it.

				Assess Relevance and Credibility of Modelling studies for Informing Healthcare Decision Making – used to assess study quality.	whether low-intensity interventions are more cost effective then high intensity.	
Robertson, C. (2012). The role of the nurse practitioner in the diagnosis and early management of type 2 diabetes. *Journal of the American Academy of Nurse Practitioners, 24*, 225–233. https://doi.org/10.1111/j.1745-7599.2012.00719.x	Discuss the state of knowledge of effective therapeutic approaches to preventing or dallying T2DM	N/A	Scoping Review of Literature Level IV	N/A	Multifactorial approach is required to deal with T2DM. -Lifestyle changes most important -Metformin and TZDs – effective with IGT and higher BMI	Treatment that is multifactorial and personalized is most effective. Lifestyle changes such as increasing exercise or activity and reducing weight are most important, but metformin shown to be effective in patients with IGT and higher BMI. Pharmacological treatment and lifestyle interventions together with the control of cardiovascular risk factors are main strategies.
Sheng, Z., Cao, J. Y., Pang, Y. C., Xu, H. C., Chen, J. W., Wang, R., Zhang, C. S., Wang, L. X., & Dong, J. (2019). Effects of lifestyle modification and anti-diabetic medicine on prediabetes progress: A systematic review and meta-analysis. *Frontiers in Endocrinology, 10*(455), 1-15. https://doi.org/10.3389/fendo.2019.00455	With the understanding that pre-diabetes is a risk factor for T2DM it is essential to identify effective preventive strategies, and to clarify direction of future research	32 RCT comprising of 43,669 patients and 14 interventions were analyzed	Systematic Review and Meta-Analysis Level I	PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched Network meta-analysis applies to multiple comparison among various diabetic prevention strategies, traditional meta-analysis for	Lifestyle modifications and anti-diabetic medications improved physical conditions, including weight loss, blood glucose and pressure Progression of diabetes can be delayed to varying degrees by lifestyle and pharmacological interventions, except for ACE Inhibitors, statins, sulfonylureas, and vitamin D	There is firm evidence that lifestyle modifications and metformin reduce incidence of diabetes with an average reduction of 20percent Lifestyle modifications promising long-term strategies involving nutrition, exercise, and weight loss contributed to the following: reduction of BMI, body weight, waist and hip circumference, systolic and diastolic pressure, fasting and 2-h postprandial blood glucose, and total cholesterol Complications of diabetes increases patient suffering and mortality

				syntheses of basal metabolic changes after interventions, and trial sequential analysis for determinations as to whether analysis conclusions meet expectation		Effective interventions early on can reduce the personal and public health burden of diabetes More relevant trials needed to reinforce or complement review, focusing on clinical complications and cost-effectiveness
Souto, S., Souto, E., Braga, D., & Medina, J. (2011). Prevention and current onset delay approaches of type 2 diabetes mellitus (T2DM). *European Journal of Clinical Pharmacology*, *67*(7), 653–661. https://doi.org/10.1007/s00228-011-1038-z	Discuss the state of knowledge of effective therapeutic approaches to preventing or dallying T2DM	N/A	Scoping Review of Literature Level IV	N/A	Multifactorial approach is required to deal with T2DM. -Lifestyle changes most important -Metformin and TZDs – effective with IGT and higher BMI	Treatment that is multifactorial and personalized is most effective. Lifestyle changes such as increasing exercise or activity and reducing weight are most important, but metformin shown to be effective in patients with IGT and higher BMI. Pharmacological treatment and lifestyle interventions together with the control of cardiovascular risk factors are main strategies.
Tseng, E., Greer, R., O'Rourke, P., Yeh, H.-C., McGuire, M., Clark, J., & Maruthur, N. M. (2017). Survey of primary care providers' knowledge of screening for, diagnosing and managing prediabetes. *Journal of General Internal Medicine*, *32*(11), 1172–1178. https://doi.org/10.1007/s11606-017-4103-1	Assess PCPs' knowledge of risk factors that should prompt prediabetes screening, laboratory criteria for diagnosing prediabetes and guidelines for management of prediabetes; management practices around prediabetes; attitudes and beliefs about prediabetes	n = 155 PCPs	Cross-sectional Studies Level V	Descriptive analyses of survey questions conducted. Multivariate logistic regression used to determine association between provider characteristics and knowledge, management, and attitudes/beliefs	6percent PCPs correctly identified all risk factors that should prompt screening 17percent PCPs correctly identified laboratory parameters for diagnosis 90percent PCPs reported close follow-up 11percent PCPs referred to a behavioral weight loss program	PCPs need to address gaps in knowledge regarding prediabetes (risk factors and diagnostic parameters) and the underutilization of behavioral weight loss programs

				about prediabetes	Patient-related factors are important barriers to lifestyle change and metformin use	
UK Prospective Diabetes Study Group. (1998). Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet*, *352*(9131), 854-865. https://doi.org/10.1016/S0140-6736(98)07037-8	Patients with T2DM, blood glucose control decreases progression of microvascular disease and risk of heart attacks. Investigated whether intensive glucose control with metformin has any specific advantage or disadvantage	n = 4,209 patients from 15 centers	Randomized Control Trial Level II	4,209 eligible patients. 2,505 were non-overweight. 1,704 were overweight. Of the 1,704, 411 were assigned conventional treatment (diet alone), 342 were assigned intensive control with metformin, and 951 were assigned intensive control. Of the 951, 265 were as assigned chlorpropamide, 277 glibenclamide, and 409 insulin. 1,234 patients (overweight and non-overweight) assigned to sulphonylurea. 86 died or no longer attended clinics. Of the 1148 patients left (who had elevated FPG), 211 not eligible due to FPG <6.	A1C was 7.4percent in the metformin group compared to 8.0percent in conventional group Patients taking metformin had risk reduction of 32percent for any diabetes-related endpoint, 42percent for diabetes-related death, and 36percent for all-cause mortality compared to conventional group Metformin showed greater effect than chlopropamide, glibenclamide, or insulin for any diabetes-related endpoint, all-cause mortality, and stroke Adding metformin to sulphonylurea-treated patients increased risk of diabetes-related death Patients taking metformin had fewer diabetes-related endpoints	Metformin appears to decrease the risk of diabetes related endpoints in overweight diabetic patients Associated with less weight gain and fewer hypoglycemic attacks than insulin and sulphonylureas, and should be considered first-line pharmacological therapy for diet-treated overweight patients Additional research and studies need to be conducted on the addition of metformin in patients already treated with sulphonylureas Findings may not apply to non-overweight patients, but metformin seems to lower glycaemia in patients, regardless of obesity status (overweight or not)

				537 eligible for randomization and 411 not eligible due to FPG > 15. Of the 537 eligible 269 were on sulphonylurea along and 269 on sulphonylurea and metformin		
Wang, T., Eguale, T. & Tamblyn, R. (2013). Guidelines adherence in the treatment of patients with newly diagnosed type 2 diabetes: A historical cohort comparing the use of metformin in Quebec pre and post-Canadian Diabetes Association guidelines. *BMC Health Service Research, 13*, 442. https://doi.org/10.1186/1472-6963-13-442	Measure the response of PCP who changed their initial therapy for patient with T2DM in relation to guideline changes	n = 1279 patients and 111 physicians	Cohort Study Level IV	EMR Research Network Multivariate GEE logistic regression was used to estimate impact of guideline change on treatment choice	With new guidelines there was an increased use of metformin with a decreased use of thiazolidinediones, and sulfonylureas. Physicians attitudes did not change regarding evidence-based practice	When new guidelines are initiated this change the practice of prescribing. If metformin is shown to be effective in preventing or delaying the progression to T2DM, the guidelines need to reflect this.