Past, Present, and Future Research Avenues for Metformin: A Literature Review

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Abstract

Objective: To review why metformin is considered first-line therapy for type 2 diabetes mellitus (T2DM) and review newer avenues of research currently being evaluated. **Data Sources:** The Cochrane Library and Medline (to January 2014) were searched for case-control and cohort studies, clinical trials, and systematic reviews and meta-analyses involving metformin for any indication. **Study Selection and Data Extraction:** The literature search found 5 major avenues of research for metformin: reduction in mortality, delayed-onset or prevention of T2DM in the presence of prediabetes, nonalcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome (PCOS), and decreased cancer risk. When available, multi-center, double-blind, controlled clinical trials or meta-analyses thereof were selected for review. If these types of studies did not exist, other types of studies were chosen for review. **Data Synthesis:** Metformin significantly decreases all-cause and diabetes-related mortality in overweight and obese patients with T2DM. It may also decrease risk of progression to T2DM in patients with prediabetes. Metformin has been studied for the treatment of NAFLD though data are limited. Metformin alone or combined with clomiphene may increase pregnancy and ovulation rates but has not yet been shown to increase live-birth rates in patients with PCOS. Metformin may decrease risk of colorectal cancer but not all-cancer risk. **Conclusions:** Metformin's clinical role in T2DM and prediabetes is well established. Other avenues of research being evaluated at this time are NAFLD, PCOS, and reduced risk of cancer; more data are needed before it has a clinical role in these indications.

Keywords

antihyperglycemics, diabetes, cancer, infertility, cardiology

Introduction

Diabetes is chronic and incurable but treatable medical condition affecting 382 million people worldwide, and with the prevalence increasing in every country, that number is expected to increase to 592 million by 2035.¹ According to both the American Diabetes Association (ADA) and the American Academy of Clinical Endocrinologists (AACE) as well as many international guidelines, all patients with type 2 diabetes mellitus (T2DM) should be prescribed metformin as first-line therapy unless it is contraindicated.^{2–4} There are multiple reasons that metformin therapy is considered firstline. It is low cost, easily available, has no risk of hypoglycemia as monotherapy, is weight neutral, and has favorable effects on high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG). Perhaps the most important and impactful reason is that metformin decreases all-cause and cardiovascular mortality risk in overweight and obese patients, which constitutes the majority of patients with T2DM.⁵

Introduced in the 1950s, metformin is a biguanide, anti-hyperglycemic agent approved for the treatment of T2DM and commonly used off-label for prevention of T2DM in patients with prediabetes. Biguanides including metformin and its predecessors buformin and phenformin were originally derived from the French Lilac. Metformin's effects on lowering blood glucose in rabbits was first described in the 1920s.⁶ Its pharmacologic effects include decreased hepatic production of glucose, decreased intestinal absorption of glucose, and increased sensitivity to insulin. These effects cause reduction in both fasting and postprandial glucose levels.⁷ Other possible uses and effects that will be

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discussed within this article include nonalcoholic fatty liver disease (NAFLD), increased ovulation and pregnancy rate in females with polycystic ovarian syndrome (PCOS), and reduced risk of cancer in patients with T2DM.

The overall effects of metformin lead to its favorable risk–benefit profile compared with other options. For example, the fact that its mechanism does not involve insulin production means that it does not cause hypoglycemia when used as monotherapy. Having a mechanism independent of insulin also makes it weight neutral. Effects of insulin include increased hunger and increased uptake of glucose into adipose tissue; therefore, insulin and insulin secretagogues such as sulfonylureas cause weight gain as a common adverse effect.⁷ Metformin's ability to decrease both fasting and postprandial blood glucose readings result in marked glycated hemoglobin (A1C) reductions; it typically reduces A1C an average of 1% as monotherapy.⁸

The most common contraindication of metformin use is renal dysfunction. According to Food and Drug Administration (FDA) labeling, serum creatinine 1.5 mg/dL or higher in male patients or 1.4 mg/dL or higher in female patients is considered a contraindication to metformin use.⁷ These strict guidelines were set due to the rare adverse event of lactic acidosis historically associated with first-generation biguanides including phenformin and buformin, an adverse event more common in the presence of renal dysfunction. Lactic acidosis is a life-threatening condition that occurs when lactic acid in the blood rises due to hypoperfusion and subsequent hypoxia of muscle tissue causing marked acidosis and an increased ion gap. According to the FDA's Black Box Warning, the prevalence of lactic acidosis with metformin is approximately 3 cases per 100 000 patient-years, though it is known that T2DM itself is also a risk factor for lactic acidosis introducing confounding bias to these data.⁴ Many of the reported cases of lactic acidosis occurred in the presence of another acute condition such as renal failure, which can cause lactic acidosis with or without metformin exposure. Numerous studies and reviews have shown that any increased risk of lactic acidosis with metformin is minimal if it exists at all including a Cochrane review with approximately 67 000 patient-years of data that revealed that the prevalence of lactic acidosis and increased lactate with metformin use is similar to other antihyperglycemic agents. The investigators in this study found the risk of increased lactate and lactic acidosis was similar in subjects taking metformin to subjects taking placebo or active comparator and concluded that metformin likely does not increase risk of lactic acidosis.⁹

Based on these data, guidelines in the United Kingdom, Canada, and Australia have become less stringent with regard to metformin use in the presence of renal dysfunction. In all 3 cases, national guidelines consider an estimated glomerular filtration rate (eGFR) < 30 mL/min to be an absolute contraindication to metformin use, but

mild-moderately impaired renal function including serum creatinine greater than or equal to 1.5 mg/dL and eGFR between 30 and 60 is only a precaution under these less stringent guidelines.⁴ US guidelines such as ADA and AACE have yet to weigh in on this controversy,^{2,3} and it is doubtful that the FDA labeling will be changed because drug manufacturers are unlikely to sponsor a label change for an inexpensive, generic medication.

Metformin is contraindicated in other conditions where the risk of lactic acidosis is elevated. The use of iodinated contrast media causes anuria, and therefore, metformin should not be used during and at least 48 hours after use or until renal function has returned to normal. It should also be discontinued prior to any surgery. Hospitalized patients who may experience acute renal failure including those with sepsis, dehydration, metabolic acidosis, diabetic ketoacidosis, and hypoxemia should not take metformin during hospitalization and until the condition has recovered.⁷

Diarrhea is one of the most common adverse effects that leads to patients discontinuing metformin. Other gastrointestinal (GI) effects include nausea, indigestion, and flatulence. GI effects including diarrhea can be mitigated with proper dose titration and the use of dosage forms with less potential for this adverse effect. For example, placebo-controlled trials of metformin extended-release (XR) show an incidence of diarrhea between 9.6% and 12.5%, while placebo-controlled trials of the immediate release (IR) form show incidence of 53.2%.¹⁰ Both forms are now available generically and considered equally effective.¹¹ Using lower starting doses and titrating slowly can reduce the risk of these effects. Metformin IR is typically started at 500 mg once or twice daily and increased 500 mg weekly as tolerated to a dose of 1000 mg twice daily. It can also be started at 850 mg daily and titrated 850 mg every other week as tolerated to a maximum dose of 850 mg 3 times daily; however, the use of 3 daily doses introduces a major adherence barrier and this dosing regimen is not as commonly used as 1000 mg twice daily. Metformin XR is typically dosed 500 mg once daily and increased 500 mg weekly as tolerated to a dose of 2000 mg once daily or 1000 mg twice a day. Both forms of metformin are to be taken with a meal; the XR version should preferably be taken with the evening meal.⁷

A long-term adverse effect seen with chronic metformin use, especially at high doses, is vitamin B₁₂ deficiency due to malabsorption. Patients taking metformin chronically, especially at higher doses, should be monitored for vitamin B₁₂ levels every 2 to 3 years. They should also be monitored for vitamin B₁₂ levels as clinically indicated by symptoms including peripheral neuropathy. Before treating peripheral neuropathy as diabetes-induced and starting potentially unnecessary pharmacotherapy, vitamin B₁₂ deficiency should be ruled out in patients with a high-dose and/or long-term metformin exposure. If vitamin B₁₂ deficiency occurs, it can be treated with appropriate supplementation based on

the patient's vitamin B₁₂ level and does not require discontinuation of metformin.⁷

LKB1 and AMPK Pathways

At the molecular level, many of metformin's effects are mediated by the liver-kinase B1 (LKB1) and adenosine monophosphate activated protein kinase (AMPK) pathways. Metformin acts on a molecule known as adiponectin, which enhances activation of both of the aforementioned kinases. LKB1 is a known tumor suppressor, which may explain the reduced risk of colorectal cancer found in metformin users.¹²

Some of the downstream effects of AMPK result in metformin's effects as an antihyperglycemic agent. Effects on the muscle include induction of hexokinase II expression and GLUT4 gene upregulation, both of which cause the muscle to increase glucose uptake. AMPK also phosphorylates glycogen synthase, thereby inhibiting it, and glycogen synthesis. AMPK acts in the liver to phosphorylate CREB-binding protein (CBP), which leads to decreased gluconeogenesis. All of these biochemical mechanisms ultimately decrease blood glucose both preprandially and postprandially.¹²

This pathway is also the reason for metformin's favorable effect on lipid profiles and possible effect in NAFLD. AMPK causes inhibition of HMG-CoA reductase, the enzyme responsible for the rate-limiting step in cholesterol synthesis, as well as several other enzymes involved in cholesterol synthesis, leading to its favorable effects on HDL, LDL, and TGs. It has been studied in NAFLD because AMPK inhibits sterol regulatory element-binding protein-1c (SREBP-1c), a regulatory factor for fatty acid synthesis that is known to be increased in patients with NAFLD. Investigators hypothesized this effect may benefit NAFLD; however, current available data have not shown a clinical benefit.¹²

Decreased Mortality Risk

The superiority of medication therapy over lifestyle modification alone was first established in the United Kingdom Prospective Diabetes Study (UKPDS), a landmark trial. In this study, more than 5000 subjects between the age of 25 and 65 with newly diagnosed T2DM were recruited to compare lifestyle modification alone, the standard of therapy at the time, to intensive treatment with either insulin or a sulfonylurea (namely glyburide or chlorpropamide). Additionally, several centers in the study were given the third option of using metformin, but this option was limited to overweight and obese subjects. The original published results focused on sulfonylureas and insulin and found there was a reduced risk of microvascular complications but not mortality. This study is the reason we now use pharmacologic therapy, in addition to lifestyle changes, in all patients with T2DM.⁵

In 1998, a post hoc analysis involving a subsection of 1704 overweight subjects in the UKPDS followed for an average of 10.7 years given metformin, sulfonylurea, insulin therapy, or lifestyle modification was published. Subjects in this subset were an average age of 53 years, had an average A1C of 7.2%, and were overweight or obese with an average body mass index (BMI) of 31. The researchers targeted maximum labeled doses for metformin (2550 mg daily) as well as the sulfonylureas, and in both cases, most subjects reached these doses. The data showed metformin decreases macrovascular complications. This includes a 42% reduced risk of diabetes-related death and a 36% reduced risk of all-cause mortality compared with lifestyle modification. The analysis also found statistically significant reductions in the risk of diabetes-related endpoints, all-cause mortality, and stroke in the metformin group compared with sulfonylurea or insulin. These results suggest that first-line therapy should be pharmacological intervention, not lifestyle modification, and that the drug of choice for the overweight population should be metformin.⁵

Published in 2008, a 10-year follow-up of the UKPDS confirmed the previous results long-term. As more time elapsed and more events occurred, a reduction in all-cause mortality of 13% was discovered in the sulfonylurea group. It is important to note, however, that as beta-cell function declines, insulin secretagogues, which act on beta-cells, become less effective, thus limiting their use long-term. Additionally, the risk reduction in the sulfonylurea group was still inferior to metformin, which had a reduction of 27%. These data further demonstrated metformin's utility in the overweight and obese populations but did not provide clinical evidence of its utility in the general population.¹³

Evidence for decreased mortality with metformin use in the general population exists in a 2002 cohort study by Johnson et al, which compared sulfonylureas and metformin. The investigators reviewed the medical records of over 12 000 patients who were new users of oral antihyperglycemic agents. With an average follow-up of 5 years, metformin was found to have a lower all-cause mortality rate and cardiovascular-related mortality rates compared with sulfonylurea users. Moreover, users of metformin alone had similar mortality rates as users of metformin combined with sulfonylureas. A major limitation of the study was the researchers did not have access to subjects' BMI.¹⁴

Among several meta-analyses that have questioned metformin's reduction in mortality in the general population was Lamanna et al published in 2011. The analysis including 35 trials with a duration of no less than 52 weeks. It included trials comparing metformin to both placebo and active comparators. It did not account for dosage; metformin's dosage ranged from 500 to 2500 mg. It also did not include separate analysis for overweight and obese populations, and therefore, its results cannot dispute the positive findings of UKPDS in these populations. The final analysis

included about 7000 subjects in the metformin group and 11 000 subjects in the placebo group. Metformin had a significant reduction in risk of cardiovascular event and all-cause mortality compared with placebo but not active comparator. The analysis also showed a statistically significant increased risk of mortality with concomitant use of metformin and sulfonylureas in 2 of the included trials that evaluated combination therapy.¹⁵ The benefit and risks of using of sulfonylureas as monotherapy and in combination needs to be considered in light of the possibility of increased risk of mortality this study noted.

Metformin's role as a life-prolonging drug in the overweight and obese populations, which constitutes a large majority of the population with T2DM, is well established by clinical data. However, meta-analyses have shown neither mortality-risk reduction nor increase in the general population compared with active comparators. More data are needed to establish metformin's ability to reduce mortality risk in the general population. Large, multi-center trials comparing metformin to sulfonylureas in the general population would provide these data. Nevertheless, its low cost, high tolerability, weight-neutrality, favorable effects on lipid panel, and efficacy in reducing A1C all still justify its status as first-line therapy in all patients with T2DM who can tolerate it and have adequate renal function.

Prevention of Diabetes in Patients With Prediabetes

Prediabetes is defined as impaired glucose tolerance (IGT), impaired fasting glucose (IFT), and/or A1C 5.7% to 6.4%; A1C 6.5% or higher is considered diagnostic for T2DM. There is significant evidence in the form of a large meta-analysis that metformin may reduce the risk of patients with prediabetes progressing to new-onset T2DM. The ADA recognizes metformin's possible effect on progression to T2DM and recommends it as an option for an adjunct to lifestyle modification, especially in patients less than 60 years of age, with BMI greater than 35 and/or with history of gestational diabetes mellitus (GDM). However, it is important to note that metformin is not a replacement for lifestyle modification and metformin was found to be less effective than intensive lifestyle modification by one clinical trial that compared the two.¹⁶ Due to the limited costs and risks associated with metformin use, it is a not unreasonable to give patients with prediabetes metformin especially if they fall into the 3 groups specifically mentioned by ADA as an adjunct to the education and lifestyle changes patients with prediabetes require.

A meta-analysis by Salpeter et al showed a beneficial effect in using metformin in the presence of prediabetes compared with placebo or no control. The systematic review produced 31 randomized control trials (RCTs) at least 8 weeks in duration comparing metformin with placebo or no

treatment; the total number of subjects was 4570 and the mean trial duration was 1.8 years. Participants in the treatment group were on average 45.7 years of age with BMI of 32.3 and 45.1 years of age with BMI of 32.7 in the control group. This means the majority of subjects were less than 60 years of age and obese and therefore at high risk for progressing to T2DM. The mean dose of metformin was 1600 mg per day. The data showed a 40% decreased risk of progressing to T2DM, a 5.3% BMI reduction, increased HDL, decreased LDL, and decreased TG levels with use of metformin versus placebo or no treatment.¹⁷

Knowler et al assessed metformin as well as lifestyle change in prevention of T2DM.¹⁶ The trial was a multicenter, placebo-controlled trial comparing metformin 850 mg twice daily plus standard lifestyle modification, placebo plus standard lifestyle modification, and intensive lifestyle change (7% reduction in body weight with low-fat diet and 150 minutes/week of physical activity). The study included 3200 participants with elevated fasting and/or postprandial glucose readings not severe enough to be indicative of T2DM; at the time of the study A1C had not yet been established as a diagnostic parameter in the most recent ADA guidelines published in 1997. Like the meta-analysis by Salpeter et al, subjects' baseline characteristics put them at high risk for progression to T2DM—about 16.1% of female subjects had a history of GDM, the average age was 50.6, and BMI was 34, indicative of obesity. The study found that for every 100 person-years, there were 11 cases of progression to T2DM in the placebo group, 7.8 in the metformin group, and 4.8 in the intensive lifestyle change group. These data further demonstrate metformin's effectiveness in prevention of T2DM but limit its use to adjunct to lifestyle modification, a more effective therapy.¹⁶ Using metformin for prevention of T2DM may be an attractive option for those at high risk of progression. Providers must weigh the costs of drug therapy and monitoring, adverse effects, and lack of outcome data showing prevention of meaningful endpoints such as prevention of renal failure and mortality. That being said, metformin is low cost and relatively free of serious adverse effects, and therefore, reduced risk of progression to T2DM alone may outweigh associated risks and costs of drug therapy.

NAFLD

NAFLD refers to a group of medical conditions that are the most common cause of chronic liver disease. It occurs when the supply of fatty acids in the liver exceed the amount needed for cholesterol synthesis such as triglyceride, phospholipid, and cholesterol synthesis. NAFLD is more common in overweight and obese patients, and the prevalence increases with the degree of obesity. It is also common in patients with T2DM or other disorders of insulin sensitivity.¹⁸

There are several types of NAFLD with different prognoses. With proper treatment, nonalcoholic fatty liver (NAFL) can be reversed and carries low risk of progression to cirrhosis. However, a form of NAFLD known as nonalcoholic steatohepatitis (NASH) occurs when cellular damage has already occurred, is progressive in nature, and is a major cause of cirrhosis and rarely cancer. Once progression to NASH occurs, the course of the disease can be altered but not reversed.¹⁸

Due to the fact that metformin improves insulin sensitivity, is weight neutral, and its AMPK pathway has downstream effects on fatty acid synthesis mentioned above, its use has been studied in NASH, but data are limited to small clinical trials and show no effect on histologic or biologic outcomes. Therefore, metformin is not recommended by major guidelines. The guidelines do give a recommendation for the use of pioglitazone as a possible option in biopsy-proven NASH with the disclaimer that long-term risk-benefit data in NASH are not established and that the agent carries risk of heart failure, bladder cancer, and bone loss. No medication is nearly as effective as or a substitute for the lifestyle changes that these patients require; the mainstays of therapy are weight loss, improved nutrition, and increased physical activity.¹⁸

The limited data available on the use of metformin in NASH was systematically reviewed by Rakoski et al as they evaluated insulin sensitizers' effects on the histologic and biochemical features of the disease. Some histologic features of the disease used as markers in studies are steatosis, ballooning of hepatocytes, lobular inflammation, and possibly fibrosis, while the primary biochemical marker studied has been alanine transaminase (ALT). In a review of 4 randomized trials and only 150 subjects evaluating metformin's effect on biologic and histologic outcomes, neither of these outcomes proved to be significantly improved.¹⁹

For now, intensive lifestyle changes will remain the mainstay of therapy in NAFLD. While current data show pioglitazone may be effective in treating this condition and major guidelines consider it an option, the agent carries substantial risk and this must be addressed with long-term trials before it is considered a safe and effective mainstay of therapy. Metformin should also be studied more closely for the disease because while current data limited by sample size show it may be ineffective, larger trials may prove otherwise and its safety profile is preferable to that of pioglitazone.

PCOS

Metformin has been studied in subjects with PCOS to see if it may increase pregnancy, ovulation, and/or live birth rates as well as decrease symptoms of the disease. A major contributing factor of this syndrome is believed to be insulin resistance and subsequent hyperinsulinemia. Insulin

influences ovarian synthesis of androgens by binding both insulin and insulin-like growth factor 1 (IGF-1) receptors. Its effects on both these receptors directly increase steroidogenesis in the pituitary and indirectly increases luteinizing hormone (LH) release from the pituitary, which also increases steroidogenesis. Insulin may also work in the liver to decrease production of sex hormone-binding globulin, thus increasing free androgen levels. This increase in androgen levels is the ultimate cause of the effects of PCOS.²⁰

There are limited data available to suggest that metformin may increase pregnancy and ovulation rates but not live birth rate in patients with PCOS. Current data show that metformin alone or in combination with clomiphene may improve pregnancy rate compared with placebo. It may also improve pregnancy rate in combination with clomiphene better than clomiphene alone. However, current data have not proven it improves live birth rates better than clomiphene or placebo. These data come primarily from a Cochrane systematic review of 44 trials and 3992 subjects with PCOS; the review was limited by heterogeneity and included several smaller subsets of similar trials limiting sample size.²⁰ Due to this limited quantity and quality of data available, the American Congress of Obstetricians and Gynecologists (ACOG) recommends metformin only as a last-line option for ovulation induction in combination with clomiphene to induce ovulation at 1500 to 2000 mg daily. The guidelines do note that the agent carries limited risk. ACOG mentions both metformin and pioglitazone as options for anovulation and amenorrhea; however, they note that metformin has the more favorable risk-benefit ratio of the 2 agents.²¹

Trials comparing metformin to placebo analyzed by the Cochrane review have found no significant difference in live birth rates but have found significant improvement in clinical pregnancy rate and ovulation rate. Only 3 trials with 115 subjects evaluated live birth rate resulting in a wide confidence interval of 0.52 to 6.16; an effect of metformin versus placebo on live birth rate cannot be ruled in or out without further research. In 8 trials and 707 subjects that evaluated clinical pregnancy rate, the number needed to treat (NNT) was 6 to 21. In 15 trials with 1208 subjects evaluating increased ovulation rate, the NNT was 5 to 47. These data are limited by small sample size and heterogeneity, and more research is warranted.²⁰

The review also analyzed trials that compared combination of metformin with clomiphene with clomiphene alone. Again, no difference in live birth rate was found in 7 trials and 907 subjects. However, the combination therapy did improve clinical pregnancy rate in 11 trials with 1208 subjects with an NNT of 7 to 32. In 18 trials with 3265 subjects evaluating ovulation rate, the NNT was 6 to 10. These data warrant further clinical research into metformin's role as combination therapy.²⁰

Due to the high variability of design and quality between the trials evaluated, more clinical data are required before a strong recommendation to use metformin in PCOS is made. There are also insufficient data to determine whether metformin improves the final desired outcome of live births. It has also not been studied whether metformin is more effective in patients with both PCOS and IGT, and this may be another future avenue of research. Another area addressed only by very small trials is a possible role for metformin to improve in vitro fertilization results. Metformin has also been studied in several complications associated with PCOS including menstrual regularity, obesity, glucose tolerance, hirsutism, and acne; however, these data are very limited. Future research should address all of these issues so that the true role of metformin in improving fertility in PCOS and complications of PCOS can be better established and incorporated into clinical practice.²²

Cancer

Metformin has been evaluated regarding risk reduction of cancer in patients with T2DM. It is well established that patients with T2DM are at an increased risk for development of several different types of cancer perhaps due to the effect of hyperinsulinemia on insulin-like growth factor 1 (IGF-1), a factor known to be involved in cancer pathogenesis. The most significant data on this topic come from 2 large meta-analyses have researched this possible effect.

The meta-analysis performed by Thakkar et al included all completed RCTs and case-control and cohort studies that evaluated all-cancer risk in metformin and/or sulfonylureas. The final analysis was of 24 studies for metformin and 18 studies for sulfonylureas. The review produced inconclusive results. With regard to metformin, reduction in cancer risk was found in both case-control and cohort studies but not RCTs. In the sulfonylurea trials, an increased risk of cancer was found in cohort studies but RCTs and case-control studies failed to find any difference in risk. A major limitation of the study identified by the authors was heterogeneity between the studies analyzed. Most of the studies included also identified major confounding variables with regard to baseline statistics including age, BMI, gender, duration of diabetes, and duration of metformin use. Highly variable follow-up periods between the studies included could also have had a major impact on the results as studying cancer risk requires a long follow-up period to allow the cancer to develop. Since the minimum trial duration was just 6 months, shorter trials could have swayed the results toward no difference even if a difference indeed exists. Ultimately, this large heterogeneity prevented the authors of the meta-analysis from providing a clear indication of what the baseline characteristics of their studies and subjects were overall. The authors concluded that the data

were weak and confirmation in large-scale RCTs was required before clinicians could use the data in practice.²³

The inclusion criteria for the review by Stevens et al included only RCTs comparing metformin with active or placebo comparator with greater than 500 participants and a minimum 1-year follow-up; however, they did not require their included trials specifically evaluate cancer risk. Similar to Thakkar's findings on RCTs, Stevens found no difference in cancer risk between metformin and active comparator or placebo. Limitations identified by the authors included heterogeneity of the trials and short duration that was likely not sufficient to evaluate a long-term outcome such as cancer. With regard to their analysis of RCTs with active comparator, the results were dominated by 2 trials that used rosiglitazone as an active comparator. Rosiglitazone is rarely used in practice due to its extremely poor safety profile and has a close relative pioglitazone known to increase risk of bladder cancer. Other confounding variables similar to the Thakkar et al study existed and this clinical heterogeneity between the studies limits clinicians' ability to interpret the data from a practical standpoint.²⁴

While data regarding all-cancer risk in patients with T2DM taking metformin is limited and inconclusive, there are positive data available on its reduced risk of colorectal cancer in the form of a large meta-analysis. Zhang et al reviewed 5 trials consisting of over 108 000 subjects taking metformin or comparator for T2DM. All 5 studies evaluated colorectal neoplasm and a significant RR of 0.63 was discovered. All but one relatively small study analyzed colorectal cancer and found a similarly promising RR of 0.63. Unlike the aforementioned studies that analyzed all-cancer risk, statistical analyses in this study showed low heterogeneity between the studies. These data are limited by the fact that only observational studies were available for review. Moreover, the studies included identified many confounding variables that had to be adjusted for, including gender, personal history, smoking, BMI, use of other antihyperglycemic agents, age, duration of diabetes, and A1C. However, these data are significant enough to further demonstrate metformin's favorable risk-benefit ratio.²⁴

Overall, data regarding metformin's ability to reduce all-cancer risk in patients with T2DM are limited. However, there are significant data suggesting it lowers risk of colorectal cancer. As discussed, Zhang et al reviewed 5 trials with over 108 000 subjects taking metformin versus a comparator for T2DM. These further show metformin's favorable risk-benefit ratio. While it is unlikely that metformin reduces risk of all types of cancer, it is likely that it reduces risk of some specific types of cancer. Research into metformin's ability to lower risk of other specific cancers, especially those that are more prevalent in patients with diabetes, would be helpful in determining metformin's true role in lowering cancer risk.

Conclusions

Metformin remains first-line therapy for treatment of T2DM according to leading national guidelines for several reasons, but importantly due to its strong mortality data in overweight and obese populations. If dosed correctly, it is also a very well-tolerated agent causing primarily GI-related adverse effects that are largely preventable through proper dosing and having no hypoglycemic reactions as monotherapy nor any weight gain.⁶ Its major contraindications are conditions such as renal insufficiency that increase risk of lactic acidosis, but metformin-induced lactic acidosis is rare or nonexistent.⁴ Metformin also prevents progression to T2DM in patients with prediabetes.^{16,17} This is especially true for patients at high risk for progression such as those with BMI > 35, those with history of GDM, and those under 60 years of age.²

There are other areas of research where some promising data exist and more research is warranted. Insulin sensitizers including metformin as well as thiazolidinediones show some promise in the treatment of biopsy-proven NASH as adjunct to the mainstays of treatment: better nutrition, physical activity, and weight loss.¹⁹ PCOS is an area of research with metformin use that has shown some promise.^{20,22} While current data are only sufficient enough for leading guidelines to recommend metformin as last-line therapy in combination with clomiphene, future trials may prove it is effective and warrant its use earlier in the treatment algorithm.²⁰ Metformin's ability to reduce risk of colorectal cancer is well established and risk of other individual cancers should be evaluated further.²³⁻²⁵ Metformin has long been recognized as a highly effective antihyperglycemic agent with a favorable risk-benefit ratio, and other benefits may be discovered as research continues on this drug.

Declaration of Conflicting Interests

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.
2. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36(suppl 1):S4-S10.
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm. *Endocr Pract*. 2013;19:327-336.
4. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care*. 2011;34:1431-1437.
5. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-865.
6. Witters LA. The blooming of the French lilac. *J Clin Invest*. 2001;108:1105-1107.
7. Metformin. In: DRUGDEX System [Internet database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically.
8. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007;147:386-399.
9. Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;(4):CD002967.
10. GLUCOPHAGE, GLUCOPHAGE-XR oral tablets, extended-release oral tablets, metformin hydrochloride oral tablets, extended-release oral tablets [product information]. Princeton, NJ: Bristol-Myers Squibb; 2009.
11. Gao H, Xiao W, Wang C. The metabolic effects of once daily extended-release metformin in patients with type 2 diabetes: a multicentre study. *Int J Clin Pract*. 2008;62:695-700.
12. Mazza A, Fruci B, Garinis GA, Giuliano S, Malaguarnera R, Belfiore A. The role of metformin in the management of NAFLD. *Exp Diabetes Res*. 2012;2012:716404.
13. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589.
14. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care*. 2002;12:2244-2248.
15. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2011;13:221-228.
16. Knowler WC, Barrett-Connor E, Fowler SE. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.
17. Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am J Med*. 2008;121:149-157.e2.
18. American Gastroenterological Association, American Association for the Study of Liver Diseases, American College of Gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology*. 2012;142:1592-1609.
19. Rakoski MO, Singal AG, Rogers MA, Conjeevaram H. Meta-analysis: insulin sensitizers for the treatment of non-alcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2010;32:1211-1221.

20. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev*. 2012;(5):CD003053.
21. American College of Obstetricians and Gynecologists. *Polycystic Ovary Syndrome*. Washington, DC: American College of Obstetricians and Gynecologists; 2009 (ACOG Practice Bulletin, No. 108).
22. Raskauskas TA. Metformin in polycystic ovary syndrome. *N Engl J Med*. 2008;358:1866-1867.
23. Thakkar B, Aronis KN, Vamvini MT, Shields K, Mantzoros CS. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. *Metab Clin Exp*. 2013;62:922-934.
24. Stevens RJ, Ali R, Bankhead CR, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. *Diabetologia*. 2012;55:2593-2603.
25. Zhang ZJ, Zheng ZJ, Kan H, et al. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. *Diabetes Care*. 2011;34:2323-2328.