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METFORMIN BEYOND DIABETES: EXPLORING OFF-LABEL APPLICATIONS ACROSS MEDICAL FRONTIERS

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Abstract: *Metformin, widely used for T2D, is increasingly explored for off-label use in both endocrine and non-endocrine conditions, showing promise for improving patient outcomes. In polycystic ovary syndrome, metformin has demonstrated efficacy in lowering anti-Müllerian hormone levels and improving hormonal and metabolic parameters, though its role in managing hirsutism, especially in adolescents, remains uncertain. In gestational diabetes mellitus, metformin effectively reduces maternal weight gain, lowers the risk of preeclampsia, neonatal hypoglycemia, and macrosomia, and improves glycemic control without affecting fetal neurodevelopment.*
Beyond endocrine disorders, metformin's broader applications are under investigation. Although early observational studies suggested that metformin reduces cancer risk in diabetics, subsequent analyses revealed significant biases, and randomized clinical trials found no anticancer benefit. This highlights the need for caution when interpreting observational data and the importance of robust randomized trials to assess metformin's true impact on cancer outcomes. In cardiovascular diseases, metformin shows promise in reducing mortality and adverse cardiovascular events. Research also suggests metformin's potential to protect against diabetic kidney disease and neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. However, additional studies are needed to better understand and enhance metformin's clinical effectiveness across various patient groups.

Key words: *metformin, PCOS, gestational diabetes, cardiovascular, neuroprotective.*

1. Introduction

Metformin acts as an oral antihyperglycemic medication, successfully lowering both fasting and after-meal blood sugar levels in people with type 2 diabetes (T2D). Metformin exerts its anti-diabetic effects primarily by inhibiting hepatic gluconeogenesis, thereby lowering blood glucose levels and impacting lipid metabolism in the liver [1]. Metformin has many effects, including

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reducing free fatty acid levels, increasing insulin-stimulated systemic glucose clearance (particularly in skeletal muscle), inhibiting lipid synthesis, and stimulating fatty acid oxidation [2–4]. Besides peripheral glucose elimination, metformin affects extra-hepatic locations, with gut studies underway [3]. Intestinal processes, including duodenal AMPK pathway modulation of GLP-1 levels and alterations in gut microbiota composition, enhance metformin's anti-hyperglycemic effects [4–6].

Metformin possesses neuroprotective qualities and may provide therapeutic advantages for mild cognitive impairment and Alzheimer's disease (AD), while also enhancing cognitive function and decreasing the occurrence of dementia [7–10]. Moreover, it has been associated with advantageous outcomes in cardiovascular ailments. The 20-year UKPDS found that type 2 diabetics used metformin more, highlighting its cardiovascular advantages [11]. Research has shown that taking metformin orally every day can improve kidney fibrosis and restore normal kidney structure and function, suggesting potential advantages for renal health.

2. Metformin Pharmacology

Metformin's anti-diabetic effects occur mainly in the liver, where it improves glucose and lipid metabolism [1]. Metformin improves glucose metabolism by preventing gluconeogenesis and enhances insulin-stimulated glucose clearance in skeletal muscle [2,12,13]. Metformin does this via activating AMPK, a glucose and lipid metabolism regulator. AMPK activation suppresses hepatic gluconeogenesis and increases insulin sensitivity, muscular glucose uptake, and fatty acid oxidation [5,14]. It controls GLP-1 levels via the duodenal AMPK pathway, which contributes to its anti-hyperglycemic actions [2,4,5]. AMPK inhibitory phosphorylation inhibits PEPCK and G6Pase, two essential enzymes in gluconeogenesis, reducing glucose synthesis [14,15].

Whether AMPK activation is AMP-dependent or AMP-independent depends on metformin concentration and target organelles like mitochondria or lysosomes [15,16]. Metformin affects glucose metabolism via both AMP-dependent and AMP-independent activation pathways; the former is defined by a low energy state with higher AMP to ATP ratios [6].

Metformin also inhibits mitochondrial respiratory chain complex I, regulating cell energy metabolism [6,15]. This inhibition reduces ATP synthesis, increases AMP, and alters cellular redox potential [17]. Thus, suppressing ATP-dependent activities and altering the cytosolic redox state reduces glucose synthesis from gluconeogenic substrates [18].

Metformin reduces mitochondrial glycerol phosphate dehydrogenase activity, disrupting the glycerophosphate shuttle. This disruption affects hepatic glucose synthesis by changing the ratio of cytosolic NADH to NAD+ and decreasing mitochondrial NAD+ renewal [18–20].

Metformin activates AMP-kappa B, inhibits mitochondrial complex I, and alters cytosolic redox state and glycerophosphate shuttle activity to increase glucose metabolism and reduce hepatic gluconeogenesis [6]. Metformin's effects on complex biological systems and therapeutic efficacy vary, making it difficult to completely explain.

3. Potential mechanisms underlying metformin's beneficial effects beyond its primary indication

It is at the prescribing doctor's discretion to decide if the off-label use of a medication constitutes a medical error, typically ensuring such usage remains controlled, except when it strays from approved indications [21]. Furthermore, if two disorders have comparable clinical or physiological features, a physician may choose to use a medicine that has been licensed for one of these conditions to treat both [22].

3.1. Polycystic ovary syndrome

Polycystic ovarian syndrome (PCOS) is a common metabolic disorder in reproductive-aged women. Hyperinsulinemia, insulin resistance, and hypothalamic-pituitary-ovarian abnormalities cause androgen excess. Hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology are the Rotterdam Criteria's three diagnostic criteria [23–25]. Metabolic problems during pregnancy, obesity, diabetes, heart disease, and sleep apnea are all more common in PCOS patients [26–28].

The 2018 International Evidence-based Guidelines on PCOS recommend using metformin in addition to lifestyle management to address weight, hormone, and metabolic consequences [24,29]. Although the primary focus was on preventing weight gain, its efficacy for weight loss is acknowledged to be limited [30–32]. Given the major concern of weight gain in PCOS patients, there is an immediate need for alternative pharmaceutical treatments to aid in weight reduction.

When comparing the efficacy of metformin and oral contraceptive pills (OCP) in reducing excessive facial and body hair in adult women with PCOS, metformin may have a lower impact for women with a body mass index (BMI) ranging from 25 to 30 kg/m2, and its efficacy is unclear for those with a BMI lower than 25 or higher than 30 kg/m2 [29]. Metformin is more likely to cause gastrointestinal side effects (such as nausea, vomiting, and diarrhea) compared to OCP, but other side effects are less common. Combining metformin with OCP may be more effective than either alone for improving excessive hair growth, although the difference in severe adverse events remains uncertain [33]. There is limited high-quality information on the efficacy and safety of metformin compared to OCP or both in the treatment of hirsutism in teenagers [34].

A 2020 Cochrane meta-analysis compared metformin to placebo or no therapy in PCOS patients before or during in vitro fertilization or intracytoplasmic sperm injection [35]. Metformin did not increase live birth rates, according to the analysis. Metformin may reduce live birth rates when used with a short-protocol GnRH-antagonist but not with a long-protocol [35]. For long-term GnRH-agonists, metformin increases clinical pregnancy rates, but for short-term GnRH-antagonists, it is unknown. Metformin can reduce ovarian hyperstimulation syndrome but may increase side effects. Uncertain impact on miscarriage frequency [35].

3.2. Gestational diabetes

Diabetes – pregestational and gestational – is the most common

antenatal complication [36]. The US has seen an abrupt increase in gestational diabetes [37,38]. About 1–2% of pregnant women have pre-existing diabetes, and 1–14% have GDM [39]. Diabetes during pregnancy increases the risk of gestational hypertension, preeclampsia, and hypoglycemia, which can lead to T2D [40]. They also have a higher risk of cesarean section and premature delivery. Diabetes during pregnancy can cause macrosomia, tiny newborns, hypoxia, hypoglycemia, congenital malformations, prematurity, preterm delivery, and neonatal respiratory distress [41]. Women with T2D planning to become pregnant are recommended to take insulin and metformin, as the effects of other anti-diabetic medications on embryogenesis are unknown [38]. It has not been shown that prenatal exposure to metformin negatively impacts brain development in children up to the age of fourteen [42].

Randomized controlled trials have shown metformin's efficacy in overweight pregnant women varies. Ethnicity, median BMI, and metformin dose may affect study results. Metformin reduced weekly average gestational weight increase in obese women with a median BMI of 32.3 kg/m² against placebo in the GROW trial, but macrosomia rates did not change [43]. The metformin and placebo groups had similar maternal weight increases, newborn weights, and GDM risks. In contrast, the EMPOWAR study included obese women with a median BMI of 37.8 kg/m² [44]. The MOP study found that metformin reduced GWG and preeclampsia risk in women with a median BMI of 38 kg/m² compared to placebo [45]. Two meta-analyses found that metformin somewhat decreased gestational weight growth and the risk of gestational diabetes [46,47].

Metformin reduced maternal gestational weight gain, maternal hypoglycemia, neonatal hypoglycemia, and low birth weight better than insulin in a meta-analysis of 38 randomized controlled trials with 6086 women [48]. In another meta-analysis of 8038 women, metformin reduced preeclampsia risk more than other therapies. [49]. A meta-analysis of RCTs found metformin reduced macrosomia, NICU hospitalizations, and newborn hypoglycemia compared to insulin [50]. In the MITy randomized controlled trial, pregnant women with T2D who received metformin or placebo had similar fetus and newborn outcomes. Metformin users had lower third trimester hemoglobin A1c levels, met glycemic goals better, needed less insulin, and had fewer cesarean sections [51].

3.3. Obesity

Metformin induces weight loss by reducing insulin requirements and triggering gastrointestinal side effects such as nausea, diarrhea, and taste alterations [52]. Recent study reveals that gut flora and hypothalamic appetite regulatory modifications facilitate numerous pathways that cause this effect. These mechanisms may involve the gut-brain axis [52].

Metformin's weight loss or primary therapy efficacy in non-diabetic obese people is unclear. The ADA advises metformin for high-risk individuals, such as those with a BMI over 35 kg/m² and other risk factors, based on the Diabetes Prevention Program's findings of impaired glucose tolerance (IGT) and fasting plasma glucose levels of 95-125 mg/dL [53]. In a 2-year, double-blind trial, metformin

reduced weight, waist circumference, and T2D by 31% compared to placebo. These benefits lasted over 15 years [54]. According to Hostalek et al., who conducted extensive research and presented solid evidence from many clinical trials and clinical experience, metformin prevents diabetes safely and effectively [55].

Literature reviews show that metformin may help with metabolic syndrome symptoms beyond obesity and prediabetes. Studies show that metformin alone can improve dyslipidemia in newly diagnosed T2D patients without statins [56].

3.4. Anticancer properties

Initial 2005 observational studies showed metformin reduced cancer risk in diabetics, spurring further research into its anticancer properties. [57]. Metformin may reduce cancer cell growth by affecting insulin-dependent and insulin-independent pathways, according to lab studies. These pathways include AMPK activation, which inhibits the carcinogenic mTOR signaling pathway [58].

In observational studies before 2012, metformin reduced cancer incidence or mortality in breast, colorectal, prostate, liver, lung, urothelial, and bone cancers [59–62]. Metformin users had a 30% lower total cancer incidence, according to a meta-analysis [63]. Many observational studies have been criticized for biases, including the immortal time bias, which occurs when exposure is misclassified and artificially prolongs cancer incidence or death, giving the impression of a protective effect [64]. A cohort analysis of colorectal cancer incidence showed that metformin's preventive effect disappeared after correcting for immortal time bias [65]. Meta-analyses that excluded this bias found no association between metformin use and pancreatic cancer mortality. Those with this bias were asymmetrically protective [66].

After promising initial results, randomized clinical trials, the gold standard for evidence, found no anticancer effects of metformin [64]. Metformin did not increase cancer risk in a meta-analysis of seven randomized studies of T2D treatment [67]. Studies like the ADOPT and RECORD trials also indicated that metformin did not reduce cancer risk compared to other diabetes treatments [68]. A meta-analysis of nine phase 2 trials and other randomized studies evaluating metformin as an adjuvant treatment for different types of cancer found no substantial improvement in tumor response, progression-free survival, or overall survival [69]. Additionally, there was no statistically significant difference in invasive disease-free survival or death rates between the metformin and placebo groups in a big 5-year phase 3 trial included 3,649 women with high-risk nonmetastatic breast cancer [70].

In conclusion, time-related biases, particularly eternal time bias, can overstate metformin's protective effects, and randomized clinical trials have unexpectedly failed to show significant benefits [66].

3.5. Cardiovascular diseases

Metformin shows promise in safeguarding against cardiovascular illnesses and related mortality in patients with a diagnosis of T2D [71]. Metformin modifies HDL function, decreases reactive oxygen species formation, and inhibits the synthesis of advanced glycation end

products, among other mechanisms, which may explain its possible cardiovascular advantages [72]. Metformin may affect HDL function by activating AMPK to maintain paraoxonase-1 activity and prevent alpha-dicarbonyl-induced apolipoprotein changes. This reduces HDL dysfunction and LDL damage [73,74].

Metformin may also help heart failure patients by regulating heart muscle energy metabolism. By activating AMPK and increasing nitric oxide, metformin may reduce interstitial fibrosis, cardiomyocyte death, and cardiac remodelling. This helps maintain left ventricle systolic and diastolic functions, reducing heart failure risk [75–77].

Zhang et al. conducted a meta-analysis in 2020 that found a decreased risk of mortality and serious cardiovascular events among 701,843 patients with T2D who were treated with metformin [78]. A separate meta-analysis conducted by Han et al. shown that metformin effectively decreased both overall mortality and mortality related to cardiovascular issues in individuals diagnosed with coronary artery disease [79]. The "MetCool ACS" trial (NCT05305898) is expected to finish in 2025 and will determine if metformin is useful in preventing cardiovascular diseases in non-diabetic people with acute coronary syndrome.

3.6. Diabetic kidney disease

Diabetic kidney disease is characterized by important pathophysiological processes, such as the loss of podocytes, increase of mesangial cells, and fibrosis in the tubulointerstitial area [80,81]. Due to its diverse pharmacological effects, metformin has been extensively studied for its nephroprotective effects, including reducing mortality and cardiovascular disease risk in diabetic ketoacidosis (DKD), delaying end-stage renal disease progression, and reducing renal oxidative stress, inflammation, and fibrosis [82–85].

Metformin therapy was associated with a significant reduction in mortality in individuals with stage G3 chronic kidney disease (CKD), according to Rousse et al [86]. Swedish researchers examined National Diabetes Register data and found that metformin-based regimens reduced mortality risk in stage G3a chronic kidney disease (CKD) patients but not in stage G3b patients [87]. Another study that looked at US veterans confirmed this finding [82].

Evidence suggests that metformin may reduce the likelihood of mortality and serious adverse cardiovascular events [81]. Metformin use is independently linked to a lower risk of death from any cause, cardiovascular events, and renal disease composite, according to studies [83,84]. Whitlock's research and Crowley's systematic analysis showed that metformin improved clinical outcomes in mild chronic kidney disease patients [85,88].

3.7. Cognitive disfunction

Neurodegeneration encompasses complex processes involving multiple signalling pathways, with aging playing a significant role in increasing oxidative stress and inflammation [89]. Metformin has been studied for its potential gero-suppressive effects by activating AMPK, which inhibits the mTOR pathway, which causes aging, cancer, and neurodegenerative diseases [89]. Metformin may reduce insulin levels and

oxidative stress, but its effects on neurodegeneration and specific conditions like Alzheimer's and Parkinson's are still being studied [15,90,91]

Brain imaging shows structural changes, including a decrease in grey matter volume, due to diabetes-related cognitive loss caused by hyperglycemia and insulin resistance. [92,93]. The neuroprotective effects of metformin may be due to its actions in enhancing insulin sensitivity, decreasing inflammation, and promoting autophagy [92,94,95]. Metformin reduces dementia in older veterans, according to a meta-analysis [96]. However, other research suggests a worsening of cognitive impairment in older Korean patients. [97].

Studies suggest that metabolic abnormalities like hyperglycemia, hyperinsulinemia, and obesity contribute to AD progression, particularly in individuals with T2D [8].

The effects of metformin on AD, which is marked by neurofibrillary tangles and amyloid plaques, have been inconsistent [98]. While some animal studies show that metformin can prevent amyloid-beta aggregation, promote neurogenesis, and improve mitochondrial function [99–103], other studies suggest that metformin might increase amyloid-beta levels and worsen AD symptoms [104]. There has been conflicting evidence in clinical trials that have looked at the link between metformin and AD [105–108]. Metformin's effects on AD are mixed. Some studies show a preventive benefit, while others show no effect or even side effects like cognitive impairment [109–111]. These different results can be due to factors including dose, exposure time, and patient characteristics.

Despite conflicting evidence, metformin and AD research continues. Clinical trials like the Metformin in Alzheimer's Dementia Prevention (MAP) study aim to determine metformin's AD prevention potential (https://classic.clinicaltrials.gov/ct2/show/NCT04098666). Metformin may reduce AD risk, but more research is needed to determine its limits and optimal use.

Parkinson's disease is characterized by dopaminergic neuron degeneration and Lewy bodies [112]. Metformin has been studied for its potential benefits, including reducing inflammation, improving mitochondrial dysfunction, preventing neuron loss, and inhibiting α-synuclein phosphorylation [113–117]. The results are inconsistent, however; some research has shown a preventive benefit against PD, while other investigations have shown either no link or an increased risk [15]. Since metformin is linked to lower blood vitamin B12 levels, the potential association between low levels of this vitamin and PD is cause for worry [118–120]. To learn more about metformin's effect on PD risk, we need clinical studies with people who do not have diabetes.

3.8. Antiaging

Metformin's complex effect on stem cell exhaustion pathways may slow age-related stem cell function reduction [121,122]. Biguanides like metformin, geroprotectors since the 1980s, may lengthen life and postpone aging [123].

Campbell et al. found that metformin decreased all-cause mortality in accelerated-aging illnesses including cancer and cardiovascular disease as well as diabetes in 53 investigations. Metformin may improve health and longevity in age-related illness patients without managing diabetes [124].

Podhorecka and Kumari studied metformin's health and lifespan advantages [125,126].

Metformin stimulates AMPK, slowing ATP production and consumption to save energy. Metformin influences PPAR co-activator, which may boost mitochondrial biosynthesis. AMPK activated by metformin improves autophagy and cell health [127]. Through the IGF-1 signalling route, metformin may lower blood glucose, prevent aging, and extend longevity [128,129].

4. Conclusion

In conclusion, off-label metformin use in endocrine disorders may improve patient outcomes beyond T2DM. Metformin helps manage hormonal imbalances, insulin sensitivity, and metabolic complications in PCOS, gestational diabetes, and obesity. It may help manage weight and reduce PCOS symptoms like hyperandrogenism and irregular menstrual cycles, according to clinical evidence. Studies show that metformin can improve maternal glycemic control and reduce neonatal complications in gestational diabetes. Metformin's ability to improve insulin sensitivity and promote modest weight loss in obesity suggests it may be a treatment option for people at risk of T2D or with comorbid metabolic conditions. Metformin's off-label endocrinology uses demonstrate its versatility as a pharmacological agent and the need for more research to optimize its clinical use in diverse patient populations.

Metformin's off-label use in cancer, cardiovascular disease, diabetic kidney disease, cognitive dysfunction, Alzheimer's, Parkinson's, and antiaging interventions has many potential benefits. Metformin may improve patient outcomes beyond T2D mellitus, despite mixed results and ongoing research. AMPK activation, metabolic pathway modulation, and anti-inflammatory properties demonstrate its pharmacological versatility. Further research is needed to optimize its clinical utility, resolve conflicting evidence, and clarify its role in different disease contexts. The breadth of evidence supporting metformin's efficacy in diverse conditions emphasizes its potential to improve patient care and the need for continued research into its off label uses.

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