

Literature Review

Metformin and its role beyond glycemic control: a narrative review

Metformina y su rol más allá del control glucémico: una revisión narrativa

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ABSTRACT

This narrative review aims to examine the potential benefits of metformin beyond its well established antihyperglycemic effects. A historical synopsis of the evolution of the drug, and a complete analysis of the published evidence regarding its mechanism of action and the potential contribution of metformin beyond the glycemic control. The studies about biguanides began in the early twenties of the past century, up to its medical use as metformin, as an antidiabetic option, in 1957. Since then, metformin has become one of the most study and prescribed initial oral drug treatment for type 2 diabetes. An analysis of the mechanism of action of the drug points mainly at; to diminish hepatic glucose output and increasing, although moderately, insulin sensitivity, as well as an inhibition of intestinal glucose absorption. In the last past decades, there has been a growing interest to study metformin regarding its potential benefits, beyond its antidiabetic and metabolic effects, on most chronic health conditions; an apparent antiinflammatory action interacting on the ageing process, on neuromuscular and neurovascular conditions, and possible benefits on some oncologic pathologies. After almost seven decades of metformin use it become evident that apart of the disglycemia modulation, it does exert some of its benefits through pleiotropic effects, as antiinflammatory, antitumoral, antiatherosclerotic, and antiobesity. Even though, many of these and other actions of this medication remains to be carefully studied to amplify even more our knowledge on this always amazing drug.

Keywords: Metformin, Mechanism of action, Review, Potential effects beyond glycemia.

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RESUMEN

Esta revisión narrativa sobre la metformina con objetivo de abordar potenciales beneficios más allá de su efecto como antidiabético oral bien reconocido. Se realizó una sinopsis histórica, análisis de su mecanismo de acción y de la evidencia acumulada sobre otros beneficios de la droga más allá del control glucémico. Los estudios en humanos iniciaron en los años 50 por el médico francés Jean Sterne e introducida como medicación en Francia, en 1957. Es la medicación antidiabética oral más ampliamente utilizada, sola o combinada, en el tratamiento de la diabetes tipo 2, en todas las Guías o Consensos de Manejo. Actúa fundamentalmente a nivel hepático disminuyendo el gasto hepático de glucosa e incrementando ligeramente la insulinosensibilidad y a nivel intestinal actúa sobre la absorción de glucosa. En las últimas dos décadas se la ha analizado en cuanto a potenciales efectos beneficiosos más allá del control glucémico y metabólico: una aparente acción o efecto antiinflamatorio, actuando eventualmente sobre el proceso de envejecimiento, como "droga de la edad", además, acciones a nivel neuromuscular, en trastornos neurovasculares o degenerativos y con aparentes beneficios en algunas patologías oncológicas. A casi siete décadas de uso de metformina resulta evidente que la misma ejerce efectos pleiotrópicos más allá del manejo de la disglucemia de grado variable. Además del efecto antihiper glucemiante, destaca particularmente el efecto antiinflamatorio, el antitumoral, antiaterosclerótico y antiobesidad. Sin embargo, muchos de los mecanismos mediante los cuales está siempre sorprendente medicación ejerce estos y otros efectos, quedan aún por ser mejor estudiados y comprendidos.

Palabras clave: Metformina, Mecanismo de acción, Revisión, Potenciales efectos más allá de glucemia.

"Es imposible, para cualquiera, empezar a aprender algo, si piensa que lo conoce Todo". Epicteto (55 – 135 d.C.)

Introduction

Metformin is a biguanide discovered in 1922. Human studies began in the 1950s by the French physician Jean Sterne, and it was introduced as a medication in France in 1957. In Paraguay, it was incorporated into the therapeutic arsenal for type 2 diabetes mellitus (T2DM or DM2) in 1990, and in the USA in 1995.

Metformin is the most widely used oral antidiabetic drug (OAD), included as initial antihyperglycemic therapy, either alone or in combination, in the treatment of T2DM in all management guidelines and consensus statements, as well as in the prediabetes state ⁽¹⁾. The accumulated evidence in this regard over the years is practically unquestionable; it is safe, inexpensive, and effective, which confirms its continued relevance to this day ^(1,2).

It acts primarily at the hepatic level by reducing hepatic glucose output (HGO) and slightly increasing insulin sensitivity. It also acts at the intestinal level by affecting glucose absorption, depending on its concentrations. Additionally, it exerts effects in conjunction with GLP-1 or glucagon-like peptides. The main adverse effect is gastrointestinal (diarrhea and/or gastritis), leading to discontinuation in 20% or fewer of metformin users ⁽³⁾. It has been included in the World Health Organization's List of Essential Medicines since 2011 as one of the most important medications to be available in any country's health system.

Over the past decade and beyond, it has been analyzed for potential beneficial effects beyond glycemic and metabolic control in general: an apparent anti-inflammatory effect, its role as an "anti-aging drug," potential actions at the

neuromuscular level (Parkinson's disease) and neurovascular/cognitive level (Alzheimer's disease), neurovascular or degenerative retinal disorders, apparent benefits in certain oncological conditions, and an increasing number of chronic diseases that may potentially benefit from its use.

The purpose of this narrative review is precisely to analyze metformin, now approaching 70 years of use, in a balanced and critical manner, placing it above all in context, from our perspective as specialists with experience refined over the years and a continually renewed enthusiasm for its constant rediscovery.

Historical overview: Metformin is a drug belonging to the biguanide family, compounds rich in guanidine. It was synthesized (*dimethyl biguanide*) in 1922. Historically linked to *Galega officinalis*, commonly known as goat's rue, a herbaceous species of the Fabaceae family traditionally used as a medicinal plant, according to reports from late 18th-century Europe. Between 1918 and 1922, reports of its use in animals showed a reduction in blood glucose levels. Guanidine derivatives were synthesized and used to treat diabetes in humans during the 1920s and 1930s, but were discontinued due to their apparent toxicity. In the 1940s, metformin (1,1-dimethylbiguanide) was identified as a drug while searching for antimalarial agents, when clinical testing revealed a reduction in glycemia ⁽³⁾.

This apparent hypoglycemic property was further studied by the French physician Jean Sterne and collaborators, and it was he who ultimately reported its use to treat diabetes in 1957 ⁽³⁾.

Between 1957 and 1959, two other biguanides (phenformin and buformin), apparently more potent than metformin, were used for the treatment of diabetes. However, in the United Kingdom and several European countries, metformin was the one introduced into the therapeutic *armamentarium* of what was then still a very limited set of treatments for type 2 diabetes mellitus (T2DM or DM2), currently

known as oral antidiabetic drugs (OADs). The two previously mentioned biguanides were eventually withdrawn and discontinued due to their high risk of inducing lactic acidosis, a potential adverse effect that also delayed the introduction of metformin in the United States and other countries. The incidence of lactic acidosis with metformin use has nevertheless always been low, almost anecdotal, and most often associated with inappropriate indication or clear contraindications to its prescription, such as severely impaired renal function due to chronic kidney disease, acute renal failure, or patients with severe circulatory or respiratory compromise ^(3,4).

Extensive studies on the efficacy and safety of metformin during the 1980s and early 1990s ultimately led to its approval for use in the United States in 1995 ^(5,6).

The accumulated evidence over the past twenty-five years regarding the benefits of metformin is substantial, both in terms of glycemic control through its antihyperglycemic action—mediated by various mechanisms that continue to be studied even today, nearly seventy years later—as well as its minimal or absent risk of hypoglycemia and little to no weight gain. These characteristics established it, as previously mentioned, as the initial pharmacotherapy of choice in the management of hyperglycemia or dysglycemia ^(1,2).

Likewise, the potential long-term cardiovascular benefits, as reported and reaffirmed in the UKPDS (United Kingdom Prospective Diabetes Study) ^(7,8), further consolidated the central role of metformin at the initiation and continuation of treatment in patients with T2DM ⁽⁹⁾.

Metformin Beyond Glycemic Control – Analysis of Mechanisms of Action and Potential Benefits

However, research over decades on the molecular mechanisms by which metformin exerts its effects on various tissues and organs continues to be actively studied. When analyzing results published by different

research groups, discrepancies cannot be ignored, due to differences in dosing and therefore drug bioavailability, as well as the role that genetic variations may play in the response to metformin ⁽¹⁰⁾.

Some researchers have demonstrated that chronic oral administration of metformin increases fasting and postprandial levels of peptide tyrosine or PYY in humans. This gastrointestinal hormone, PYY 1–36, is produced by enteroendocrine L cells located in the distal small intestine and colon, and once secreted, triggers paracrine and neuroendocrine signaling effects. Therefore, among the multiple actions of metformin at the metabolic endocrine system level, it is likely that its effects facilitate some degree of weight loss or prevent easy weight gain, mediated by its action on PYY, which, once in circulation, completes its effect at the hypothalamic satiety center ⁽¹¹⁾.

Recent studies have attributed its antihyperglycemic effect to inhibition of mitochondrial complex I (MCI) of the electron transport chain (ETC) in vitro, occurring in a reversible manner. Likewise, metformin appears to modulate the production of GDF-15 (growth differentiation factor), an inflammatory cytokine induced by stress, produced in the intestines and kidneys, with modulatory effects on inflammation. Very recent studies also indicate that it is closely related to weight loss and particularly to cancer-related cachexia ^(12,13,14).

The Aging Process and Metformin

The combination of increased life expectancy and the evident growth of the elderly population is closely associated with a rise in the prevalence of multiple chronic diseases and their related morbidity and mortality. This is currently a reality in both developed and developing countries. Although there are sociocultural and personal differences regarding what is understood as an “older adult,” or the chronological age at which a person is considered “elderly,” general consensus places

this threshold at approximately ≥ 65 years.

The accepted definition of aging from a biological perspective includes “a reduced ability to regenerate damaged tissues” or “a deterioration in the maintenance of homeostasis over time, leading to functional decline, increased disease, and death” ^(15,16).

The aging process is complex and multifactorial. Insulin resistance and inflammation are associated with so-called non-communicable chronic diseases, including T2DM, cardiovascular disease (CVD), cancer, depression, psychological and cognitive decline, and dementia. Individually and collectively, these conditions contribute to what is currently known as a “*frailty state*” or increased vulnerability, compromising the health and quality of life of older adults ^(17,18).

Physiological and evolutionary theories have been proposed to better understand the mechanisms underlying the aging process. As individuals age, senescent cells accumulate due to a reduced capacity or inability of the immune system to clear or eliminate these cells—a process known as immunosenescence ^(15,17). These senescent cells secrete pro-inflammatory factors that create a chronic inflammatory environment, potentially damaging neighboring cells and further amplifying the process. This contributes to the development of age-related diseases or pathologies. Thus, the concept of “*cellular senescence*” is currently considered the central framework for understanding the aging process ^(15,16,18,19).

DNA damage has been an area of active research for years, with the aim of identifying pathways that could be modified to halt or at least delay the aging process itself. Endogenous sources of DNA damage include ROS (*reactive oxygen species*), hydrolysis, and alkylation, all of which are subjects of ongoing investigation. Exogenous factors contributing to genetic damage include chemicals, ultraviolet radiation, and other forms of radiation, among others, which may affect

DNA and protein translation, thereby partially explaining mechanisms of aging^(17,19).

Metformin, as emphasized, has proven efficacy in the prevention and management of T2DM. Although in the initial phase of the Diabetes Prevention Program (DPP) the efficacy of metformin in adults over 60 years of age was not evident, subsequent long-term follow-up (DPPOS) demonstrated a 21% reduction in diabetes risk in individuals aged 60 years or older at baseline⁽²⁰⁾. Nevertheless, the body of knowledge regarding the potential benefits of metformin continues to expand. It appears to act primarily by reducing inflammation rather than directly eliminating senescent cells per se⁽²¹⁾. Therefore, its potential impact on clinical-pathological conditions commonly associated with aging remains an area of ongoing research, particularly with drugs such as metformin.

Neurological-Cognitive Decline and Mental Health

The diagnosis of dementia in an individual has devastating consequences for the family, the social environment, and entails a significant medical and healthcare burden. T2DM is associated with a higher risk of cognitive impairment and dementia. Other major cardiovascular and endocrine-metabolic risk factors, often coexisting, include arterial hypertension (HTN), obesity—especially when these risk factors begin in young adulthood—and the addition of harmful habits such as smoking, which further increase, both individually and synergistically, the risk of neurocognitive decline and the development of dementia^(22–25).

Diabetes promotes the development of dementia by accelerating cerebrovascular and neurodegenerative damage through hyperglycemia. In particular, the high glycemic variability observed in diabetic patients, including those under treatment, appears to be responsible for the “acceleration” of dementia onset. Hyperinsulinemia preceding the clinical onset of T2DM, as well as drug-

induced or sustained hyperinsulinemia from certain antidiabetic medications, seems to contribute to neurocognitive damage through mechanisms that are not yet fully understood. Increased oxidative stress and sustained inflammation, especially in T2DM, contribute to the earlier onset and higher prevalence of neurocognitive impairment, particularly in the pathogenesis of Alzheimer’s disease. Evidence suggests that diabetes influences amyloid deposition and clearance mechanisms at the cerebral level^(23,25).

Based on the above, ongoing research into the potential impact of metformin on these processes appears justified.

Metformin reduces advanced glycation end products, which are responsible for promoting tissue degeneration and microvascular damage. Preclinical and clinical studies have demonstrated that metformin may have neuroprotective effects on brain structure and function⁽²⁶⁾.

In a recent prospective observational study aimed at determining the association between metformin use and the incidence of dementia and cognitive impairment over a 6-year follow-up, older adults aged 70 to 90 years (n=1037) were included: 123 with T2DM; 67 were treated with metformin and others without metformin, with 6 years of follow-up using neuropsychological tests to assess cognitive impairment, as well as MRI studies to determine brain volume at baseline and after two years, in addition to considering other covariates⁽²⁷⁾. The findings showed that those treated with metformin had significantly less cognitive decline compared to those with T2DM not treated with metformin. Despite the relatively small sample size, this study, due to its design and results, can be considered as providing interesting evidence.

More recently, comparative studies evaluating metformin versus other oral antidiabetic drugs (OADs) have been published, with results confirming a slowing of cognitive decline or dementia⁽²⁸⁾, as well as controversial findings

regarding neurodegenerative conditions such as Parkinson's disease (PD) ^(28,29).

However, the role of metformin in the development of dementia and other neurocognitive disorders, particularly in individuals without diabetes or in the general population, will continue to be the subject of future larger and more comprehensive randomized studies. These studies will aim to elucidate mechanisms of action ⁽³⁰⁾ and explore predictability through genetics and pharmacogenetics, thereby providing further insight into the effects of metformin beyond dysglycemia itself.

Metformin and Cancer Risk

Cancer is the second leading cause of death in both developing and developed countries. Furthermore, it is estimated that the burden of cancer-related health impairment will increase significantly as the global population ages ⁽²¹⁾.

Findings reported in several population-based studies have shown that diabetic patients have a higher risk of developing various types of cancer ^(31,32). This has led to growing interest in recent years in investigating the relationship between cancer and T2DM, more specifically focusing on the potential modification of this risk through oral antidiabetic medications.

Insulin resistance, obesity, and other components of metabolic syndrome appear to play an important role as risk factors linking certain types of cancer and diabetes ⁽³¹⁻³⁵⁾. Likewise, hyperinsulinemia itself, frequently associated with T2DM and obesity, appears to be negatively associated with cancer prognosis ^(32,35). Elevated insulin levels in obese men exacerbate carcinogenic potential and increase tumor growth at the cellular level ⁽³²⁾. Metabolic syndrome (MS), as a "pathological clinical cluster" ⁽³⁵⁾, increases the risk of several common cancers, such as colorectal cancer and postmenopausal breast cancer ^(36,37).

Some studies conducted years ago ⁽³¹⁾ already suggested that metformin could reduce cancer incidence, its progression, and even improve

prognosis ^(31,38,39).

Metformin inhibits the mitosis of cancer cells by inducing activation of adenosine monophosphate-activated protein kinase (AMPK) at the hepatic level, inhibiting gluconeogenesis and consequently reducing signaling for tumor growth factors. This appears to block tumor growth by lowering circulating insulin levels ^(32,34). Laboratory studies suggest that metformin reduces inflammation through its action on the mitochondrial complex ⁽¹²⁾. The chelation of various metals, such as copper, nickel, and cobalt, has also been reported as part of metformin's biochemical activity ^(12,33,34). In particular, metformin seems to induce changes in copper dynamics, thereby impacting mitochondrial function, which in turn contributes to its anticancer activity ^(12,33). Other possible mechanisms that may explain the apparent antineoplastic effect of metformin include its anti-obesity effect, through the reduction of systemic inflammatory activity commonly associated with overweight and obesity ^(32,34-37).

Although findings are heterogeneous, particularly regarding the populations studied, several studies have reported that metformin may reduce the risk of various types of cancer affecting different organs or tissues in the diabetic population, such as thyroid cancer, oral cancer, gastric cancer, liver cancer, bladder cancer, prostate cancer, breast cancer, endometrial cancer, and ovarian cancer ^(32,34,36-45). More recently, reports have also addressed the use of metformin and the risk of non-melanoma skin cancer ⁽⁴⁶⁾.

However, when critically analyzing the accumulated evidence, particularly in diabetic populations, the considerable heterogeneity among study populations may contribute to a possible overestimation of the anticancer effects of metformin. This may be due to confounding factors and synergistic influences, such as the concomitant use of insulin or sulfonylureas in several studies.

Evidence, Gray Areas, and Expectations to Be Unveiled

The body of evidence accumulated to date clearly positions metabolic syndrome (MS) as a major risk factor for the development of non-communicable chronic diseases. This cluster of clinical-pathological conditions is responsible for a fivefold increase in T2DM, a 2.5-fold increase in cardiovascular mortality, a twofold higher risk of coronary and cerebrovascular disease, as well as their consequences and/or comorbidities ^(35,37,47), and also represents a 1.5-fold increase in overall mortality risk ^(48,49). In a very recent publication, findings strongly suggest a reduction in the progression from MS to diabetes through the timely and appropriate use of metformin, together with other measures that promote a healthier lifestyle ⁽⁵⁰⁾.

As this narrative review on the use of metformin and its potential benefits draws to a close, it becomes evident that it exerts pleiotropic effects beyond the management of dysglycemia or hyperglycemia of varying degrees. In addition to its well-known antihyperglycemic effect, its anti-inflammatory, antitumor, anti-atherosclerotic, and anti-obesity effects are particularly noteworthy. However, despite the significant progress made in recent decades, many of the mechanisms through which metformin exerts these and other effects remain to be further elucidated and better understood.

All that has been analyzed here makes the path forward even more challenging and, at the same time, fascinating, as research in the coming years will undoubtedly continue to expand our understanding of this unique medication with nearly seven decades of use.

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References

1. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022; 45:2753–2786. doi: 10.2337/dci22-0034.
2. Pharmacologic approaches to glycemic treatments. Standards of Care in Diabetes-2024. *Diabetes Care* 2024; 47(Suppl. 1): S158–S178. doi: 10.2337/dc24-er07a.
3. Bailey CJ. Metformin: historical overview. *Diabetologia* 2017; 60:1566–1576. doi: 10.1007/s00125-017-4318-z.
4. Nattrass M, Alberti KGMM. Biguanides. *Diabetologia* 1978; 14:71–74.
5. DeFronzo RA, Goodman AM. Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulindependent diabetes. *N Engl J Med* 1995; 333:541–549. doi: 10.1056/NEJM199508313330902.
6. Bailey CJ, Turner RC. Drug therapy: metformin. *N Engl J Med* 1996; 334:574–579. doi: 10.1056/NEJM199602293340906.
7. 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.
8. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil H. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359:1577–1589. doi: 10.1056/NEJMoa0806470.
9. Bailey CJ. Metformin: Therapeutic profile in the treatment of type 2 diabetes. *Diabetes Obes Metab* 2024; 26, 3–19. doi: 10.1111/dom.15663.
10. Sundelin E, Jensen EJ, Jakobsen S, Gormsen LC, Jessen N. Metformin biodistribution: A key to mechanisms of action? *J Clin Endocrinol Metab.* 2020; 105, 3374–3383. doi: 10.1210/clinem/dgaa907.
11. Sun EW, Martin AM, Wattchow DA et al. Metformin triggers PYY secretion in human gut mucosa. *J Clin Endo Metab.*, 2019; 104:2668–2674. doi: 10.1210/jc.2018-02460.
12. Foretz M, Guigas B, Viollet B. Metformin: Update on mechanisms of action and repurposing potential. *Nat Rev Endocrinol* 2023; 19, 460–476. doi: 10.1038/s41574-023-00833-4.
13. Reczek CR, Chakrabarty CP et al. Metformin targets mitochondrial complex I to lower blood glucose. *Science Adv.* 2024; 10:1–8. doi: 10.1126/sciadv.ads5466.
14. Zhang SY, Bruce K, Danaei Z, Li RJW, Barros DR, Kuah R, Lim Y-M, Mariani LH, Cherney DZ, Chiu FM, Reich HN, Lam TKT. Metformin triggers a kidney GDF15-dependent area postrema axis to regulate food intake

- and body weight. *Cell Metab* 2023; 35: 875–886. doi: 10.1016/j.cmet.2023.03.014.
15. Losordo DW, Henry TD. New definition of aging?: measuring regenerative capacity in patients. *Circ Res* 2016; 119:774–775. doi: 10.1161/CIRCRESAHA.116.309622.
 16. Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. *Diabetes* 2012; 61:1315–1322. doi: 10.2337/db11-1300.
 17. Bonora E, Kiechl S, Willeit J et al. Insulin resistance as estimated by homeostatis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. *Diabetes Care* 2007; 30:318–324. doi: 10.2337/dc06-0919.
 18. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. *Diabetes* 2014 63:2262–2272. doi: 10.2337/db13-1954.
 19. Hoeijmakers JHJ. DNA damage, aging, and cancer. *N Engl J Med* 2009; 361:1475–1485. doi: 10.1056/NEJMra0804615.
 20. Knowler W et al. (DPP research group). HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention Program: a randomized clinical trial. *Diabetes Care* 2014; 38:51–58. doi: 10.2337/dc14-0886.
 21. Valencia WM, Palacio A, Tamariz L, Florez H. Metformin and ageing: improving ageing outcomes beyond glycaemic control. *Diabetologia* 2017; 60:1630-1638. doi: 10.1007/s00125-017-4349-5.
 22. Biessels GJ, Whitmer RA. Cognitive dysfunction in diabetes: how to implement emerging guidelines. *Diabetologia* 2020; 63 (1):3-9. doi: 10.1007/s00125-019-04977-9.
 23. Chatterjee S, Peters SA, Woodward M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care* 2016; 39:300-307. doi: 10.2337/dc15-1588.
 24. Gilsanz P, Mayeda ER, Glymour MM, et al. Female sex, early-onset hypertension, and risk of dementia. *Neurology* 2017; 89:1886–1893. doi: 10.1212/WNL.0000000000004602.
 25. Li W, Huang E. An update on type 2 diabetes mellitus as a risk factor for dementia. *J Alzheimers Dis* 2016; 53:393–402. doi: 10.3233/JAD-160114.
 26. Campbell JM, Stephenson MD, de Courten B, Chapman I, Bellman SM, Aromataris E. Metformin use associated with reduced risk of dementia in patients with diabetes: a systematic review and meta-analysis. *J Alzheimers Dis* 2018;65: 1225–1236. doi: 10.3233/JAD-180263.
 27. Samaras K, Makkar S, Crawford JD, et al. Metformin use associated with slowed cognition declined and reduced incident dementia in older adults with type 2 diabetes: the Sydney Memory and Ageing study. *Diabetes Care* 2020; 43:2691-2701. doi: 10.2337/dc20-0892.
 28. Newby D, Linden AB, Fernandes M, et al. Comparative effect of metformin versus sulfonylureas with dementia and Parkinson's disease risk in US patients over 50 with type 2 diabetes mellitus. *BMJ OpenDiab Res Care* 2022;10: e003036. doi: 10.1136/bmjdr-2022-003036.
 29. Doran W, Tunnicliffe L, Muzambi R, et al. Incident dementia risk among patients with type 2 diabetes receiving metformin versus alternative oral lowering-glucose therapy: an observational cohort study using UK primary health records. *BMJ Open Diab Res Care* 2024; 12:e003548. doi: 10.1136/bmjdr-2023-003548.
 30. Zheng J, Xu M, Walker V, et al. Evaluating the efficacy and mechanism of metformin targets on reducing Alzheimer's disease risk in the general population: a Mendelian randomisation study. *Diabetologia* 2022; 65:1664-1675. doi: 10.1007/s00125-022-05743-0.
 31. Evans JM, Donnelly LA, Emslie AM Smith, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ* 2005; 330:1304 5. doi: 10.1136/bmj.38415.708634.F7.
 32. Silidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: Umbrella review of meta-analyses of observational studies. *BMJ* 2015;350: g7606. doi: 10.1136/bmj.g7607.
 33. Logie L, Harthill J, Patel K, et al. Cellular responses to the metal-binding properties of metformin. *Diabetes* 2012; 61:1423–33. doi: 10.2337/db11-0961.
 34. Sahra IB, Le Marchand Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: A new perspective for an old antidiabetic drug? *Mol Cancer Ther* 2010;9:1092 9. doi: 10.1158/1535-7163.MCT-09-1186.
 35. Alberti KGMM, Eckel RH, Grundy SM, et al.; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120 (16):1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644.
 36. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr.* 2007; 86:836S–842S. doi: 10.1093/ajcn/86.3.836S.
 37. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care* 2012; 35:2402–2411. doi: 10.2337/dc12-0336.
 38. Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, Zhu J, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: A system-

- matic review and meta analysis. *Diabetes Res Clin Pract* 2014; 106:19-26. doi: 10.1016/j.diabres.2014.04.007.
39. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gen-nari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: A systematic review and meta analy-sis. *Cancer Prev Res (Phila)* 2010; 3:1451-61. doi: 10.1158/1940-6207.CAPR-10-0157.
 40. Thakkar B, Aronis KN, Vamvini MT, Shields K, Mant-zoros CS. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: A meta analysis using primary data of published studies. *Metabolism* 2013; 62:922-34. doi: 10.1016/j.metabol.2013.01.014.
 41. Zhang ZJ, Zheng ZJ, Kan H, Song Y, Cui W, Zhao G, et al. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: A meta analy-sis. *Diabetes Care* 2011; 34:2323-8. doi: 10.2337/dc11-0512.
 42. Zhang ZJ, Zheng ZJ, Shi R, Su Q, Jiang Q, Kip KE. Me-tformin for liver cancer prevention in patients with type 2 diabetes: A systematic review and meta analysis. *J Clin Endocrinol Metab* 2012; 97:2347-53. doi: 10.1210/jc.2012-1267.
 43. Sun W, Lu J, Wu S, Bi Y, Mu Y, Zhao J, et al. Association of insulin resistance with breast, ovarian, endometrial and cervical cancers in non diabetic women. *Am J Can-cer Res* 2016; 6:2334-44.
 44. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabeto-logia*. 2004; 47:1071–1078. doi: 10.1007/s00125-004-1415-6.
 45. Tseng CH. Metformin may reduce bladder cancer risk in Taiwanese patients with type 2 diabetes. *Acta Diabetol* 2014; 51:295-303. doi: 10.1007/s00592-014-0562-6.
 46. Haq Z, Mirza FN, Abdi P, Diaz MJ, Libby TJ. Metformin use and risk of non-melanoma skin cancer: A propen-sity-matched case-control study. *J Drugs Dermatol*. 2024;23(12):1089-1093. doi:10.36849/JDD.8249
 47. Lim YZ, Wang Y, Urquhart DM, et al. Metformin for knee osteoarthritis with obesity: study protocol for a randomised, double-blind, placebo-controlled trial. *BMJ Open*. 2023;13(12): e079489. doi:10.1136/bm-jopen-2023-079489.
 48. Neven E, Vervaet B, Brand K, et al. Metformin prevents the development of severe chronic kidney disease and its associated mineral and bone disorder. *Kidney Int* 2018; 94:102–113. doi: 10.1016/j.kint.2018.01.027.
 49. Ning H-H, Le J, Wang Q, et al. The effects of metformin on simple obesity: a meta-analysis. *Endocrine* 2018; 62:528–534. doi: 10.1177/2042018820926000.
 50. Pasanisi P, Oliverio A, Baldassari I, Bruno E, Venturelli E et al. Metformin treatment with or without mediterranean diet for the prevention of age-related diseases in people with Metabolic Syndrome: The MeMeMe ran-domized trial. *Diabetes Care* 2025; 48:265-277. doi: 10.2337/dc24-1597.