Metformin revisited – an 'old' drug with a 'new' beginning

Sandro Vella MD, MSc (Roehampton), MRCP (UK)

Consultant Physician, Diabetologist and Endocrinologist, Mater Dei Hospital, Malta
Visiting Assistant Lecturer, Department of Medicine, University of Malta Medical School, Malta
Email: svell11@um.edu.mt

Educational aims

- To highlight the mechanism of action of metformin
- To identify metformin's role as an oral glucose lowering agent with favourable pleiotropic effects on cardiovascular outcomes.
- To discuss potential new roles for this drug in type 1 diabetes, as well as in the fields of obstetrics and gynaecology, nephrology, hepatology and oncology
- To discuss the cost-effectiveness and safety of metformin pharmacotherapy, with particular reference to established prescription guidelines

Key words
metformin - diabetes - cardiovascular - pregnancy - cancer

Abstract

Acting as a weak activator of AMP-activated protein kinase, metformin has established itself as a cost-effective first line agent in the management of type 2 diabetes (T2DM). Besides slowing progression to this condition, its use is associated with improved survival and lower rates of myocardial infarction in T2DM, as well as benefits in stable patients with heart failure. Metformin may play a valuable role in early nephropathy, non-alcoholic fatty liver disease and as adjunct therapy in type 1 diabetes. It is increasingly advocated in patients with gestational diabetes and polycystic ovary syndrome. Its role as an anti-cancer agent remains controversial.

Abbreviations

AMP adenosine monophosphate
AMPK AMP-activated protein kinase
ATP adenosine-5'-triphosphate
BMI body mass index
DARTS Diabetes and Audit in Research Tayside Scotland
DPP Diabetes Prevention Programme
eGFR estimated glomerular filtration rate
HbA1c glycosylated haemoglobin
HF heart failure
HOME Hyperinsulinaemia: the Outcome of its Metabolic Effects
IGT impaired glucose tolerance
MIG Metformin in Gestational Diabetes
mTOR mammalian Target Of Rapamycin
NAFLD non-alcoholic fatty liver disease
NASH non-alcoholic steatohepatosis
OCT1 organic cationic transporter 1
OR Odds ratio
PRESTO Prevention of Restenosis with Tranilast and its Outcomes
QALY quality-adjusted life year
RR relative risk
T1DM type 1 diabetes mellitus
T2DM type 2 diabetes mellitus
UKPDS United Kingdom Prospective Diabetes Study

Introduction

Derived from the French Lilac plant *Galega Officinalis,* metformin (*N*,*N*-dimethylimidodicarbonimidic diamide) has widely established itself as a safe as well as clinically effective oral glucose lowering agents. Used for 55 years in the United Kingdom (although for only the last eighteen years or so in the United States),[1-3] this drug has been virtually uniformly advocated as a first line agent in the management of type 2 diabetes (T2DM) by local, national and international treatment guidelines. This review will seek to address the evidence underpinning its widespread use in T2DM patients, as well as potentially exciting new roles in type 1 diabetes (T1DM) and beyond.

Pharmacology

Perhaps surprisingly, the mechanism of action of metformin had remained obscure until relatively recently. This biguanide is now recognised as a weak activator of an important, ubiquitous, phylogenetically conserved serine/threonine protein kinase called AMP-activated protein kinase (AMPK).[4] Acting as a gauge of systemic and cellular energy status, AMPK is activated by an increase in intracellular adenosine monophosphate / adenosine-5'-triphosphate (AMP/ATP) ratio, and serves to protect cellular functions under energy restricted conditions by switching from an anabolic to a catabolic state. The latter is achieved through phosphorylation of key metabolic enzymes and transcription factors/co-activators modulating gene expression.[5] Following hepatic uptake through the organic cationic transporter 1 (OCT1),[6] metformin exerts additional specific and AMPK independent inhibition of complex 1 of the respiratory chain,[7] leading to an acute and transient inhibition of gluconeogenesis, as well as an inhibition of key gluconeogenic enzymes.[8, 9] AMPK activation also reduces hepatic lipogenesis through phosphorylation and inactivation of acetyl-Co-A carboxylase [4] while suppressing lipogenic genes such as fatty acid synthase.[10]

Cost effectiveness

Data from the Diabetes Prevention Programme (DPP) suggests that metformin is cost-effective in individuals below the age of 65. Intervening with this drug over a lifetime is expected to prevent diabetes in 8%, delay onset of T2DM by 3.4 years, increase life expectancy by 0.2 year and reduce the cumulative incidence of coronary artery disease, stroke, amputation, end-stage renal

disease and blindness by 2%, 3%, 16%, 17% and 16% respectively.[11] The estimated cost per quality-adjusted life year (QALY) gained for (generic) use of metformin over a lifetime is $1755 compared to placebo.[11]

Metformin in pre-diabetes and obesity

The DPP reported that metformin prescribed at a dose of 850mg twice daily decreased progression from impaired glucose tolerance (IGT) to diabetes by 31% over three years. Benefits were greater in patients with a body mass index (BMI) exceeding 35 kg/m^2 (mean reduction of 53%) compared with those whose BMI ranged between 22 and 30 kg/m^2 (mean reduction 3%). Metformin therapy was as effective as lifestyle intervention in younger individuals and those with a higher BMI.[12] These effects appear to be durable, as demonstrated in the ten-year follow-up data of the DPP, resulting in comparable diabetes incidence rates between metformin-treated individuals and those adopting intensive lifestyle interventions.[13]

Metformin in type 2 diabetes

The United Kingdom Prospective Diabetes Study (UKPDS) was the first major study to suggest a cardiovascular benefit in T2DM. Randomising 1704 overweight T2DM patients to initial treatment with metformin (342 patients), sulphonylurea or insulin (951 patients), or dietary measures alone (411 patients), metformin therapy (but not sulphonylurea/insulin therapy) was associated with a 32% lower incidence of any diabetes related endpoint (micro- and macrovascular) (p = 0.002), 42% fewer diabetes related deaths (p = 0.017), 36% lower all cause mortality (p = 0.011), and 39% fewer myocardial infarctions (MIs) (p = 0.010).[14] These effects persisted after 10 years of follow-up (risk reductions of 21% for any diabetes related end-point (p = 0.01), 33% for myocardial infarction (p = 0.005), and 27% for death from any cause (p = 0.002), despite the fact that differences in glycaemic control (as assessed by glycosylated haemoglobin [HbA1c] levels) were no longer evident after one year of follow-up.[15] These potential cardiovascular benefits in high risk patients with T2DM have been corroborated by subgroup analyses of other trials, such as the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. In a retrospective review of a subgroup of 1997 participants with diabetes who had undergone a percutaneous coronary intervention, those treated with metformin (with or without additional therapy, n = 887) were at a significantly lower risk of death (OR 0.39 [95% CI 0.19, 0.77]; p = 0.007) and myocardial infarction (OR 0.31 [95% CI 0.15, 0.66]; p = 0.002) compared with those treated with insulin and /or sulphonylurea (n = 1110).[16] Data from the Diabetes and Audit in Research Tayside Scotland (DARTS) study reported that mortality was significantly lower after five years among drug-naive T2DM patients initially treated with metformin compared with a sulphonylurea.[17] McAfee *et al* reached similar conclusions, reporting a 23% reduction in the composite endpoint of myocardial infarction and coronary artery revascularisation in metformin treated patients compared with sulphonylurea therapy after five years of follow-up.[18] Use of metformin in higher risk T2DM patients with heart failure was associated with a significant reduction in all-cause hospitalization at one year (OR 0.85 [95% CI 0.76, 0.95]; p = 0.004) compared with non-sensitisers (sulphonylureas, non-sulphonylurea insulin secretagogues, alpha glucosidase inhibitors or insulin) in a systematic review and meta-analysis of eight controlled studies.[19] In a similar vein, Eurich *et al* reported that metformin monotherapy in this setting translates into a lower risk of mortality (HR 0.70 [95% CI 0.54, 0.91]) as well as a lower risk of the composite outcome of deaths or hospitalization (HR 0.83 [95% CI 0.70, 0.99]) compared to sulphonylurea therapy.[20] In a retrospective study of 8063 insulin-treated patients with no prior history of heart failure (HF), Nichols *et al,* reported that metformin therapy reduced the congestive HF rate ratio to 0.63 (95% CI 0.37, 1.07), a development which is particularly desirable given that initial insulin therapy was associated with a higher incidence of HF.[21]

Is there a role for adjunct metformin in type 1 diabetes?

An ever increasing proportion of T1DM patients harbour a phenotypic and metabolic profile typical of patients with the metabolic syndrome. Indeed insulin resistance has been shown to accelerate progression to macrovascular and microvascular outcomes in T1DM.[22] These observations generated considerable interest in a potential role for adjunct metformin, also given that achieving tight glycaemic control is particularly challenging in this setting, particularly with its attendant risk of hypoglycaemia. Data from the Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) study was reassuring, albeit comparing outcomes in 390 insulin treated T2DM patients randomised to treatment with metformin or placebo therapy and followed up for 4.3 years. Use of this biguanide led to significant reductions in body weight (-3.07 kg [range -3.85 to -2.28]; p<0.001), HbA1c (mean -0.4% [95% CI = -0.25, -0.55]; p < 0.001) and insulin requirements (mean -19.63 IU/day [95% CI = -14.36, -24.91]; p < 0.001). Additionally, metformin was reported to decrease macrovascular morbidity and mortality (HR 0.61 [95% CI = 0.40, 0.94]; p = 0.02), an effect that was partly explained by the difference in weight.[23] While prospective data remains scanty, a formal meta-analysis of available studies published by the undersigned suggested that use of adjunct metformin use in T1DM is associated with a significant reduction in total daily insulin dose (6.6 units / day; p < 0.001), albeit no improvement in glycaemic control.[24]

Polycystic ovary syndrome and gestational diabetes

Affecting at least 5-15% of women of childbearing age, insulin resistance is a hallmark (though not imperative feature) of this condition characterised by hyperandrogenism, hirsutism, acne, menstrual irregularities and infertility. A meta-analysis of 31 clinical trials demonstrated that metformin therapy may increase ovulation, improve menstrual cyclicity and reduce serum androgen levels in these patients.[25] A recently published systematic review of metformin use in pregnant women with the polycystic ovary syndrome reported lower pooled risks of early pregnancy loss (OR 0.32; [95% CI 0.19, 0.55]), gestational diabetes (OR 0.37; [95% CI 0.25, 0.56]), pre-eclampsia (OR 0.53; [95% CI 0.30, 0.95]) and preterm delivery (OR 0.30 [95% CI 0.13, 0.68]).[26] Current guidelines tend to advocate a role for metformin in the management of gestational diabetes.[2, 27] Despite concerns that metformin crosses the placenta, two meta-analyses (one in women prescribed metformin monotherapy, and the other recruiting women using metformin and/or a sulphonylurea) have not reported an increase in congenital malformations or neonatal deaths [28, 29]. The Metformin in Gestational Diabetes (MIG) trial reported no significant difference in the composite neonatal outcome of neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score < 7, or prematurity), albeit higher rates of preterm births and less weight gain among the 363 patients treated with metformin (±

Practice points

- Metformin is a cheap, effective first line oral glucose lowering agent, that has proven to be cost-effective in type two diabetes patients aged below the age of 65 years.
- Metformin has been shown to delay or prevent progression to diabetes, improve life expectancy, and reduce the cumulative incidence of macrovascular and microvascular complications in diabetes.
- Prescribed in the right setting, metformin decreases heart failure incidence, and improves outcomes in established heart failure patients with type 2 diabetes
- Risks of metformin-associated lactic acidosis remain low provided that this biguanide is prescribed outwith clinical scenarios associated with hypoxia or a tendency for acidosis (such as sepsis, acute heart failure, cardiogenic shock, respiratory failure).

supplemental insulin) compared to patients randomised to insulin therapy (n = 370).[30] A recently published, albeit smaller (n = 94), trial largely showed that metformin improved glycaemic control (lower mean glucose levels throughout the day), with the added advantages of less weight gain and lower rates of neonatal hypoglycaemia compared with insulin therapy.[31]

Metformin and cancer

Data from several studies suggests that metformin use is associated with significantly lower incidence rates across multiple cancers. Two meta-analyses, integrating results from several observational and randomised controlled trials, reported relative risks of 0.69 (95% CI 0.61, 0.79) [32] and 0.67 (95% CI 0.53, 0.85) [33] respectively. While impressive, such results should be interpreted with caution, given the inherent limitations of observational studies, and the potential of including studies with 'immortal time bias'. At least one study employing statistical techniques which avoided immortal time bias reported no association between metformin use and cancer incidence.[34] At a cellular level, the anti-neoplastic action of metformin appear to be mediated by both AMPK-dependent and -independent mechanisms, leading to an inhibition of the cell cycle (through a reduction in cyclin D1 level) and mammalian Target Of Rapamycin (mTOR) signalling, a stimulation of the p53/p21 axis, and a suppression of fatty acid synthesis, angiogenesis, inflammation, hyperinsulinaemia and prevalent insulin growth factors.[35]

Metformin and non-alcoholic fatty liver disease

The majority of patients with T2DM are characterised by non-alcoholic fatty liver disease (NAFLD) and up to 50% may develop non-alcoholic steatohepatosis (NASH), a harbringer of cirrhosis. Metformin prescription in patients with NAFLD may translate into a reduction in plasma aminotransferases, albeit without evidence of improvement in liver histology. [36-38]

Metformin and nephropathy

Metformin should be prescribed with caution in individuals with an estimated glomerular filtration rate (eGFR) ranging between 30 and 45 mls/min/1.73m^2 and is absolutely contraindicated if eGFR <30 mls/min/1.73m^2. Nonetheless, data from animal models suggests that metformin pharmacotherapy ameliorates tubular injury associated with hyperglycaemia (partly by reducing oxygen consumption and hypoxia-inducible factor- 1 expression) [39] as well as reactive oxygen species-mediated lipotoxicity of renal podocytes.[40] Both mechanisms underpin the development of diabetic nephropathy. Additionally, data from murine models suggests that metformin reduces cystic growth in autosomal dominant polycystic kidney disease.[41] Such promising roles remain to be confirmed in clinical studies.

Adverse effects

A Cochrane review has largely dispelled the myth that the benefits of metformin may be offset by an unacceptably high risk of lactic acidosis. Indeed, the authors reported no additional risk of developing this complication in prospective comparative trials or from observational cohort studies, provided metformin is prescribed in the appropriate setting.[42] To this effect, use of this oral glucose lowering agent is not recommended in acute situations associated with hypoxia or a tendency for acidosis (such as sepsis, acute heart failure, cardiogenic shock, respiratory failure) as well as in moderate to severe renal impairment (as outlined earlier). Gastro-intestinal adverse effects (bloating, diarrhoea, abdominal cramps, flatulence) are best avoided if metformin is dosed gradually over a few days to weeks. Tolerability may be improved by switching to an extended release formulation.[43] Vitamin B12 deficiency is a recognised, albeit rare, adverse effect, and should be borne in mind in patients with macrocytic anaemia, peripheral neuropathy and cognitive impairment.[44,45]

Conclusion - the way forward

Metformin's pivotal role in the management of T2DM is clearly established, and likely to remain undisputed, at least in the near future. Available evidence suggests that it is safer than initially thought, particularly if prescribed in the right clinical setting. A better understanding of the mechanisms underpinning its diverse actions at a cellular level, particularly in humans, is likely to unravel exciting new roles for this cheap, widely prescribed, biguanide.

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