Metformin and its clinical use: new insights for an old drug in clinical practice

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Abstract

Metformin is generally recommended as first-line treatment in type 2 diabetes, especially in overweight patients, but in recent years new indications for its use have emerged. Metformin has been found to be safe and efficacious both as monotherapy and in combination with all oral antidiabetic agents and insulins. If metformin use during pregnancy and the lactation period is supported by few data, it could be indicated for women with polycystic ovary syndrome, since it could diminish circulating androgens and insulin resistance, thus ameliorating the ovulation rate. Metformin seems to reduce cancer risk, which appears to be increased in diabetics, and is a promising agent for oncoprevention and chemotherapy combinations. Moreover, metformin could find a place in the treatment of non-alcoholic fatty liver disease. Lactic acidosis could be decreased by avoiding metformin use in patients with hypovolemia, sepsis, renal impairment, hypoxic respiratory diseases and heart failure, in the preoperative period and before intravenous injection of contrast media.

Key words: metformin, type 2 diabetes, efficacy, safety, cancer.

Introduction

The biguanide metformin, put on the market 50 years ago, is now generally accepted as first-line treatment in type 2 diabetes mellitus (T2DM), especially in overweight patients. It improves peripheral and liver sensitivity to insulin, reduces basal liver glucose production, increases insulin-stimulated uptake and utilization of glucose by peripheral tissues, decreases appetite and causes weight reduction (Figure 1). Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists and American College of Endocrinology (referred to as AACE) recommend metformin as first-line therapy in T2DM [1]. In recent years, new indications for metformin use in clinical practice have emerged, besides diabetes. The aim of this review is to summarize these new fields according to reports in the medical literature (Table I).

Metformin in type 2 diabetes treatment: what's old and what's new?

Metformin monotherapy has been estimated to reduce glycated hemoglobin (HbA_{1c}) by approximately 1.5% with a dose-dependent glucose lowering effect [2, 3]. Garber *et al*. [4] and Fujioka *et al*. [5] described a clear dose-response relationship of treatment with metformin and found that

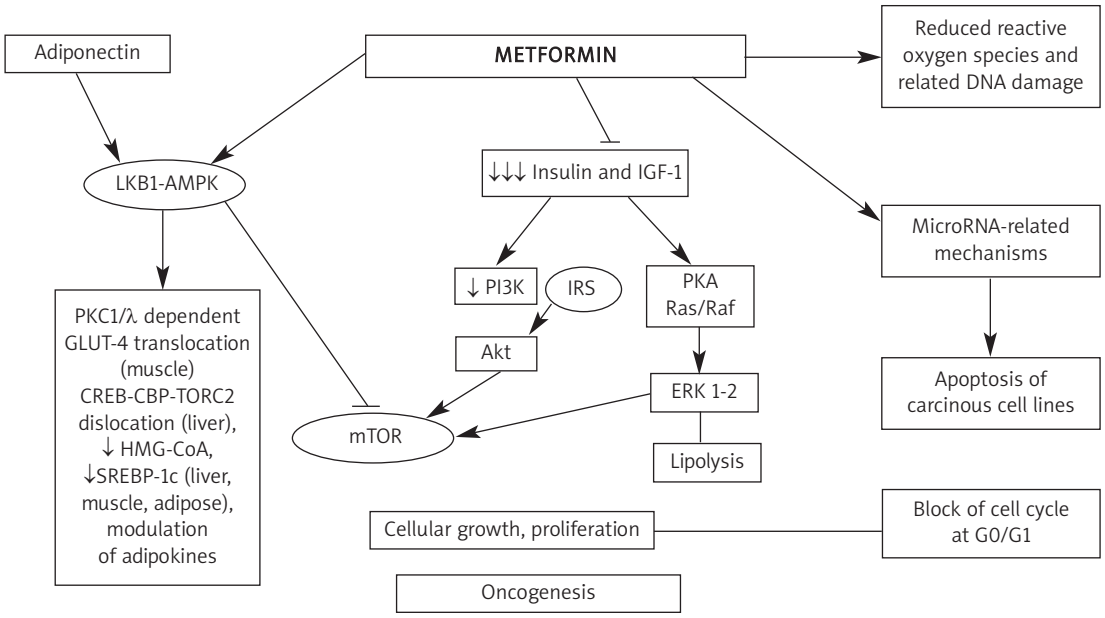

Figure 1. Metformin mechanism of action

LKB1-AMPK – liver kinase B1-adenosine monophosphate activated protein kinase, PI3K – phosphoinositide 3-kinase inhibitor, IRS – insulin receptor substrate, mTOR – mammalian target of rapamycin, IGF-1 – insulin-like growth factor 1, PKA – protein kinase A, ERK – extracellular-signal-regulated kinases, GLUT-4 – glucose transporter type 4, HMG-CoA – 3-hydroxy-3-methyl-glutaryl-CoA reductase, SREBP-1c – sterol regulatory element binding proteins

Table I. Summary of metformin molecular and metabolic actions

Anti-obesity effects: • Decreased appetite • Increased GLP-1 secretion
Anti-hyperglycemic effects: • Decreased intestinal carbohydrate absorption (decreased postprandial hyperglycemia) • Inhibition of hepatic gluconeogenesis: inhibition of the Krebs cycle and/or oxidative phosphorylation by activation of AMPK • Enhancement of insulin-stimulated glucose transport in skeletal muscle: increased recruitment and activity of GLUT-4 and enhanced non-oxidative disposal into skeletal muscle
Anti-lipidemic effects: • Increased free fatty acid esterification and inhibition of lipolysis in adipose tissue
Anti-diabetic protective effects: • Protection of β-cells from glucose toxicity and lipotoxicity: protection of β-cell secretory capacity, prevention of acceleration to severe diabetes
Hepatoprotective effects: • Decreased hepatic insulin resistance and improved lipemia levels
Anti-neoplastic effects: • Indirect effect: via decreased insulin resistance and decreased IGF-1 levels • Direct effect: via AMPK-related and AMPK-independentcellular pathways
Cardioprotective effects: • Cumulative effects of decreased weight gain and better lipid profile provided by long-term use • Undefined serologic or endothelial factors such as PAI-1

GLP-1 – glucagon-like peptide-1, AMPK – AMP-activated protein kinase, GLUT-4 – glucose transporter type 4, IGF-1 – insulin-like growth factor 1, PAI-1 – plasminogen activator inhibitor-1

its therapeutic dose is between 1500 mg/day and 2000 mg/day.

Hoffmann *et al.* [6] showed that metformin 850 mg twice daily and acarbose 100 mg three times a day are equally effective when compared with placebo. In another study [7], 250 patients were randomized to metformin or pioglitazone: a similar reduction in HbA_{1c} and fasting blood glucose was observed, although pioglitazone was significantly more effective in improving insulin sensitivity defined by homeostasis model assessment for insulin sensitivity (HOMA-S).

Previously, the ADOPT (A Diabetes Outcomes Progression Trial) study considered rosiglitazone, metformin and glyburide as the initial treatment of newly diagnosed type 2 diabetics [8]. There was no difference in the proportion of patients reaching the HbA_{1c} target of < 7%, but the incidence of monotherapy failure was higher with glyburide and metformin, despite the fact that metformin-treated patients had significantly lower body weight compared with rosiglitazone-treated ones.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are new drugs for T2DM treatment [9, 10]. Goldstein *et al.* [11] compared sitagliptin, metformin and placebo: both agents accomplished significant reductions in HbA_{1c}, slightly more pronounced with metformin. Also, Derosa *et al.* [12] compared sitagliptin or metformin in addition to pioglitazone: both treatments improved HbA_{1c}, but metformin also led to a decrease of body weight and to a faster and better improvement of insulin resistance and inflammatory state parameters. Sitagliptin + metformin also improved β-cell function defined by HOMA-β better than metformin alone [13]. Similar results were found in a placebo-controlled, randomized trial with vildagliptin, another DPP-4 inhibitor [14-16].

The efficacy of metformin treatment was thoroughly evaluated in a Cochrane review considering 29 trials and 5,259 participants [17]. In this paper, metformin was compared with sulfonylureas (13 trials), glitazones (3 trials), meglitinides (2 trials), α-glucosidase inhibitors (2 trials), placebo (12 trials), diet (3 trials) and insulin (2 trials). Metformin monotherapy was associated with significant improvements in weight, lipemia and diastolic blood pressure; glycemic control was better when compared with placebo or diet and modestly better when compared with sulfonylureas.

Metformin can safely and efficaciously be combined with all oral antidiabetic agents and insulins. Metformin-glibenclamide combination caused greater reduction in fasting blood glucose [18], whereas metformin-glyburide combination improved the hypoglycemic effect of this sulfonylurea, leading to lower HbA_{1c} levels [19]. In another study with glimepiride, a reduction in postprandial glycemia was also observed, but the risk of hypoglycemia was increased [20]. Similar results were also reported with glibenclamide and glipizide [21, 22].

Nateglinide and repaglinide are other drugs commonly used in combination with metformin. Metformin-nateglinide combination resulted in better HbA_{1c} levels and modest decrease in fasting glucose levels [23]. Combination with repaglinide caused reduced fasting glucose by 39.6 mg/dl and HbA_{1c} by 1.4% [24]. Metformin-acarbose combination led to a reduction of 20.38 mg/dl in fasting glucose levels and of 1.02% in HbA_{1c} [25], but a potential increase in gastrointestinal side effects should be considered. In a multicenter study, metformin-miglitol combination significantly improved HbA_{1c}, postprandial glucose levels and fasting glucose [26].

Glitazones, another group of antiglycemic agents, have also been adequately studied in combination with metformin [27, 28]. Although rosiglitazone is no longer available in current treatment of T2DM after new evidence suggested an increased cardiovascular risk linked to this drug [29], in previous studies its association with metformin allowed the glycemic target (HbA_{1c} < 7.0%) to be reached in 54-58% of patients [30, 31] and in the Karamanos *et al.* study [32] this combination significantly increased high-density lipoprotein (HDL) cholesterol levels. Pioglitazone was studied in combination with metformin, as well [33, 34]. Besides improving glycemic values, this combination showed beneficial effects on lipid profile with a significant decrease in triglycerides and a slight increase in HDL levels [35].

Combination of metformin with DPP-4 inhibitors is another therapeutic option that brings a few benefits, such as weight reduction and better glycemic control [9, 10]. In a placebo-controlled study involving diabetics poorly controlled with metformin > 1500 mg/day, the addition of sitagliptin reduced HbA_{1c} and fasting blood glucose, and more patients treated with sitagliptin reached the HbA_{1c} target of < 7% (47%) compared with those receiving placebo (18.3%), with no increase in hypoglycemias. Another study with 780 drug-naïve patients showed that more patients attained HbA_{1c} < 7% with metformin-vildagliptin combination than using each drug alone [36]. A randomized, double-blind, placebo-controlled study considering saxagliptin or placebo addition to metformin 1500-2000 mg/day in 743 patients reported a significant, dose-dependent reduction in HbA_{1c} and fasting blood glucose [37].

Metformin combination with glucagon-like peptide-1 (GLP-1) analogues exenatide and liraglutide was found to be safe and efficacious [38-40]. When comparing liraglutide, metformin, metformin plus glimepiride and metformin plus liraglutide, this last association was the most effective treatment, reducing fasting blood glucose by 70.2 mg/dl and HbA_{1c} by 0.8% [41]. In a study with 150 patients poorly controlled with maximal doses of metformin, the addi-

tion of exenatide resulted in mean reduction in HbA_{1c} of 1% which persisted after 82 weeks [42].

Metformin-insulin combinations are commonly used to decrease insulin resistance, reduce insulin need and minimize weight gain. Studies with new analogue insulins showed efficacy of this combination as well, with decreased side effects such as hypoglycemia and weight gain [43].

Metformin in gestational diabetes

Gestational diabetes is an interesting research area for metformin. Insulin treatment is effective and considered safe during pregnancy, but it requires sufficient education and patient skills to provide good compliance and prevent hypoglycemias. Therefore, oral antidiabetic treatments are being researched as more convenient alternatives to insulin during this period and the medical literature reveals many studies about fetal and maternal outcomes after metformin use in gestational diabetes. Available data are mainly from patients with polycystic ovary syndrome (PCOS) during pregnancy.

Non-diabetic women with PCOS who conceived during metformin treatment had a 10-fold reduction of gestational diabetes [44] and prospective studies showed similar results with no increase in congenital defects in newborns or spontaneous abortions [45]. These results supported the idea of using insulin-sensitizers in this group of subjects [46]. Other studies underlined a reduction of complications with metformin use during pregnancy in patients with PCOS [47]. Metformin pharmacokinetics are similar in pregnant and non-pregnant women; metformin easily crosses the placenta so the fetus is exposed to drug concentrations comparable with those of the mother [48]. In 2008 Rowan *et al.* [49] studied 751 women at 20-33 weeks of pregnancy with gestational diabetes during the MiG trial (Metformin versus Insulin for the treatment of Gestational diabetes). They found that metformin treatment, alone or in association with insulin, was not linked to increased perinatal complications or serious adverse effects.

Although recent studies with larger populations support the safety of metformin during pregnancy [50], the risk of macrosomia [51] and preeclampsia [52] is still not clear and there are also studies with conflicting results [53].

Few studies are available about metformin use during the lactation period. In small studies considering metformin treatment versus formula feeding, no adverse effect was observed on growth, motor-social development and intercurrent illness during the first 6 months of life [54].

So far, evidence for safety of continued therapy throughout gestation is insufficient; published papers are limited in design and might mask fetal toxic outcomes due to metformin therapy. Therefore, patients should be informed about benefits and risks of metformin use during pregnancy before starting a therapy.

Metformin in pre-diabetes and in prevention of cardiovascular disease

Pre-diabetes (defined as impaired glucose tolerance, impaired fasting glucose or both) represents an intermediate state that often progresses to overt T2DM within a few years; therefore it should be increasingly screened for [55]. In addition, pre-diabetes may be associated with a higher risk of microvascular and macrovascular complications [56]. In this context, treatment modalities to revert pre-diabetes to normal are a current challenge for many clinicians [57]. Apart from lifestyle modifications, the use of drugs such as metformin, thiazolidinediones and acarbose is usually needed in high-risk patients [58]. In the analysis of Lilly *et al.* [59], metformin significantly reduced the rate of conversion of pre-diabetes to diabetes for both high (850 mg twice a day) and low doses (250 mg twice or 3 times a day). Therefore, metformin is important for prevention of T2DM and it is recommended for patients < 60 years of age, individuals with body mass index (BMI) ≥ 35 kg/m^2 and those with risk factors such as family history of diabetes in first-degree relatives, elevated triglycerides, reduced HDL cholesterol, hypertension or $HbA_{1c} > 6\%$ [60].

Another positive effect of metformin could be cardioprotection. As is well known, the presence of T2DM increases the risk of cardiovascular disease (CVD). Previous studies suggest that metformin monotherapy is associated with a lower death rate when compared with sulfonylureas; death due to CVD is lower in metformin users after adjusting for age, gender, nitrate use and chronic disease score [61, 62]. This difference could be the result of the "healthier" group of patients who use metformin, since metformin is contraindicated in heart failure and renal impairment, or it could be due to additional benefits of metformin on weight gain and lipid profile [63]. Another study showed that, in subjects with MetS without diabetes or CVD, metformin can give a considerable CVD risk reduction together with multifactorial treatment of MetS [64].

Metformin in obesity

Metformin is the first-line treatment for obese type 2 diabetic patients, but a possible role in non-diabetic obese people was also suggested on the basis of its effects on insulin resistance and weight loss. Desilets *et al.* [65] considered all the studies with metformin concerning weight loss and they reported a significant weight reduction in overweight or obese adults and adolescents without diabetes; positive effects on metabolic parameters such as blood pressure, waist

circumference, lipid and glucose/insulin levels were also observed. Many studies have evaluated metformin treatment in patients with weight gain secondary to antipsychotic drug use and the results were encouraging [66, 67]. Beneficial effects on obesity promoted new studies on the pediatric age group, as well [68]; although it has modest, but favorable effects on body weight and glucose homeostasis in insulin-resistant children, more studies are still needed before suggesting metformin use for weight reduction in non-diabetic obese children [69]. However, when compared with other anti-obesity drugs, i.e. orlistat and sibutramine, metformin appeared to be less effective [70]. Its combination with orlistat for obesity treatment did not result in any additional benefit whereas it had a higher risk of gastrointestinal side effects [71]. The association of metformin and thiazolidinediones also compensates the weight gain associated with the use of these drugs [72]. Finally metformin could be a beneficial treatment in patients with impaired fasting blood glucose or impaired glucose tolerance for weight reduction. There is also evidence that metformin has some effects on peptides regulating food intake such as leptin, adiponectin, ghrelin and neuropeptide Y [73, 74].

Metformin in hepatology

Non-alcoholic fatty liver disease (NAFLD) and its end result non-alcoholic steatohepatitis (NASH) are the most common liver disorders worldwide. Their prevalence ranges from 10% to 24% in the general population [75], reaching 60-95% and 28-55% in obese and diabetic patients, respectively [76]. Although the etiology of NAFLD is still unclear, several lines of evidence have indicated a pathogenetic role of insulin resistance in this disorder and it is generally considered as the hepatic component of the metabolic syndrome (MetS). Since NAFLD patients have comorbidities such as obesity, impaired glucose levels, dyslipidemia and hypertension, treatment with an insulin-sensitizing agent may correct several of these aspects. Metformin has beneficial effects on glycemia levels, cardiovascular risk and metabolic complications and improves serum transaminases [77], and weight loss in these patients [78], as also shown in post-hoc analyses of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) [79] and the Assessing The Treatment Effect in Metabolic syndrome without PercepTible diabetes (ATTEMPT) study [80]. Down-regulation of secretory phospholipase A2 mRNA expression, decrease in serum secretory phospholipase A2, lysophosphatidylcholine and inflammatory response and protection of mitochondrial function are the possible liver protective mechanisms of metformin in NAFLD [81].

Another potential area of interest is the use of metformin during viral hepatitis treatment, but the currently available small studies about hepatitis C patients are still conflicting [82, 83].

Metformin in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous syndrome with increased risk of cardiovascular morbidities and diabetes involving 6.6-6.8% of the women of reproductive age [84]. Insulin resistance and hyperinsulinism have been known as pathogenetic mechanisms for the last 15 years, present in 50-70% of these women, whereas MetS prevalence is higher than in age and weight-matched controls [85]. Even in the absence of obesity or MetS, these patients may have insulin resistance and increased cardiovascular risk [86]. High insulin levels affect the hypothalamus-pituitary-ovarian function, as well as glucose utilization in peripheral tissues [87]. This syndrome was particularly considered in the evaluation of the use of metformin in adolescent patients and in pediatric clinical practice [88].

Metformin reduces circulating androgens and insulin resistance, thus ameliorating the ovulation rate [89]. In the analysis of Tang *et al.* the ovulation rate was improved by metformin compared with placebo (Pooled OR 2.12, 95% CI: 1.50-3.0) and by metformin plus clomiphene versus clomiphene alone (Pooled OR = 3.46, 95% CI: 1.97-6.07) [90]. The medical literature agrees that metformin alone is not sufficient to restore regular menstruation and ovulation in PCOS patients, and if treatment fails with clomiphene citrate, metformin will not be effective, because it is beneficial only in combination and in obese and/or diabetic/prediabetic PCOS patients [91]. Since women with PCOS constitute a very heterogeneous group of patients, responses to metformin may also be different; in the small but interesting study of Tomova *et al.* the patients who responded to metformin treatment by restoring regular menstruation and decreasing anti-Mullerian hormone levels (which represent folliculogenesis and quantity and quality of the follicle pool) were significantly overweight, with higher BMI, waist circumference, body fat and blood pressure compared with non-responders [92]. This finding shows that metformin's beneficial effects in PCOS are mainly observed in obese and highly insulin-resistant patient subgroups. Therefore, treatment should be addressed to specific metabolic or reproductive problems and insulin sensitizing drugs are not always the optimum therapy to restore ovulation or reduce hyperandrogenism.

Another review showed that metformin may affect ovulation induction, menstrual irregularities, fertility and hirsutism, as well as lipids, markers of atherosclerosis and inflammation, obesity parameters and quality of life in PCOS women. Metformin seems to improve these features, although con-

flicting results were also reported [93]. There are also many studies supporting the continuation of metformin throughout pregnancy in PCOS patients but more data are needed, as explained above.

Metformin and cancer

Diabetes itself increases the risk of cancer; although T1DM emerges at an earlier age, intrinsic hyperinsulinemia probably causes higher risk of cancer in type 2 diabetics compared with type 1 diabetic patients. Obesity in type 2 diabetics may be a predisposing factor, as well as high insulin and insulin-like growth factor 1 (IGF-1) levels because of the proliferative effects of insulin; some studies have suggested extrinsic insulin preparations to be another possible cause [94]. Insulin and the IGF-1 axis, indeed, function in an integrated fashion to promote cell growth and survival; chronic exposure to these growth factors enhances carcinogenesis, so factors that influence bioactive IGF-1 will affect cancer risk. Despite the increase in cancer risk in diabetics, patients on metformin show a reduction in cancer risk by nearly 40% [95, 96].

Through antiglycemic actions such as enhancing insulin receptor activation and downstream signaling, biguanides were found to impair mitochondrial adenosine-5'-triphosphate (ATP) production, which resulted in activation of the liver kinase B (LKB1)-5' adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. This pathway is central for the regulation of cellular energy homeostasis and its activation in conditions of energy stress leads to a physiologic down-regulation of energy consuming processes, such as protein and fatty acid synthesis, restoring ATP levels [97]. Moreover, LKB1 has been recognized as a tumor suppressor gene [98]. *In vitro* studies showed that metformin activates the LKB1-AMPK pathway, resulting in inhibition of mammalian target of rapamycin (mTOR) and protein synthesis (consistent with the need to reduce energy expenditure) and thereby reducing proliferation [99, 100]. In addition, metformin exhibited an opposite effect on tumor cells with regard to its insulin-sensitizing action: it inhibited insulin-stimulated mTOR activation and proliferation in an AMPK-dependent manner [101].

Therefore, metformin exerts both an indirect effect by decreasing insulin resistance and IGF-1-related proliferative pathways, and a direct one at the cellular level by reducing the production of endogenous reactive oxygen species and associated DNA damage [102], inhibiting cell proliferation, invasion and migration with the up-regulation of miR-26 expression, increasing cell apoptosis in some cancer cell lines [103, 104] and blocking the cell cycle in G0/G1 *in vitro* and *in vivo* [105].

In a recent study with 2,763 pancreas cancer patients taken from the UK-based General Practice Research Database, long-term use of metformin was linked to a decrease in pancreas cancer prevalence in women, whereas the use of sulfonylureas and insulin was highly associated with that pathology. In another study with 341 ovarian cancer patients, among whom 28 were diabetic and 16 were on metformin therapy, metformin improved progression-free survival [106]. In the study of He *et al.* [107] considering 1,983 patients with HER2+ breast cancer, analyses showed that metformin and thiazolidinediones were associated with longer survival and decreased breast cancer-induced mortality. Despite some contradictory results, a recent meta-analysis by Zhang *et al.* [108] conducted on 107,961 patients with T2DM revealed that metformin treatment was related to a lower risk of colorectal cancers (0.63 [0.47-0.84]; $p = 0.002$). Metformin-induced beneficial effects were also observed in prostate cancer patients receiving androgen deprivation therapy [109].

Metformin may also be proven useful in lung cancer therapy due to its apoptosis-inducing effect via activation of the JNK/p38 MAPK pathway and GADD153 [110]. In trastuzumab-resistant breast cancer cell lines which were also resistant to rapamycin-induced changes in mTOR activity and cell growth, metformin could still be effective via inhibition of erbB2/IGF-1 receptor interactions [111].

In a study with a doxorubicin-resistant thyroid cancer cell line, metformin showed an antimitogenic effect, as well [112]. Studies with melanoma cell lines also revealed a potential p53 suppressor effect of metformin, in addition to the apoptotic effects on these cells [113].

Metformin was related to improved survival in diabetic patients with the diagnosis of cancer compared with the use of other antidiabetic drugs and with non-diabetic patients [114]. In a study that analyzed hospital discharge records from 2.5 million individuals in the Netherlands, metformin was found to be associated with a lower risk of cancer in general with a hazard ratio of 0.90 (95% CI: 0.88-0.91) compared with the use of sulfonylurea derivatives [115]. In the analysis of DeCensi *et al.* [116], overall a 31% decrease in cancer incidence was found with metformin compared with other antidiabetic treatments; the highest reductions were seen in colon and pancreatic cancers.

Inhibition of cell proliferation and modulation of mTOR may potentiate the effects of chemotherapeutic drugs [117]. In this context, metformin may be a promising agent for oncoprevention and chemotherapy combinations [118, 119].

Metformin in other areas of clinical use

New-onset diabetes after solid-organ transplantations is one of the major complications. Metformin may be a good alternative to meglitinides

with beneficial effects on MetS components, lipid-lowering properties, and anti-neoplastic and cardiovascular protection potential [120].

Beneficial effects of metformin on thyroid nodules are another area of discussion in the medical literature, but larger studies are still needed to make any comment [121].

Metformin and safety

Metformin is one of the most frequently used drugs worldwide, with an estimated 40 million prescriptions in the USA alone in the year 2008, its safety allowing a large area of use [122]. The most common adverse effect of metformin is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting and increased flatulence. However, the main concern about safety is focused on the risk of lactic acidosis, and cases are still seen in medical practice [123]. Metformin-associated lactic acidosis (MALA) is a severe metabolic failure with high related mortality; in severe cases patients may need renal replacement therapy [124]. However, MALA risk could be decreased by avoiding metformin use in patients with high risk of hypovolemia, sepsis, renal impairment, reduced renal capacity (such as the elderly), hypoxic respiratory diseases, and in heart failure [125]. However, a recent review commenting on the relationship between metformin and heart failure mentions that metformin may even reduce the risk of heart failure morbidity and mortality in diabetics [126].

Moreover, metformin administration should be avoided in the 24-78 h of the preoperative period as well as before intravenous injection of contrast media, since its use may increase the risk of nephropathy. However, the recent evaluation of MALA cases from 347 trials by Salpeter *et al.* [127] showed that the risk of lactic acidosis with metformin was not significantly increased compared with other anti-glycemic agents.

Another important but generally underestimated issue during metformin treatment is the risk of vitamin B_{12} deficiency [128]. Since diabetes itself exerts a risk of peripheral polyneuropathy, vitamin B_{12} deficiency-related neuropathy may confuse clinicians in long-term metformin-treated patients [129]. This decrease in vitamin levels could also cause higher homocysteine levels [130]. The amount of vitamin B12 recommended by the Institute of Medicine (IOM) (2.4 μg/day) and the amount available in general multivitamins (6 μg) may not be enough to correct the deficiency in subjects with diabetes [131].

Conclusions

New indications for metformin use are emerging in the medical literature, mainly related to its beneficial effects on insulin resistance and weight loss. Treatment with metformin in pregnant women and in cancer patients is promising, but more data are needed in order to assess drug efficacy and safety in such specific populations.

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