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Review Article

The Anticancer Effect of Metformin, the Most Commonly Used Anti-Diabetes Drug

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Abstract

Metformin as the first line therapy for type 2 diabetes mellitus has its unique attraction for its weight loss and possible macrovascular benefit. In addition, recent accumulating epidemiological and clinical evidence suggests metformin maybe a potential anticancer medication as an adjuvant therapy or a chemoprevention given the increased prevalence of obesity and diabetes mellitus in cancer patients and the low cost and safety of the drug. Metformin may work through multiple pathways to inhibit cancer cell growth and proliferation. Epidemiological and clinical data were summarized in this review. More carefully designed longer and larger randomized controlled trials in selected cancer population in the future are needed.

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ABBREVIATION

DM: Diabetes Mellitus; UKPDS: UK Prospective Diabetic Studies; AMPK: AMP-Activated Protein Kinase; mTOR: Mammalian Target Of Rapamycin; ROS: Reactive Oxygen Species; ADVANCE: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; ACCORD: Action to Control Cardiovascular Risk in Diabetes; VADT: Veterans Affairs Diabetes Trial; PRO active: PROspectivepioglitAzone Clinical Trial In macro Vascular Events; RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; ADOPT: A Diabetes Outcome Progression Trial; RECORD: Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes; HCC: Hepatic Cell Carcinoma; pCR: Pathologic Complete Response; RCT: Randomized Controlled Trials

INTRODUCTION

Metformin is a biguanide that known for many decades to lower glucose in Diabetes Mellitus (DM) patients. Not only has it been used as first line anti-diabetes medication in the world, but also been widely used in polycystic ovarian syndrome, metabolic syndrome, non-alcoholic fatty liver disease and other conditions. In type 2 DM patient, metformin reduces hepatic gluconeogenesis and improves insulin sensitivity. It has been associated with better cardiovascular outcome in type 2 DM based on UKPDS (UK Prospective Diabetic Studies) [1]. Accumulating data indicating that metformin may play an inhibitory role in cancer cell in addition to hypoglycemic effect. However the mechanism is still unclear. Otto Warburg has proposed a unique metabolic fact in cancer cells, so called "Warburg effect", which describes the characteristic of lactate production through glycolysis in cancer cells even when oxygen is present [2]. How Metformin link the cancer cell growth, proliferation and glucose metabolism is a very interesting area that needs to be further investigated. This review discusses the history and proposed anti-cancer mechanisms of metformin and summarizes the epidemiological data and observational and prospective evidence of anti-cancer effect of metformin.

HISTORY

Found in French lilac (Galegaofficinalis), Metformin was first synthesized in 1920's, but it was well recognized as an effective treatment for diabetes till 1950s after French physician Jean Sterne published the first clinical trial of Glucophage (trade name for metformin) to treat diabetes [3,4]. Due to stronger interest in insulin and other anti-diabetes medication, metformin was not introduced to the United States until 1995. Metformin is now believed to be the most widely prescribed anti-diabetes drug in the world. Interestingly, other members of the biguanide family, buformin and phenformin, were abandoned from the world in 1970's due to their risk for lactic acidosis. The theoretical rate of lactic acidosis associated with metformin was about 3 cases per 100,000 patient-years while phenformin had a rate of more than 20 times higher [5-7].

Since the first report of association of metformin with a reduced risk of cancer in type 2 diabetic patients [8], more evidence has accumulated regarding a possible higher incidence of cancer in DM patients and decreased cancer incidence associated with metformin use.

MECHANISMS

The primary molecular target of metformin is believed to be

mitochondria, where it inhibits complex I of the electron transport chain, resulting in a reduction in oxidative phosphorylation and ultimately a reduction in the synthesis of ATP. Increased AMP binds to the AMP-activated protein kinase (AMPK) binding domain and causes allosteric conformational change, thus activates the catalytic domain of AMPK [9]. Metformin has been shown to activate AMPK through an upstream kinase, LKB1, when the ratio of AMP/ATP increases [10].The activation of AMPK switches the cell from an anabolic to a catabolic state. However whether metformin activates AMPK directly by altering the cell's energy status, thus AMP/ATP ratio, or by a LKB1 mediated process is still a controversial topic [7,11-13].

Through activating AMPK, metformin transcriptionally regulates gluconeogenesis genes in the liver and genes that encode glucose transporters in muscle cells (e.g., GLUT1), thus metformin inhibits gluconeogenesis, induces glucose uptake into muscle cells and lowers blood glucose and insulin level in type 2 DM [7]. Study has showed that metformin works differently from insulin to maintain the glucose hemostasis in type 2 DM [14].

However how does metformin inhibit cancer cell growth and proliferation is still unclear. Metformin activates AMPK, which reduces mammalian target of rapamycin (mTOR)complex 1 levels through phosphorylation and activation of tuberous sclerosis complex 2, resulting in activation of GTPase-activating protein, which inhibits a downstream small GTPase, RHEB, causing a reduction in mTOR signaling. AMPK also directly inhibit raptor, the regulatory associated protein of mTOR, playing a key role in controlling cell growth, proliferation, and metabolism [12-13].

Metformin dose and time dependently caused ATP reduction, AMP accumulation, increased ratio of AMP to ATP and AMPK activity [15]. Therefore metformin generally is believed to work on cancer cells by activation of AMPK, acting on mitochondrial respiration and leading to imbalance of energy homeostasis in cancer cells.

Interestingly, study also suggests that metformin can directly inhibit mTORC1 signaling by suppressing RAG GTPase protein independent of AMPK activation. However the detailed mechanism is not clear [16].

In human prostate cancer cell lines, metformin also induced cell cycle arrest by inhibiting the expression of cyclin D1 and retinoblastoma-protein, two key regulators of the cell cycle, resulting in reduction of cyclin D1 level and eventually G1 cell cycle arrest, independent on AMPK activation [17].

Metformin may also indirectly affect the host metabolism through reduction in hepatic gluconeogenesis, leading to reduced circulating insulin levels and decreased insulin/IGF-1 receptor-mediated activation of the PI3K pathway [18]. Serum insulin level has been correlated with the increased risk for prostate cancer and breast cancer. Metformin significantly lowered insulin levels and improved insulin resistance in non-DM women with breast cancer. However, whether the lower insulin level leads to better cancer outcomes has not been proven [19,20]. Some recent clinical trials did not show favorable effect of IGF-1 antibody or somatostatin analog on anti-cancer outcome despite the reduction of insulin and IGF-I levels [21-23].

Preoperative treatment with Metformin did not significantly affect tumor cell proliferationas estimated by Ki-67 staining in primary breast cancer tissue, but a different impact on Ki-67 was observed according to different level of insulin resistance with a small decline in Ki-67 in patients who have HOMA index more than 2.8, suggesting high insulin resistance [24]. This observation is consistent with the finding that the reduction in hyperglycemia by metformin at postprandial state is more than at fasting state and the decrease in hyperinsulinemia is greater if it was present as baseline [25].

In addition to activation of AMPK and inhibition of mTOR, metformin has also been proposed to increase the activity of tumor suppressor p53. AMPK is also involved in p53-mediated cell cycle arrest induced by metformin [14,26]. A recent study [27] discovered the increased oxidative phosphorylation in family members of Li-Fraumeni patient who carries the TP53 mutation suggesting that p53 regulates mitochondrial respiration and metformin may have therapeutic value by reducing oxidative phosphorylation in Li-Fraumeni patients.

Metformin reduces chronic inflammatory responses at least partially by inhibiting the production of tumor necrosis factor alpha, preventing tumor development. In addition, studies have demonstrated that metformin reduces production of reactive oxygen species (ROS) through inhibition of mitochondrial complex I, the cellular source of ROS production, to reduce DNA damage and mutagenesis [28,29]. Metformin is also reported to inhibit drug resistance, decreases fatty acid synthesis and PGE2 synthesis [13].

AMPK inhibits the biosynthesis of estrogens and the secretion of leptin, which known to increase cancer cell proliferation and affect energy utilization and stimulates adiponectin secretion, which might inhibit tumor cell growth [19,29,30]. However, there is still lack of strong evidence to support these hypotheses.

In summary, metformin most likely works through modulating host environment as well as targeting cancer cell to effectively suppress cancer growth.

EPIDEMIOLOGICAL DATA

Based on the National Center for Health Statistics 2008 data, obesity and extremely obese in U.S continue to rise. The prevalence of obesity (BMI>=30) was about 35% and morbid obesity was about 7% (BMI >= 35) in 2006. Overweight is the second most common modifiable cancer cause, estimated to account for approximately 20% to 35% of all cancer cases, only slightly lower than tobacco use [20].

Obesity is associated with increased incidence of DM. There are 382 million people worldwide having diabetes in 2013 and by 2035 it is estimated to rise to 592 million according to DM Atlas Committee 2013 report. The total number of DM has increased to close to 28 million in North America and Caribbean. The number of people with type 2 DM is increasing in every country [22].

Meta-analysis suggested an association between DM and incidence of cancers. However, the degree of association is variable depend on type of cancer. For example, liver cancer has a relative risk (RR) of 2.50 and prostate cancer only has a RR of 0.89. However whether the observed RR is related to DM, to risk factor for DM such as overweight or to treatment regimen for DM

is not clear. Whether certain anti-DM medication is better than others is debatable [32].

In a large population-based follow-up study conducted in Netherlands by Ruiter R et al, dispensing records from community pharmacies were linked to hospital discharge records from 2.5 million individuals. It was found that the use of metformin was associated with a lower risk of cancer (hazard ratio of 0.90 [95% CI 0.88-0.91]) compared with use of sulfonylurea derivatives. Dosage-response relations were observed for metformin user, suggesting cumulative exposure to metformin maybe associated with a lower risk of cancers. However, could this indicate increased risk of cancer for the use of sulfonylurea is not clear [33].

Cancer incidence and cancer mortality among total of 11,140 participants from ADVANCE trial (the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) were compared in randomized intensive or standard glucose control groups. No significant differences in cancer incidences or cancer deaths were observed in the intensive and standard control groups after a median follow-up of 5 years. However, intensive glucose control was achieved with a regimen including greater use of gliclazide, insulin, metformin and other agents, which may cofound the findings [34].

Johnson JA and Bowker SL looked the cancer mortality and cancer incidence from major randomized controlled trials that aimed at intensified glycemic control in type 2 diabetes. The summary risk ratio for cancer mortality from UKPDS 33, UKPDS 34, ACCORD (Action to Control Cardiovascular Risk in Diabetes) and VADT (Veterans Affairs Diabetes Trial) was of 1.00. The pooled risk ratio for cancer incidence from ADVANCE, PROactive (PROspectivepioglitAzone Clinical Trial In macro Vascular Events) and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) was 0.91 (95% CI 0.79-1.05). These data suggest that improving glycemic control in type 2 diabetes did not reduce cancer risk, indicating hyperglycemia may not causally linked to increased cancer risk [35].

The reported malignancy data from ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials showed metformin did not offer any protection against malignancy compared with rosiglitazone or sulfonylurea as with 50 participants (3.4%) on metformin and 55 (3.8%) on each of rosiglitazone and sulfonylurea from ADOPT developed malignancies. On a background of sulfonylurea, 69 (6.1%) participants in RECORD developed malignancy in the metformin group, compared with 56 (5.1%) in the rosiglitazone group (HR 1.22 [0.86-1.74]). On a background of metformin, 74 (6.7%) participants in the sulfonylurea group developed malignancy, compared with 57 (5.1%) in the rosiglitazone group (HR 1.33 [0.94-1.88]) [35].

There is no consistent epidemiological evidence in clinical DM trial to support that metformin is better than other hypoglycemic agent in lowering the cancer incidence. Intensive glycemic control does not seem make a difference either. However most of those large trials were not designed specifically to look at the cancer incidence. These studies did not continue longer enough to see the full impact of metformin on mortality either. In addition, the selection bias that the participants tend to have lower incidence of malignancy than general population due to more observation and intervention may also decrease the power to detect a difference. There may be different effect of metformin on individual type of cancer, but it will not be easy to reveal given the low incidence of each specific type of cancer.

OBSERVATIONAL EVIDENCE

According to a recent meta-analysis, there was no protective or harmful association between metformin use and risk of pancreatic cancer found in patients with DM. However, considerable heterogeneity across studies may have explained this negative finding despite many reports indicate the protective effect from metformin use [36].

Compared the incidence of newly diagnosed lung cancer in patients with DM to that of age sex matched controls randomly selected from 1 million National Health Insurance claims data set from 2000-2005 in Taiwan for a period of 9 years (2000-2008, the risk of development of lung cancer with DM was not increased, but the use of anti-diabetic drugs considerably decreased the risk [37].

A met-analysis from ten studies including 22,650 cases of hepatic cell carcinoma (HCC) in 334,307 patients with type 2 DM found that there was a lower odds ratio (OR=0.5) for hepatocellular cancer with metformin use in patients with DM. This protective effect of metformin remains after adjusted for other anti-DM medications [38].

A Chinese study with 273 patients with HCC (253 were hepatitis B virus -related) demonstrated that the lower level of activation of AMPK determined by phosphorylated AMPK alpha (Thr172) status in the specimens from the HCC patient was correlated strongly with more aggressive clinic opathologic features and poor prognosis. Treatment with metformin at 5 to 10 mmol/L metformin not only inhibited cultured HCC cells growth, but also augmented cisplatin-induced growth inhibition in cultured HCC cells and in xeno graft tumors through AMPK dependent and NFKB inhibiting manner [39]. However this is not consistent with some clinical observation of metformin on hepato cellular cancer mentioned earlier, likely due to the fact that metformin concentration (5-10 mmol/L) used in vitro study is much higher than the typical plasma metformin level reached after the standard pharmacological metformin dose is given. The mechanistic involvement may be different too.

Metformin therapy was associated with a lower risk of colorectal cancer with a RR of 0.63 and 95% CI of 0.47–0.84 based on a met-analysis of several observational studies including total of 589 colorectal cancer events documented in 107,961 patients with type 2 diabetes [40]. Similar findings was also found in a retrospective cohort study from Taiwan, which showed patients with diabetes for 3 years had significant higher risk (adjusted RR of 1.185) for colon cancer compared to nondiabetes individuals. Metformin users for 3 years or more had significantly lower risk of colon cancer with a RR of 0.643 compared with nonusers [41].

A study compared the proportions of Pathologic Complete

Response (pCR) between the breast cancer study groups that receives neo-adjuvant chemotherapy for invasive breast cancer and found that the pCR was higher in the metformin treated DM group compared to non-Metformin treated DM group and non-DM group [42].

A retrospective cohort study of patients treated for uterine cancer from January 1999 through December 2009 at single-institution was conducted. Of 985 patients, 114 (12%) had diabetes and were treated with metformin, 136 (14%) were diabetic but did not use metformin, and 735 (74%) had not been diagnosed with diabetes. Greater overall survival was observed in diabetics with non-endometrioid endometrial cancer who used metformin than in diabetics who did not use metformin and non-diabetics (log rank test (p=0.02)). This association remained significant (hazard ratio=0.54, 95% CI: 0.30-0.97, p<0.04) after adjusting for age, stage, grade, chemotherapy, radiation and hyperlipidemia, indicating that metformin might be useful adjuvant therapy for non-endometrioid endometrial cancerin DM patient [43].

The evidence of the effects of metformin on ovarian cancer is still limited and inconclusive. One meta-analysis retrieved 190 studies with 3 observational studies and 1 randomized controlled trial, with result indicating that metformin tended to decrease occurrence of ovarian cancer among diabetic patients with the pooled odds ratio of 0.57 with large variation (95% confidence interval, 0.16-1.99) [44].

Despite the observational evidence suggesting the persistent relationship between the metformin use and a lower cancer incidence in several types of cancers, a causal relationship between metformin use and a decrease in cancer incidence cannot be fully established yet.

PROSPECTIVE DATA

A small Japanese study in 23 non-diabetic participants showed low dose of metformin 250 mg daily for 1 month significantly suppressed colorectal aberrant crypt foci, an endoscopic surrogate marker for colon cancer. Metformin inhibited cell proliferation without affecting apoptosis or metabolic profile, suggesting possible involvement of AMPK pathway [45]. Further multi-center prospective study on non-diabetic patients with recent colorectal polypectomy to receive 250 mg daily metformin vs. placebo for 1 year is being conducted [46].

Thirty-nine newly diagnosed, untreated, non-diabetic breast cancer patients received metformin 500 mg tid for average of 18 days after their diagnostic core biopsy were available until definitive surgery occurred. Not only did their BMI, weight and HOMA decrease significantly but also their Ki67 staining in invasive tumor tissue decreased from 36.5 to 33.5 % and TUNEL staining increased from 0.56 to 1.05, suggesting the beneficial cancer inhibitory effect of metformin. This effect did not seem mediated by insulin since the insulin level did not change significantly [47]. The large variation in baseline fasting insulin level among participants may have eliminated the significance of the metformin-induced insulin reduction.

Dr. Goodwin and her colleagues are running a multinational clinical trial in which 3500 breast cancer patients will be randomized to usual care plus a placebo or usual care plus metformin, to see if metformin helps to improve survival and prevent recurrence of the disease. Many other phase III clinical trials are currently evaluating the benefits and best uses of metformin in breast cancer patients.

There are many varieties of cancer trials with metformin are ongoing. Prospective randomized controlled trials (RCT) data are still not sufficient to draw the conclusion and current data are not always consistent. More carefully designed big size longer term prospective RCT is needed.

Another problem is that the clinically observed benefit of metformin has not been translated into mortality benefit. Cancer outcomes and all-cause mortality data were obtained from 11 published RCT comparing metformin with other DM therapy or placebo/usual care with 398 cancers identified during 51,681 person-years. Summary RRs for cancer outcomes in metformin treated people compared with any comparator were 1.02 (95% CI 0.82, 1.26) across all trials. This data showed no significant effect of metformin on all-cause mortality. However, heterogeneous comparator types and short follow-up may have posed limitation for this mortality study [48].

Lega IC, et al, followed 2,361 old breast cancer patients (mean age of 77) who had recent-onset diabetes for 4.5 years; cumulative metformin use was not associated with all-cause mortality or breast cancer-specific mortality. The study did not look at body mass index, breast cancer stage and other potential confounders that might affect interpretation of their findings. The data may not applicable to younger patients with breast cancer and diabetes [49].

DISCUSSION AND CONCLUSION

Most anti-cancer data of metformin from lab studies were obtained with a much higher concentration of metformin than clinically achieved level with typical anti-diabetes dose, and the glucose concentration in the culture medium is much higher than the physiological glucose level. A recent study showed that glucose level higher than 5 mmol/L in the culture media promoted a more aggressive breast cancer phenotype indicated by increase in cell proliferation, clonogenicity, motility, up regulation/activation of pro-oncogenic signaling, and reduction in apoptosisin triple-negative breast cancer cell lines, but 10 mmol/L or higher glucose significantly suppressed the inhibitory effects of metformin on these cells and altered efficacy and mechanisms of metformin action [50].

Another fact that contributes to this complex issue is heterogeneity of tissue level of metformin reached after oral dosing of metformin [51]. Metformin is actively transported into cells by different organic cation transporters (OCT) at different tissue. The existence of different type and express level of active transporter in different target organs makes the plasma level of metformin is not reflective of a specific tissue level of metformin. The bioactivity of metformin varies among different tissue and cell types [52-53]. After metformin is given orally, liver is exposed to higher level of metformin through the portal circulation. Hepatocytes express high level of OCT1, which may contribute to their enhanced cellular uptake of the drug [54]. The hepatic metformin concentration is 4 to 6 times higher than plasma level

in rat. Within cells, metformin is distributed variably at different cell compartment such as mitochondrial vs cytosol [55].

Despite the promising data of metformin effects on metabolism and neoplasm, many studies have done with a large range of metformin level as little as 0.01 mM to as high as 50 mM or higher [56-57]. A DM patient typically receives a maximum of 2000 mg metformin daily, which is approximately 28 mg/kg for a standard 70 Kg adult. After a single 20 mg/kg metformin dose, the plasma concentration of metformin can reach about 0.01 to 0.04 mM [58]. Future studies may use lower concentration of metformin.

Since metformin is a safe and well-tolerated medication, it can be used in combination with other agent either as adjuvant therapy or chemo-preventive therapy. A recent report [59] demonstrated that salicylate activated AMPK at concentrations that do not alter ATP production. Our own unpublished data showing salicylate may have synergistic effect on regulation of glucose metabolism. Whether there is potential additional benefit for cancer inhibition with co-administration of metformin and salicylate need to be studied.

In summary, Metformin as the first line hypoglycemic drug for type 2 DM, seems having beneficial effect on certain type of cancers but not in all cancers. Even there is some inconsistency at the current epidemiological, observational and RCT data, it is hard to ignore the signal especially considering the wide area of application given the increased prevalence of obesity and DM in cancer patients and the low cost and safety of the drug. More carefully designed study especially longer and larger RCTs in selected cancer population in the future will be helpful to answer this important question. Mechanism wise, metformin might lead to new drug development that aims to suppress cancer cell growth in addition to modulate glucose metabolism like metformin. This area definitely deserves more exploration.

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