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REVIEW

Anti-Diabetic Drugs: Cure or Risk Factors for Cancer?

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Abstract
Anti-diabetic drugs are an important group of therapeutics used worldwide. Different anti-diabetic drugs lower blood glucose level by different mechanisms. In recent years, numerous investigations have been performed based on both comparative and cohort studies, in order to establish the relationship between anti-diabetic pharmacotherapy and cancer incidence as well as mortality due to cancer. Some anti-diabetic drugs have been found to exhibit anti-cancer activity while others might increase the risk for cancer. The underlying cause for this disparity is likely to be the varying mechanisms of action of these drugs in controlling blood glucose level. This review discusses the various carcinogenic and/or anti-cancer effects of commonly used anti-diabetic drugs. The information is vital in view of the fact that diabetes mellitus is a commonly occurring disease with a rising incidence rate.

Keywords Anti- cancer effect · Anti-diabetic drugs · Cancer risk

Introduction

Diabetes mellitus and cancer are two multifactorial chronic diseases with significant impact on global health [1]. According to the latest estimates, approximately 382 million people were living with diabetes mellitus in 2013, and this number is expected to rise to 592 million by 2035 [2]. Type 1 diabetes mellitus (T1DM) is caused by the immune destruction of pancreatic β cells which leads to insufficient production of insulin in the body whereas in Type 2 diabetes mellitus (T2DM), the body becomes resistant to insulin production thus leading to hyperglycemia, or elevated levels of blood glucose. Both T1DM and T2DM lead to alterations in the metabolic, hormonal and immune imbalance, such as abnormalities in the carbohydrate and lipid metabolic pathways, increased secretion of pancreatic hormones and increased circulation of pro-inflammatory cytokines such as TNF α [3].

Like diabetes mellitus, cancer has become a global pandemic. In 2015, there were 17.5 million new cases of cancer and 8.7 million deaths globally. The rate of cancer incidence increased by 33% from 2005 to 2015 [4]. With cancer already making an enormous impact on morbidity and mortality and with T2DM on the rise, investigations specific to these two diseases have become an important area of research. Interestingly, studies conducted so far provide inconclusive evidence on the association of cancer with diabetes mellitus. Recent evidences based on a number of meta-analysis and epidemiological studies suggest that the individuals with T2DM are more prone to the risk of developing various types of cancer especially that of the pancreas, endometrium, colon, breast, esophagus and liver as compared to the non-diabetic counterparts [5–7]. Subsequent studies have reported that diabetic individuals are at a risk of two fold or more for the cancers of the liver, pancreas, and endometrium, and 1.2–1.5 fold for cancers of the colon and rectum, breast, and bladder [1]. However, the risk of prostate cancer in male was found to have an inverse association with diabetes mellitus. An increased risk of mortality was also found among the diabetic patients diagnosed with non-metastatic colorectal cancer than the non-diabetic cancer patients [8]. Moreover, T2DM diabetic patients with reduced risk of prostate cancer incidence were reported to have a higher rate of mortality [9].

Various studies suggest a strong correlation between the incidence of diabetes mellitus and cancer. Therefore investigation on the possible role of the treatment of diabetes mellitus and development/inhibition of cancer in patients is considered logical. Recent studies suggest an emerging trend of research on the development of cancer in diabetic patients receiving or not receiving anti-diabetic medications [9].

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Mechanism Linking Diabetes Mellitus and Cancer

Lifestyle changes and environmental factors play important role in the prevalence and rapid growth of diabetes mellitus and cancers [10, 11]. Clustering of three of the following factors- elevated fasting plasma glucose, disturbed insulin metabolism, overweight/abdominal obesity, hypertension, high triglycerides and low high density lipoprotein (HDL) levels in an individual gives rise to the development of metabolic syndrome [12]. Metabolic syndrome is unequivocally related to an increased risk of developing T2DM characterized by insulin resistance [13]. Moreover, studies demonstrate that metabolic syndrome or its components are also associated with the development of cancer and cancer-related mortality [14].

Studies suggest a number of factors that explain the link between the increased risk of cancer and T2DM [12]. These include altered insulin and insulin-like growth factor (IGF) signals, obesity, inflammation, hyperglycemia, ER stress and autophagy.

Insulin resistance leads to an elevated level of circulating insulin and is a common characteristic in obesity or T2DM [12]. Hyperinsulinemia in turn causes a rise in the level of free and bioactive IGF-1. Insulin and IGF-1 provide a plausible mechanistic explanation for the underlying risk of cancer in type 2 diabetic patients. The insulin and IGF-1 trigger the receptor tyrosine kinase pathway, insulin receptor (IR) and IGF-1 receptor (IGF-1R) which subsequently activates the insulin response substrate-1 (IRS-1) along with mitogen-activated protein kinase (MAPK) pathway, phosphoinositol-3 kinase/Akt (PI3KAkt) pathway, Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [12]. Activation of these pathways promotes protein synthesis, cell proliferation, protection from apoptotic stimuli and initiation and maintenance of cancer stem cells. The increased circulating insulin also leads to an increase in the bioactive sex hormones which has a strong association with higher risk of postmenopausal breast and endometrial cancer [15]. An association between increased levels of insulin/IGF and cancer of colon, breast and pancreas have also been reported in the non-diabetic population [16].

Diabetes mellitus is very closely associated with obesity. An estimated 80% - 90% of the patients diagnosed with diabetes mellitus are also obese [12]. Diabetes mellitus and obesity fuel each other mutually. In T2DM, the elevated levels of insulin and glucose in circulation are key factors for excess weight gain and obesity. On the other hand, fat cells in obese individuals release pro-inflammatory factors that help in developing insulin resistance resulting in T2DM [17]. Studies suggest that obese people have higher incidence of cancers of various types including endometrial, esophageal, colorectal, breast, prostate, and renal cancer [18]. Obesity leads to the development of cancer by promoting the establishment of tumor microenvironment. In obesity there is an increased level of pro-inflammatory molecules such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, resistin, retinol binding protein-4, plasminogen activator inhibitor-1 (PAI-1) and hepatic growth factor (HGF) [18]. Leptin is known for its mitogenic, pro-inflammatory, anti-apoptotic and pro-angiogenic activity. The increased level of leptin in obese individuals thus promotes the development and progression of cancer [19]. There is also a decreased secretion of adipokines such as adiponectin and visfatin in the adipose tissues. Adiponectin boosts insulin sensitivity, and its circulating levels are inversely related to cancer development and progression. Therefore, lower level of adiponectin in obesity is believed to be the associating factor for cancer development [18].

Hyperglycemia in diabetes mellitus has been reported to trigger many direct and indirect mechanisms that cooperate to promote cancer progression. These include induction of epithelial mesenchimal transition, increased levels of insulin/IGF-1 and inflammatory cytokines in the blood stream, increased leptin and AKT/mTOR signaling and enhancement of Wnt/ β-catenin signaling [20].

Recently, endoplasmic reticulum stress and autophagy have also emerged as important cellular mechanisms linking diabetes mellitus to cancer [12]. Additionally, the diabetes mellitus microenvironment, such as advanced glycation end-products (AGEs), hyperlipidemia, oxidative stress, extracellular matrix alterations, and altered microbiota or ischemia due to vasculopathy may recruit secondary mediators of injury that may favor the development of cancer [21].

Common Anti-Diabetic Drugs

About 3500 years ago, the ancient Egyptians were the first to record the symptoms of diuresis related to T1DM and T2DM [22]. Since then many symptoms were found leading to the realization that the root cause of diabetes mellitus lies in disorders of the pancreas [22].

Galega officinalis, a perennial herb was used in traditional medicine to treat symptoms now recognized to be of T2DM [23]. The plant extract contains major compounds like guanidine and galegine that show having hypoglycemic properties. During 1920 to 1930 two synthetic biguanides were used to treat diabetes mellitus but were soon discontinued as they caused hepatotoxicity [24]. In 1929, several glucose-lowering biguanides were synthesized out of which three biguanides- metformin, phenformin, and buformin were introduced. The potential glucose lowering properties of phenformin and buformin were first reported in 1957 and 1958 [24]. However, they caused lactic acidosis and were

soon withdrawn from the market. Currently, metformin alone or in combination with other anti-diabetic drugs is used as an effective medication for T2DM [25].

Glitazone or thiazolidinediones were discovered based on the observation that T2DM patients treated with clofibrate had lower fasting glucose levels [26, 27]. This led to the development of more potent analogs of clofibrate having positive effects on hyperglycemia, hypertriglyceridemia and hyperinsulinemia in animals with T2DM [27]. Ciglitazone was the first thiazolidinediones discovered but it was never marketed because of its weak clinical activity. In 1997, troglitazone became the first glitazone to be approved for use, but was withdrawn from the market in 2000 because it caused hepatotoxicity [27]. The second generation glitazone i.e. rosiliglitazone was banned by the US Food and Drug Administration in September 2010 because it caused high risk of myocardial infraction [27, 28].

Sulfonylureas are a class of drugs derived from the condensation of aryl sulfone group with urea moiety [29]. Sulfonylureas were discovered by Marcel Jambon and his co-workers in 1942 while studying sulfonamide antibiotics [30, 31]. They observed that some sulfonamides caused hypoglycemia in animal models. Carbutamide (1-butyl-3-sulfonylurea) was the first sulfonylurea introduced commercially to treat diabetes mellitus, but it was discontinued due to its adverse effects on bone marrow [32]. By 1960s a number of sulfonylureas were commercially available. Drugs belonging to this class were categorized into two groups or generations.

Bayliss and Starling in 1902 found that the hormone secretin secreted from intestinal mucosa increases the exocrine secretion of the pancreas [33]. Incretin mimetics are also called Glucagon-like Peptide-1 (GLP-1) receptor agonist or GLP-1. Exenatide is the first generation GLP-1 that is derived from saliva of Gila Monster [34, 35]. Exenatide injection was approved in 2005 twice daily given 40–60 min before breakfast and dinner [27]. In January 2012, exenatide was approved to be given once a week. Lirglutide was approved in 2010. There are also other classes of incretin mimetics such as Sitagliptin, Saxagliptin and Linagliptin that were approved [36, 37].

In 1963–1966 human insulin analog was chemically synthesized in Germany by Meienhofer et al. [38], in China by Kung et al. [39] and in the United States by Katsoyannis et al. [40]. Their work indicated that human insulin along with other proteins can be synthesized. The very first insulin analog (B10Asp) was withdrawn from the market in 1992 because of its carcinogenic effect found in rats. Later, human insulin for inhalation was also withdrawn from market in 2008 because of its disappointing sale [41]. The first insulin analog that was approved for human therapy is Insulin Lispro [42].

Epidemiological Evidence for the Association of Anti-Diabetic Drugs and Cancer Risk

Metformin

Metformin (1,1-dimethylbiguanide) is an orally administered anti-hyperglycemic drug recommended as a first line of medication for T2DM [43]. It is non-toxic and effective both in monotherapy as well as in combination with other oral antidiabetes mellitus drugs and insulin [44, 45]. It is an insulin sensitizer that reduces insulin resistance and lower plasma fasting insulin level. Metformin performs its anti-diabetic activity by many ways such as inhibition of hepatic glucose production, reduction of intestinal glucose absorption and increase of glucose uptake and utilization. Moreover, metformin is also effective in the treatment of obesity, hyperlipidemia and some cardiovascular complications [46]. Another important benefit of the hypoglycemic drug is that it reduces cancer incidence in diabetics taking metformin [47–49]. However, the mechanism of metformin action in cancer (Fig. 1) has only explored to a limited extent and remains disputable. Of note, anti-cancer effect of metformin on different cancers such as those of the breast [50], pancreas -[51], thyroid [52], gastric [53, 54] prostate [55] colon [56], bladder [57] and oral [58] have been reported (Table 1).

It is postulated that the anti-cancer activity of metformin is associated with both direct and indirect actions of the drug. The indirect action of metformin is exerted by the inhibition of gluconeogenesis in the liver which enhances glucose absorption in the muscle cells leading to an increase in insulin sensitivity and decrease in blood glucose level [86]. The direct anti-cancer effect of metformin involves both AMPK-dependent and AMPK-independent mechanisms. AMPK is a master regulator of cellular energy metabolism and is activated during conditions of cellular stress like ischaemia, hypoxia, glucose deprivation, oxidative stress and muscle contraction [87]. Metformin inhibits mitochondrial respiratory chain complex I leading to a weakened mitochondrial function that mimics a condition similar to cellular energy stress which leads to activation of AMPK [86, 88]. Activated AMPK inhibits the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway, a major regulator of cell growth and proliferation [89, 90]. The inhibition of mTOR signaling has a great potential for anti-cancer therapy as mTORC1 is hyperactive or upregulated in the majority of cancers [91]. Metformin can also inhibit the mTOR signaling by AMPK independent mechanism [92].

The anti-cancer action of metformin is also attributed to its ability to reduce circulating insulin level and IGF-1 [93]. Furthermore, metformin may modify the tumor microenvironment possibly by targeting the inflammatory components leading to a reduction of the tumor [12, 94].

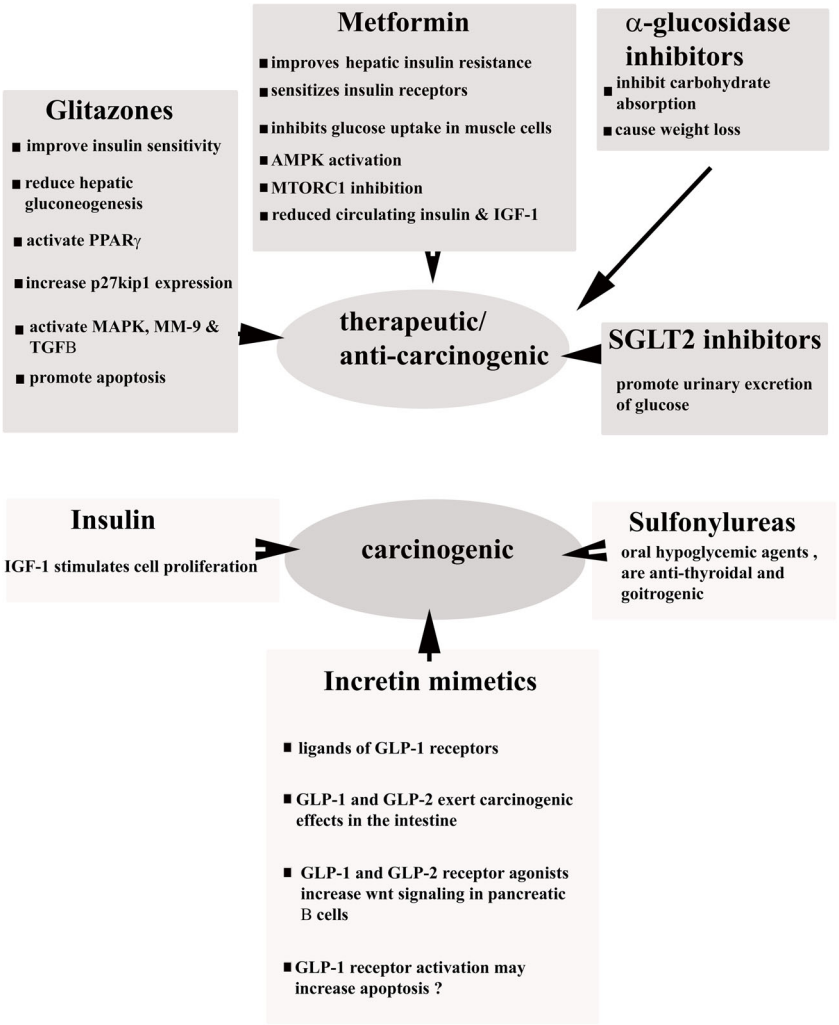

Fig. 1 Carcinogenic and anti-carcinogenic effect of common anti-diabetic drugs

Glitazones

Glitazones, also called as thiazolidinediones, improve metabolic control in T2DM patients by improving insulin sensitivity of the peripheral tissues [95]. The drugs also activate a group of nuclear hormone receptors known as peroxisome proliferator-activated receptors (PPARs), particularly PPARγ [96] (Fig. 1).

The main representatives of glitazone group of drugs are rosiglitazone, pioglitazone and troglitazone. However, rosiglitazone and troglitazone have been withdrawn from the market as it was found that rosiglitazone use leads to an increased risk of myocardial infarction whereas troglitazone causes hepatotoxicity [27, 28]. At present, only pioglitazone is in the market with some safety alerts by US FDA. Reports suggest that pioglitazone therapy lowers the risk of adverse cardiovascular events in pre-diabetic as well as diabetic patients with a statistically significant decrease in the risk of all-cause mortality [97]. However, pioglitazone therapy has been shown to cause higher risks of heart failure, bone fractures, edema and weight gain. Pioglitazone was also reported to be associated with bladder cancer with conflicting results [98]. A recommended lower dose of pioglitazone was found to have less adverse effect on weight gain, edema and heart failure without compromising the positive effects as compared to the standard- and high-dose pioglitazone therapy.

A case-control study involving 606,583 T2DM patients using rosiglitazone and pioglitazone was performed by Chang et al. [99]. It was found that these patients had a significantly reduced risk of hepatic cancer. The cancer-preventing effect of the medication was dependent on a cumulative dosage and the duration of administration. Rosiglitazone was also associated with a decreased risk of colorectal cancer (Table 1).

In a cohort study conducted by Mamtani et al. [100], patients treated with pioglitazone were recruited to access the association of the drug with cancer. It was revealed that long term exposure of the drug i.e. more than 5 years lead to an increased risk of bladder cancer. The duration of drug exposure was also taken into consideration in this study. However a short duration exposure did not have carcinogenic effect [100]. The bladder cancer risk associated with the

Table 1 Common anti-diabetic drugs and their association with cancer risk

Sl. No.	Class Of Drug	Generic Name	Major Brand	Manufacturer	Cancer Incidence/ Risk	Cancer Site/type	Reference
1	Biguanide	Metformin	Glucophage	Bristol Myers Squibb	Decreased	Lung, colorectal, oesophagus, gastric, oral, prostate, bladder, thyroid, cervix, kidney, ovary, breast, pancreas, colon, liver, endometrium,	[49, 52, 54–65]
2	Thiazolidiones	Pioglitazone	Actos	Takeda Pharmaceuticals	Increased, Decreased	Bladder, melanoma, non-Hodgkin lymphoma, Kidney/renal pelvis	[66] [67] [67]
		Rosiglitazone	Avandia	GlaxoSmithKline	Decreased	Non-melanoma skin cancer, breast	[68, 69]
3	Sulphonylureas	Glimepiride	Amaryl	Sanofi Aventis	Decreased	Liver, colorectal, lung, breast, prostate, stomach, pancreas	[70]
		Glyburide	DiaBeta	Sanofi Aventis	Increased	All types	[71]
		Glipizide	Glucotrol	Pfizer	Decreased	MCF-7 cell line, 4 T1 xenograft tumor model	[72]
4	GLP-1 receptor agonist	Exenatide	Byetta	Amylin Pharmaceuticals	Increased	Pancrease	[73]
		Liraglutide	Victoza	Novo Nordisk	Inceased	Thyroid (rodents)	[9]
5	DPP-4 Inhibitors	Sitagliptin	Januvia	Merck & Co., Inc.	Increased	Pancrease, thyroid, oral	[73–75]
		Saxagliptin,	*Onglyza*	Bristol-Myers Squibb and AstraZeneca	No risk	–	[76]
6	Insulin analogs	Human insulin	Humulin	Eli Lilly and Company	Increased	Breast, liver	[77, 78]
		Aspart	NovoLog	Novo Nordisk	Increased proliferation	MCF-7 cell line	[79]
		Lispro	Humalog	Eli Lilly and company	Induced proliferation	Thyroid, gastric cell lines	[80]
		Glargine	Lantus	Sanofi-Aventis	Increased	Skin, precancer lesion, Thyroid, gastric and endometrial cell lines	[80–82]
7	SGLT2 inhibitors	Canagliflozin	Invokana	Janssen Pharmaceuticals, Inc.	No risk	Bladder, breast	[83]
		Dapagliflozin	Farxiga	Bristol-Myers Squibb and AstraZeneca.	No risk	Bladder	[84]
8	α- glucosidase inhibitor	Acarbose	Precose	Bayer	Reduced	Colorectal	[85]

pioglitazone use has remain controversial and some uncertainty still exists surrounding the epidemiological data presented till date [98] (Table 1).

Other studies, however, demonstrated a decreased risk of cancer in diabetic patients treated with glitazones. The exact mechanisms by which they inhibit tumor growth still remain elusive. Mutation of PPARγ have been reported in various types of cancer, e.g. lung, breast, colon, liver, prostate and thyroid cancer. The glitazones are thought to confer anticancer effect by activating PPARγ leading to induction of apoptosis, reduction in inflammation, arrest of cell proliferation, inhibition of growth factor, promotion of cell redifferentiation and other mechanisms independent of PPARγ [98, 101]. Moreover, glitazones inhibit the proteasome system (ubiquitin) and the kinase signaling pathways [102–104]. PPARγ inhibits cell proliferation by the degradation of proteasomal cyclin D1 as well as by inhibiting the wnt/b catenin pathway. Activated PPARγ stops the cell cycle, thus preventing the carcinogenesis process. Additionally, glitazone also triggers $p27^{kip1}$ expression as well as the activation of several other pathways such as mitogen activated protein kinase (MAPK), inflammatory pathways (MM-9) and transforming growth factor beta (TGFβ) which contributes to its anti-tumor activity. Glitazones also promote apoptosis by increasing pro-apoptotic p53 expression and decreasing anti-apoptotic Bcl-2 [103] (Fig. 1).

Insulin and Insulin Analogs

Insulin therapy is widely used for the treatment of diabetes mellitus. The insulin molecule is a polypeptide consisting of two chains connected by the disulfide bond and the insulin analogs are the insulin polypeptides modified for better stabilization [29]. The modified insulin analogs have better activity, absorption and longer duration of action. Insulin analogs are divided into two groups based on their duration of action viz. fast acting (e.g. Lispro, Glulisine, Aspart) and long acting (e.g. Detemir, Glargine) [29, 105, 106].

Data based on epidemiological studies as well as meta-analysis suggest that insulin therapy in T2DM is associated with an increased risk of cancer [107] (Table 1). Therapeutic insulin/insulin analogs increase the cancer risk by a mechanism similar to the endogenous insulin, as discussed in the previous section. Two possible mechanisms have been put forward [108]. Firstly, the insulin/insulin analogs stimulate cell proliferation via interaction with IGF-1 receptors (Fig. 1) and its own receptors [109]. The less documented second mechanism describes the tumorigenic activity of Asp-B10 insulin, an unusual human insulin analog. Asp-B10 insulin binds to hepatocytes leading to increased signaling of MAP-kinase pathway which in turn promotes cancer progression [108]. Despite their potential cancer risks, insulin/insulin analogs are being used as therapy for their other beneficial effects.

Incretin Mimetics

Incretins are hormones secreted by enteroendocrine cells, and function to decrease blood glucose levels [110]. The widely used incretin-based therapies for T2DM comprise of two broad classes- the incretin mimetics of glucagon-like peptide-1 receptor (GLP-1R) agonists and incretin enhancers of dipeptidyl-peptidase 4 (DPP-4) inhibitors [111]. The incretin mimetics bind to the GLP receptors present on cell membrane which further stimulates the glucose dependent insulin secretion as well as β-cell proliferation and survival (Fig. 1). GLP-1 is usually degraded by the action of dipeptidyl peptidase (DPP-4) [110]. Therefore, drugs that inhibit the DPP-4 activity have been developed and are presently being used as incretin enhancers for the treatment of T2DM.

The incretin-based therapies have been found to be associated with an increased risk of cancer, especially pancreatic and thyroid cancer [73, 111]. It has been reported that GLP-1 and GLP-2 receptor agonists increase wnt signaling, myc mRNA expression and cyclin D1 in pancreatic β cells [112]. The wnt signaling pathway may play an important role in tumor proliferation. Association of DDP-4 inhibitors and GLP-1 receptor agonist with both thyroid and pancreatic cancer have been reported, however no excess risk of either outcome associated with liraglutide, a GLP-1 analog was observed [113]. More studies are required to further assess the cancer risks associated with the incretin therapy. The beneficial effects of these drugs overshadow their cancer causing activity and hence they are being used for the treatment of T2DM with some regulations.

Sulfonylurea

Sulfonylureas are a group of oral hypoglycemic agents that increase secretion of insulin in the pancreas. Sulfonylureas are classified as: 1) first generation sulphonylureas, including chlorpropamide, acetohexamide, tolazamide and tolbutamide and 2) second generation sulphonylureas including glipizide, glyburide and glimepiride [29]. These drugs lower blood glucose level very rapidly and therefore there posing a risk of hypoglycemia. Sulfonylureas inhibit potassium channels in the pancreatic β cells by binding to an ATP-dependent K^+ channel on the membrane which in turn causes depolarization of the cell. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium thus stimulates endogenous insulin secretion [110, 114].

Tseng [115], reported that tobultamide, chlorpropamide, acetohexamide and tolazamide caused a higher risk of thyroid cancer. The cause of this carcinogenicity was attributed to the anti-thyroidal and goitrogenic effects of sulfonylureas that causes hypothyroidism and raises thyrotropin (TSH) level [115] (Fig. 1). In a case-control study, Monami et al. [116] showed that exposure to glibenclamide for 12 and 36 months

was associated with increased risk of cancer whereas gliclazide was found to reduce cancer risk. The author thus recommended thorough examinations to assess this tendency. Li et al. [117] evaluated the association of anti-diabetic drugs on the prevalence of pancreatic cancer. The study revealed that the T2DM patients who had used insulin and those who had used insulin secretagogues like sulfonylureas were at higher risk of pancreatic cancer development compared to diabetic individuals who had never used the medications. As a whole, sulfonylurea was observed to be associated with an increased risk of cancer among diabetic patients. However, a reverse effect on cancer risk was reported in some studies when glibenclamide, gliclazide and tolbutamide were used [110, 118] (Table 1).

α-Glucosidase Inhibitors

The α-glucosidase inhibitors are drugs used for the treatment of T2DM. They inhibit α-glucosidase and prevent the cleavage of di-, oligo- and polysaccharides into monosaccharide in the small intestine [119]. Thus, they inhibit the absorption of carbohydrates (Fig. 1), thereby reducing the effect of carbohydrates on blood sugar. There are three inhibitors available: acarbose, miglitol and voglibose. Naturally some α-glucosidase inhibitors are also found as phytoconstituents such as flavonoids, alkaloids, terpenoids, anthocyanins, glycosides, phenolic compounds, and so on [120]. For instance α-glucosidase inhibitor have been isolated from the mushroom maitake *(Grifola frondosa)* [121].

Use of acarbose, an α-glucosidase inhibitor was found to reduce the incidence of colorectal cancer in diabetic patients in a dose dependent manner [85]. Moreover, Lai et al., [122] reported that the use of α-glucosidase inhibitors led to decreased incidence of lung cancer (Table 1).

SGLT-2 Inhibitors

Sodium glucose cotransporters (SGLTs) are the group of proteins found in small intestine (SGLT-1) and the proximal tubule of kidney (SGLT-2) [29]. SGLT-2 helps in glucose reabsorption in the kidney. Inhibition of GSLT-2 increases glucose excretion from kidney lowering plasma glucose level (Fig. 1). Use of SGLT-2 inhibitors have multiple other beneficial effects including low hypoglycemic risk, reduced high blood pressure, weight loss and cardiovascular health without exerting significant side effects [123, 124].

An increased risk of bladder and breast cancer was observed in dapagliflozin trials and hence in 2011, US FDA demanded the need of additional clinical trial data to determine the risk:benefit ratio [124, 125]. Dapagliflozin had a safety profile in vitro, in vivo and in clinical trials. Other SGLT-2 inhibitors were not found to be associated with any type of cancer risk (Table 1).

Conclusion and Future Perspective

The complex and heterogeneous nature of diabetes mellitus and cancer make it difficult to interpret the exact mechanisms that interlink the two diseases. However, it is anticipated that the cellular adaptation to diabetic microenvironment may lead to initiation of cellular transformation. Altered metabolism may initiate the cancer metabolic reprogramming, which can be aggravated by the constituents of the diabetic environment. Therefore the management of diabetes mellitus may have a potential therapeutic role in cancer prevention.

Some of the anti-diabetic drugs enhance the risk of cancer in diabetic patients whereas others have shown anti-cancer properties. All these drugs differ from each other in their efficacy and mechanism of action in lowering the glucose level in the blood [110]. In this review, an attempt has been made to study the dual role of anti-diabetic drugs on the inhibition and promotion of cancer along with their mechanisms. Insulin and insulin analogs may increase cancer risk because their mechanism of action involves IR and IGF-IR signaling pathway that enhances cancer metabolism in the cells, as evident from various reports [109, 126]. Insulin sensitizers like metformin and glitazone, on the other hand, may inhibit cancer proliferation by promoting the PPARγ and AMPK regulating pathways. The association between sulphonylureas and cancer remains inconsistent. The sulphonylureas- glimepiride and glipizide were reported to decrease cancer risks [70, 72], whereas glyburide was found to increase cancer incidence in patients with T2DM [71]. Moreover, increased cancer related mortality was also reported in diabetic patients treated with sulphonylureas [127].

These inconsistencies may be attributed to the fact that most of the epidemiological studies failed to meticulously consider a number of important confounding factors like type of anti-diabetic drugs, duration of the disease, duration of treatment, quality of metabolic controls and presence of comorbidities. Additionally, diabetic patients are treated with many other drugs and they also change their treatment quite often which makes it difficult to identify the effect of a particular drug on cancer incidence. However, as evident from Table 1, it may be concluded, that the effect of anti-diabetic drugs on cancer is not class specific but drug specific.

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Compliance with Ethical Standards

Conflict of Interest None.

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