Review Article

Muhammad Ejaz ul Haq, Muhammad Sajid Hamid Akash*, Kanwal Rehman* and Mohsin Khurshid

Therapeutic role of metformin and troglitazone to prevent cancer risk in diabetic patients: evidences from experimental studies

Diyabetik hastalarda kanser riskini önlemek için metformin ve troglitazonun terapötik rolü: deneysel çalışmalardan kanıtlar

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Abstract

Objectives: It is evident from literature that individual with diabetes mellitus is more prone to develop cancer as compared to non-diabetic one. We aimed to highlight the risk factors that trigger the tumor formation in diabetic individuals and collect evidences regarding the preventive role of anti-diabetics in cancer.

Content: A comprehensive literature was searched in English language using electronic databases including PubMed, ScienceDirect, Medline, Scopus and Embase.

Summary and outlook: Antidiabetic drugs notably metformin and troglitazone, exhibit anticancer effects. Metformin targets energy sensor pathway i. e., AMPK/mTOR which is controlled by LKB1. Whereas. troglitazone activates PPARY that modulate the transcription of insulin responsive gene which is essential for lipid and glucose metabolism. Adipocytes are highly expressed with PPARɣ which induce differentiation and regulate adipogenesis. Ligand-driven expression of PPARɣ in myoblast and fibroblast cell lines produces adipocyte differentiation in breast cancer. Prostate cancer that expresses PPARɣ may be suppressed by troglitazone and retinoid which inhibit their proliferation and initiate differentiation. The findings summarized here show that metformin and troglitazone may have the ability to inhibit the cancer cell proliferation via involvement of molecular pathways. This therapeutic intervention will help to control the progression of cancer in diabetic patients.

Keywords: diabetes mellitus; cancer; hyperinsulinemia; metformin; troglitazone.

Öz

Amaç: Literatürde diyabetes mellituslu bireylerin diyabetli olmayanlara göre kanser geliştirmeye daha yatkın oldukları açıktır. Diyabetik bireylerde tümör oluşumunu tetikleyen risk faktörlerini vurgulamayı ve anti-diyabetlilerin kanserdeki önleyici rolü hakkında kanıtlar toplamayı amaçladık.

İçerik: PubMed, ScienceDirect, Medline, Scopus ve Embase gibi elektronik veri tabanları kullanılarak İngilizce dilinde kapsamlı bir literatür taranmıştır.

Özet ve görünüm: Metformin ve troglitazon gibi antidiyabetik ilaçlar antikanser etkileri gösterir. Metformin enerji sensörü yolunu, yani LKB1 tarafından kontrol edilen AMPK/mTOR'u hedefler. Oysa troglitazon, lipit ve glikoz metabolizması için gerekli olan insüline duyarlı gen

***Corresponding authors: Muhammad Sajid Hamid Akash, PhD**, Department of Pharmaceutical Chemistry, Government College University, Faisalabad, Pakistan, E-mail: sajidakash@gmail.com; and **Kanwal Rehman, PhD**, Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan, E-mail: kanwalakash@gmail.com. https://orcid.org/0000-0002-9446-5233 (M.S.H. Akash), https://orcid.org/0000-0001-7873-6681 (K. Rehman)
Muhammad Ejaz ul Haq: Department of Pharmaceutical Chemistry, Government College University, Faisalabad, Pakistan, E-mail: beingpharmacist99@gmail.com
Mohsin Khurshid: Department of Microbiology, Government College University, Faisalabad, Pakistan, E-mail: mohsinkhurshid@gcuf.edu.pk. https://orcid.org/0000-0002-3196-2857

transkripsiyonunu modüle eden PPARy'yi aktive eder. Adipositler, farklılaşmayı indükleyen ve adipogenezi düzenleyen PPARy ile yüksek oranda eksprese edilir. Myoblast ve fibroblast hücre hatlarında ligand güdümlü PPARy ekspresyonu, meme kanserinde adiposit farklılaşması üretir. PPARy eksprese eden prostat kanseri, proliferasyonlarını inhibe eden ve farklılaşmayı başlatan troglitazon ve retinoid tarafından baskılanabilir. Burada özetlenen bulgular, metformin ve troglitazonun, moleküler yolların tutulumu yoluyla kanser hücresi çoğalmasını önleme yeteneğine sahip olabileceğini göstermektedir. Bu terapötik müdahale, diyabetik hastalarda kanserin ilerlemesini kontrol etmeye yardımcı olacaktır.

Anahtar Kelimeler: diabetes mellitus; kanser; metformin; troglitazon; hiperinsülinem.

Introduction

Individuals with diabetes mellitus (DM) have 2-4-fold higher mortality rate as compared with that of non-diabetic individuals [1–3]. The first most common death cause in DM is cardiovascular disease (CVD). But it has been observed that mortality rates from CVD in DM cases have been declined from the last decades [4, 5]. The second commonest cause of death in DM is cancer [5–7]. Thus individuals with DM have greater cancer mortality rate than those without DM. Ohkuma and colleagues, conducted meta-analysis of 32 clinical studies including 20 million individuals and one million events, reported higher cancer death rate of 26% in males and 30% in females with DM [8]. In another study, investigators assessed cause-specific mortality rate across 10 different causes of death by ethnicity in people with and without DM from Clinical Practice Research Datalink (CPRD). They observed the higher cancer-associated mortality among diabetic individuals [5]. These studies are in consistent with other studies that compared diabetics with non-diabetic individuals, individuals with DM are more prone to develop numerous common malignancies, like breast, endometrial, colorectal, liver, and pancreatic cancers [8, 9]. Exceptionally, DM is found to be associated with reduced risk of prostate cancer. This association has been exclusively observed before and after the advent of screening with prostate specific antigen [10, 11].

There are few potential risk factors associated with both DM and cancer. These factors may be either modifiable or non-modifiable such as sex, age, race, diet, physical activity, alcohol, and smoking [10]. The metabolic abnormalities linked with DM are generally developed many years before the onset of DM. Therefore, these abnormalities may contribute to cancer risk even before individuals come to know that they are at risk. A number of factors potentially contributing to cancer progression in obesity and DM include hyperinsulinemia, insulin-like growth factor I, hyperglycemia, dyslipidemia, adipokines, cytokines, and gut microbiota [12].

Antidiabetic drugs are used to reduce the cancer cell proliferation [13]. Metformin belongs to a biguanide class while, troglitazone belongs to thiazolidinedione class. Both antidiabetic drugs reduce the risk of cancer by acting on tumor cell via involvement of different mechanisms [14, 15]. In this article, we have highlighted some modifiable and non-modifiable risk factors associated with both DM and cancer. DM pathogenesis have also been highlighted which trigger tumor initiation and progression. There are some anti-diabetic drugs which also play significant role in cancer chemoprevention and we have summarized the role of these antidiabetic drugs in cancer prevention in this article.

Occurrence of cancer in diabetic conditions

Both DM and cancer are epidemic diseases worldwide. Most commonly diagnosed cancers are breast cancer, lung bronchial and colorectal cancer but the common causes of cancer deaths are liver, lung and stomach cancer [13]. Nowadays, the prevalence of DM and cancer in same individual is frequently more as compared to occur by chance in expected people. Both diseases are very life threatening and complex along with their subtypes [16]. Whereas, cancer is divided into subtypes according to its anatomic origin within which it has several subtypes. Recent studies show that various types of cancers occur with DM but prostate cancer is least commonly occurred. The relative risk included by DM is higher for liver, endometrium and pancreatic cancer and less commonly for the breast, colon/rectum, and bladder cancer [17]. Insulin is transferred to the liver through a portal circulation. The evidences show that the risk of cancer is increased by glucose intolerance and insulin resistance [18]. Abnormal glucose metabolism may be the outcome of pancreatic cancer. Both liver and pancreas are revealed to high concentration of insulin [19]. Susceptibility of liver cancer is enhanced by DM-related factors such as liver cirrhosis and non-alcoholic fatty liver disease [20]. Studies suggest that main correlation between DM and pancreatic cancer is when restricted to proper treatment is accompanied for the therapy of DM [21]. Studies have shown that DM significantly elevate mortality rate in cancer patients. For

example, patients diagnosed with both DM and cancer, show high mortality as compared to those having no DM [14].

Risk factors habitual to both cancer and diabetes mellitus

Risk factors that are habitual to both cancer and DM [22], have been classified into two types i. e., non-modifiable and modifiable.

Non-modifiable risk factors

Age

The occurrence of cancers expands with age. Although, the incidence of some cancers apex in childhood, young, and/or adulthood [22]. In developed countries, 78% of newly diagnosed cancer is approximately found in individuals of 55 years age. In association with age, DM is also common with increasing age. In parallel to age, obesity-induced T2DM become more frequently common in adolescents and young adults [23].

Sex

With increasing age, men are higher risk of DM as compared to that of women. Similarly, men also have higher incidence of cancer as compared to that of women [14]. Certain cancers are sex-specified that more frequently exposed in men e. g., testicular and prostate malignancies and in women breast, uterine, and ovarian cancer [24]. Study suggest majority of women (78.68%) also pinpoint using blood sugar lowering medications, and notably these women had a 2-fold higher rate of breast cancer [25].

Race/ethnicity

The incidence of cancer and DM varies notably among the populations of different endemics. Different factors that contribute variably in the occurrence of major risk factors are medical practices such as completeness of reporting and screening and genetic factors [19]. African and American are more prone to develop and die with cancer as compared to other race and ethnicity [26]. In United States, T2DM and its complications such as different type of cancer disproportionately affect several specific populations, including African American, Asian American, Hispanics, and Native Americans [27].

Modifiable risk factors

Diet

Diet is the major risk factor that contributes mainly in the occurrence of both DM and cancer. Studies suggest that processed meats and low in red and higher in fruits, whole grains and vegetable are associated with lower risk of cancer [16]. Diet with low processed meat and high in unsaturated fatty acids, vegetable fruits and whole grain cereals and dietary fibers may protect T2DM and improves insulin sensitivity. Diets with low carbohydrate have also been associated with improvement in glycemic control, insulin sensitivity and weight loss [13].

Physical activity

High level of physical activity is associated with modest risks of DM and also lower risk of colon, endometrial and post-menopausal breast cancer. Physical activity is also beneficial in cancers including aggressive prostate cancer, breast cancer and colorectal cancer [28]. Physical activity plays a protective role in DM. Observational data has suggested that physical activity such as daily walking routine at least 30 min in 5 days a week reduce the risk of developing T2DM [29].

Tobacco smoking

Experimental studies have found that tobacco smoking accounts for 70% respiratory-related cancers like trachea, bronchus and lung which lead to death are due to smoking. Other types of cancers such as larynx, leukemia, stomach, upper digestive tract, liver, kidney, pancreatic, bladder, cervix, uterine, and cervix, are correlated with tobacco smoking [15]. These studies exhibit that smoking is a major risk of induction of DM and cancer. It also increases the other risks like retinopathy, cardiovascular, and other complications of DM [30].

Alcohol

Alcohol consumption affects both DM and cancer. Excess consumption of alcohol is a considerable risk factor for DM both in men and women [23]. While, alcohol consumption in moderate amount, may elevate the risk of many type of cancers such as oral cavity, larynx, pharynx, esophagus, colon, liver, rectum, and female breast [30, 31].

Obesity and weight changes

The ideal and normal body mass index (BMI) is 18.5 to < 25 kg/m^2 and have less risk of many type of cancers as compared to that of overweight (BMI ≥25 kg/m^2 and < 30 kg/m^2) or obese individuals (BMI ≥30 kg/m^2) [30]. Studies conducted over a decade, have consistently indicated a strong correlation between the insulin resistance, obesity and T2DM. Studies have also found that cancer including breast, colon/rectum, endometrial, pancreas, esophagus, kidney, liver, and gallbladder, is associated with overweight likewise T2DM [24]. In women suffered with cancer, obesity may also increase the risk of mortality. Weight gain with increased adipose tissue, is majorly correlated with increased risk of cancer during the adulthood [21]. Therefore, it is better to measure the risk of cancer by total body fat than BMI.

Biological association between diabetes mellitus and risk factors of cancer

Studies suggest that cancer and DM are two common conditions and incidence of both diseases is co-diagnosed in some individuals that can be accepted. T2DM is most commonly correlated with increased risk of cancer of kidney, cancer, pancreas, and breast [32]. In diabetic patient with hyperinsulinemia and insulin resistance might promote the incidence of carcinogenesis immediately through insulin receptor and insulin-like growth factor (IGF) via involvement of inflammatory processes, disrupting adipokines homoeostasis, and sex hormone [20]. In T2DM patient with high concentration of insulin is also capable of activating insulin like growth factors I receptor (IGF-IR), these receptors are expressed virtually in all tumor cells, however insulin effect cancer cell directly and indirectly. Epidemiological study has shown that tumors fail to grow in animals with type 1 diabetes, despite markedly elevated blood glucose levels caused by the destruction of insulin producing β-cells [33]. Interestingly, another epidemiological study has demonstrated that administration of exogenous insulin restores tumor growth in rodents with type 1 diabetes [34]. Furthermore, the pharmacological blockage of IR and IGF-IR reduces the accelerated tumor growth in diabetic animals [35], thus supporting a pathophysiological role of hyperinsulinemia in the tumor promoting activity of TDM. Carcinogenesis is a complicated process in which normal human cell under multiple genetic hits undergo multiple stages such as invasion, and metastasis before the full neoplastic phenotype of growth [28]. In the transformation of cancer, initiation (irreversible step), promotion (stimulation of growth of initial cells), and progression (development of more aggressive phenotype of promoted cells) take their part (Figure 1).

Role of insulin and insulin like growth factor in occurrence of cancer

Fundamentally, insulin is related to a growth factor that is known as IGF and elevated level of insulin has shown a major risk factor for a wide variety of cancer. Insulin and IGF bind with their respective receptors but due to the huge similarity in their structure, hybrid receptors may likewise exist. Insulin receptors and IGF receptors construct an intricate network of receptors on the cell surface, such as homo-dimers and heterodimers. Insulin has high affinity to bind with insulin receptor A and B, while, less affinity for IGF receptors and no affinity for hybrid receptors. Both IGF-I, IGF-II and insulin have affinity respectively for IGF-IR and IGF-2R and activate intrinsic tyrosine kinase activity with different potencies [36]. Both receptors involved in the mediation of insulin and IGF response [18]. Generally, mitogenic (proliferation, cell survival, and growth) signaling pathways are initiated by the binding of ligands to insulin receptor A or receptor of IGF-I, while metabolic signaling is activated by ligand binding to insulin receptor B. Mitogenic/metabolic signaling of hybrid receptor depends upon insulin receptor isoform that constitute the hybrid receptor [37]. Most of the cancer cells constitute receptors of insulin and IGF-I. Commonly expressed form of insulin receptor is A isoform. Insulin-mediated mitogenesis is generated by receptor A isoform via auto-phosphorylation of adapter proteins, even in the cells deficient in IGF-I receptors by integrating with their respective ligands which mediate different signaling pathways [38]. Insulin in human body may apply mitogenic impact through IGF receptors. People with epithelial cancers, like prostate, breast, and colon cancer have increased levels of circulating IGF-I [39]. A late overview demonstrated that females having increased concentration of IGF-I are more liable to occurrence of cancer in contrast to those having low concentration of IGF-I [40].

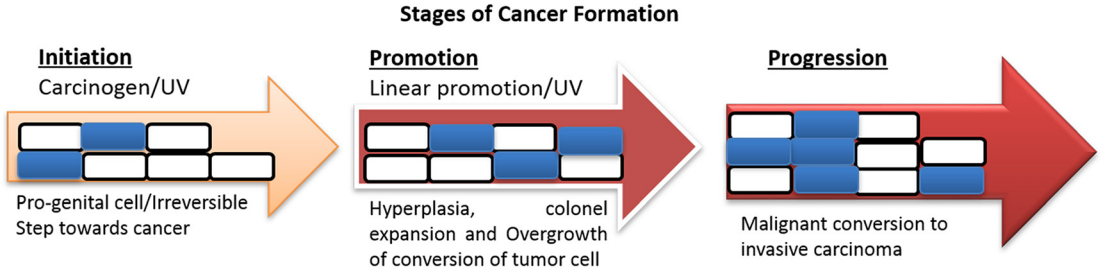


Figure 1: Cancerous cell undergoes through various stages. The first initiation stage is triggered by some carcinogen/UV radiations. It is an irreversible step toward cancer cell proliferation. During second promotion stage, there is a hyperplasia resulting in expansion of tumor. In third progression stage, cancerous cells penetrate to the surrounding tissues resulting in benign to malignant transformation.

Hyperinsulinemia decreases the production of IGF-I binding protein from the liver. Thus, less amount of IGF-I will bind with its respective protein and greater amount of free IGF-1 in systemic circulation (Figure 2). IGF-I possesses powerful mitogenic and anti-apoptotic ability [41, 42]. Most of the cancer cells express insulin receptor and IGF-1R [43]. Increased level of circulating insulin reduces the hepatic synthesis of sex hormone binding globulin. Due to decreased production of this binding globulin, there is increased level of free estrogen in circulation with subsequent increased bioavailability. It is evident from literature that elevated endogenous sex hormones are strongly associated with higher risk of risk [44, 45].

Impact of hyperinsulinemia on hormones

Hyperinsulinemia increases the estrogen level in female by reducing sex hormone binding globulin (SHBG) and increase aromatase activity [19]. Hyperinsulinemia has indirect effect on sex hormones including SHBP synthesis in liver and their concentration in blood, elevated level of estrogen in men and women, and greater level of testosterone in women only [23]. These elevated levels of estrogen are associated with increased risk of breast, post-menopausal, and other cancers [23].

Association of hyperglycemia with occurrence of cancer

It has been found that glucose act as a significant mediator while considering the multifaceted nature of connection between DM and cancer [30]. This underscores the reliance of numerous cancers on glycolysis for energy, which in turn increases the glucose level that results in more ATP generation via glycolysis than oxidative phosphorylation [13]. Indeed, tissue with high glucose uptake is detected by F-fluorodeoxy glucose positron emission tomography of cancer. Therefore, untreated hyperglycemia facilitates neoplastic proliferation [21]. *In vivo* model demonstrates that hyperglycemia do not prompt the neoplastic progression at least in insulin deficiency when tumor progression is decreased during type 1 diabetes mellitus [29]. It has been reported that hyperglycemia may act as a causative factor for the occurrence of cancer [46].

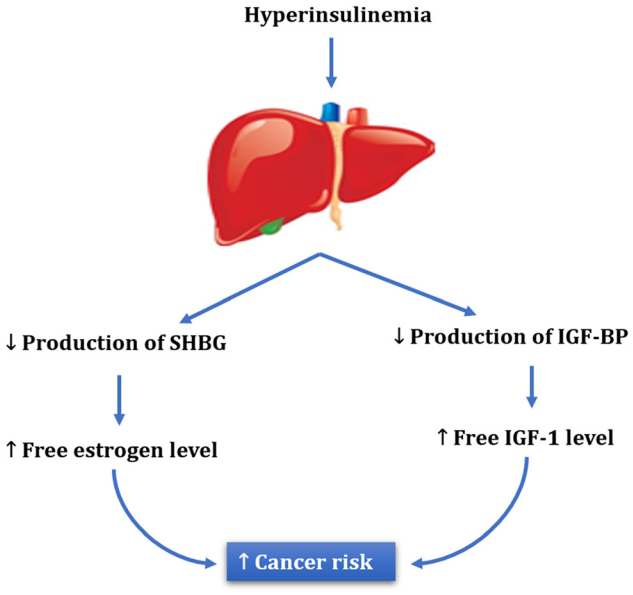


Figure 2: Hyperinsulinemia decreases the production of IGF binding protein-1 (IGF-BP) and sex hormone binding globulin (SHBG) with subsequently increased level of free IGF and estrogen which elicit the mitogenic effects.

Role of inflammatory cytokines in pathogenesis of diabetes and cancer

Inflammatory cytokines are foremost elements which promote neoplastic cell division, growth, invasion and survival, and also repress the anti-tumor immunity of the host cell [47]. Adipose tissue is dynamic endocrine organ which generates monocytes, interleukin-6, fatty acids, plasminogen activator inhibitor-1 (PAI-1), chemoattractant protein, tumor necrosis factor alpha, and adiponectin [48]. Each of these factors play crucial role in different steps of cancer transformation including malignant transformation and cancer progression [49]. For example, IL-6 is major risk factor for cancer. IL-6 enhances the neoplastic cell division, growth, invasion, survival, and also represses human anti-cancer immunity by triggering the signaling of transcription protein (STAT) and activates signal transducer.

Role of antidiabetic agents in the prevention of cancer progression

Metformin

Metformin belongs to biguanides and is most widely used for the treatment of DM. Metformin produces its systemic effects by suppressing gluconeogenesis in liver which decreases the blood glucose level. It also enhances the uptake of glucose by the muscles [50]. Furthermore, dose response relationship between metformin and cancer induction depends upon the exposure duration [51]. Observational and retrospective studies revealed that metformin treatment decreases cancer incidence and mortality rate in patients

with T2DM [52]. Metformin comparatively lessen the danger of cancers particularly prostate, breast and pancreatic cancer [52]. Association between metformin and reduced risk of cancer in T2DM patients may be explained by the improvement in blood glucose and insulin level by metformin [53].

Mechanism of cancer growth inhibition by metformin

AMPK/mTOR axis

Metformin directly affects the cancer development by the activation of AMPK/mTOR pathway by controlling the cellular proliferation through subsequent modulation of downstream pathways. Small interfering RNA (sRNA) knockdowns the AMPK or AMPK inhibitor's revert the antiproliferative action of metformin in many types of cancer such as ovarian and breast cancer [54]. Metformin activity on AMPK/mTOR pathway is provoked to contrast the tumor frequency among the users and non-users of metformin. Epidemiological studies show a decline in cancer incidence with the use of metformin in patients with DM [51]. In cancer cell, metformin plays a vital role in AMPK/mTOR energy sensor pathway, which shows that metformin interacts with energy metabolism and protein synthesis in cells. LKB1 is a serine threonine kinase which acts as a tumor suppressant and controls AMPK/mTOR pathway [55]. Metformin has antineoplastic activity through AMPK pathway leading to suppression of mTORC1 signaling which results in the inhibition of protein synthesis and cell proliferation [56]. AMPK cause the suppression of mTORC1 signaling pathway at different stages such as phosphorylation of regulatory proteins of mTOR (RAPTOR), phosphorylation of tuberous sclerosis (TSC_2) on ser^{1345} and conducting the aggregation of rheb-GDP which is the inactive form of it, It cuts of its connection with mTOR and thus inhibits activation of mTORC1 [57]. Activation of AMPK by metformin breaks up the cross linkage in pancreatic cells between G-protein coupled receptors (GPCK) and insulin/IGF-1 [58]. LKB-1 mutation is linked with increased tumor risk such as Peutz–Jeghers syndrome which is autosomal syndrome characterized by benign gastro-intestinal polyps (hematomas) and enhanced risk of tumor caused by mutation in LKB-1. The cells lacking LKB1 are more sensitive to energy stress induced by metformin. When grown in hypoglycemic culture, they remain unable to adjust with reduced cellular ATP concentration and lead to death [59]. Energy detecting kinase AMPK, which is activated in response to cellular stress through phosphorylation by upstream kinase, depletes energy level of cell and elevates ATP to AMP ratio. Both in normal cells and in cancer cells, metformin causes the activation of energy sensing kinase perhaps due to complex-1 inhibition [60]. Suppression of mTOR pathway through tuberous sclerosis-2 protein (TSC-2) occurs as a result of AMPK activation. mTOR has a vital role in modulating the cell growth by mediating mRNA translation and synthesis of ribosome through the up-regulation of energy depleting processes of cell. It has been proposed that metformin inhibits the cell proliferation and energy consuming pathway by the activation of AMPK [54].

Another mechanism of action of metformin is the regulation of fatty acid synthesis controlled by AMPK. FAS is a fundamental enzyme used in the biosynthesis of fatty acids and has been linked with cancerous phenotype [61]. Cells derived from cancer cell such as prostate, breast and colon cancer constitutively overexpressed in FAS. Activation of APMK diminishes the growth and viability of prostate cancer cells by decrease in FAS and ACC expression [51]. Another potential mechanism of metformin is its positive effect over chronic inflammation which is a prime factor in tumor development and procession [62]. Metformin also causes the reduction in tumor through AMPK-mediated inhibition of inflammatory response by targeting the inflammatory elements present in neoplastic tissues [46]. Metformin also affect the neoplastic angiogenesis which may also cause the reduction in tumor growth. It also has a prime role in the reduction of PAI-1 and vascular endothelial growth factor (VEGF) [48].

AMPK is activated by AICAR (5 amino-4imidazole-carboxamide riboside-1-β-D-ribofuranoside) patient who was bearing HCT116 tumor xenografts are treated with AICAR or PBB and tumor size is calculated over a time span. Average volume of tumor was reduced by 50% by treating with AICAR [63]. Epidemiological study suggested that there is considerable reduction in tumor size especially in p53 by daily treatment of AICAR [52]. Importance of AMPK for autophagy inducted by metformin (Figure 3) shows that treatment with metformin causes replacement of LC3 in $AMPK^{+/+}$ cells and shows no substantial change in $AMPK^{-/-}$ cell [60].

Activation of fatty acid oxidation

In hypoglycemia, metabolic reprogramming is indicated by fatty acid oxidation. Treatment with metformin or AICAR causes the stimulation of β-oxidation of fatty acids which is controlled by p53 [54]. Treatment with metformin has been described to suppress respiratory complex-1 in hepatocytes and rate of oxygen uptake. Metformin and AICAR affect the oxygen consumption and fatty acid oxidation in HCT116 $p53^{-/-}$ and $p53^{+/+}$ cells [51]. p53 is involved in cell metabolism and AMPK regulates p53 expression and phosphorylation. There is the inhibition of growth of HCT116 p53 xenografts with the treatment of metformin. Anti-diabetic drugs inhibit the tumor growth by

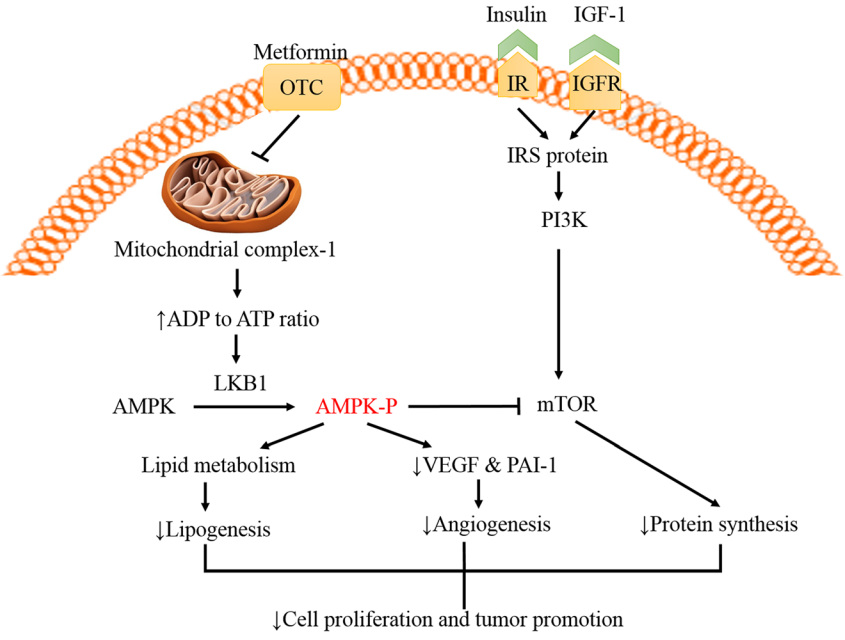


Figure 3: Proposed mode of action of metformin involved in cell proliferation and metabolism. Metformin uptake is done through OCT. It increases the ADP level through inhibition of the mitochondrial respiratory chain complex 1 leading to activation of AMPK. Activated AMPK may disrupt gene expression involved in lipogenesis, protein synthesis and angiogenesis. Abbreviations: IGF, insulin-like growth factor; LKB1, serine-threonine liver kinase B1; mTOR, mammalian target of rapamycin; PAI-1, plasminogen-activator inhibitor-1; PI3K, phosphoinositide 3-kinase; VEGF, vascular endothelial growth factor; adenosine monophosphate-activated protein kinase AMPK; OCT, organic cation transporter; IR, insulin receptor.

loss of wild type P^{53} in untreated animals with accelerated cancer generation [64]. Metformin reduced the growth of tumor in paired isogenic colon carcinoma cell line (HCT116 $p53^{+/+}$ and $p53^{-/-}$). Mean tumor burden of $p53^{-/-}$ xenografts was 50% lesser after one-month treatment with metformin. In controlled and metformin-treated mice having $p53^{+/+}$ tumor, metformin does not exhibit any effect on tumor volume, but in cells with $p53^{-/-}$ xenografts, metformin exhibits systemic effect on growth, as anti-diabetic effect of metformin depends upon AMPK. Analysis of autophagy makers in $p53^{+/+}$ and $p53^{-/-}$ Cells after treatment with metformin or AICAR shows that in nutrients depletion situation, growth factor mitophagy is a pathway for cell survival [65]. In patients with $p53^{+/+}$ tumor who were treated with metformin showed substantial increase in autophagosome positive cells. During autophagy, LC3 protein which is a microtubule light chain linked protein cleaved into membrane bound form LC3-II from cytosolic full length form [66]. The Appearance of LC3-II form in HCT116 $p53^{+/+}$ and $p53^{-/-}$ Cells activate autophagy [65]. When treated with metformin, in $p53^{+/+}$ cells, there is noticeable increase in conversion of membrane bounded LC3-II proteins from LC3-1 as compared to that in $p53^{-/-}$ cells. It is recently observed that p53 depends upon AMPK. AMPK targets and activates p53 which induces AMPK dependent Autophagy. The activation of P^{53} is also affiliated with enhanced aggregation of LC3-II [57, 65].

Metformin-induced glycolysis in p53 dependent manner

Metformin induces glycolysis when mitochondrial respiration is improper. The increased rate of glycolysis compensates the enhanced energy requirement for biogenetic processes. After treatment with metformin, consumption of glucose and lactate production are measured by MEF in $p53^{-/-}$ and $p53^{+/+}$ cell lines [57]. Oxygen consumption and lactate production was measured by dose-response manner. On the other hand, no glucose consumption and lactate production was observed in the cells that were lack of p53 [53].

The combination of 2-deoxyglucose and metformin at cellular level induced p53 apoptosis via the energy sensor pathway AMPK kinase, in p53-deficient prostate cancer cells restored caspase-3 activity by re-expression of a functional p53 [67]. 2-Deoxyglucose is an inhibitor of glucose metabolism, because it inhibits hexokinase, the first rate limiting enzyme of glycolysis [68]. It leads to intracellular energy depletion, a cell survival response lead to nutrient deprivation [69]. 2DG has been considered as a potential anticancer agent, because of tumor dependence on glycolysis, and association of chemotherapeutic agents and 2DG has been successfully in mice [69]. Furthermore, retrospective epidemiological study revealed that patients treated with metformin, a decrease in the incidence of cancer [70, 71]. Metformin similarly to 2DG, inhibits the energy sensitive signaling pathways mTOR and effect cell metabolism. It hampers the respiratory chain complex 1 in hepatocytes and inhibits oxygen consumption in colon cancers cells [28, 72].

Troglitazone

Last decade, a new class of anti-diabetic drug termed as thiazolidinedione has been developed and this class of

drug widely used for insulin resistant DM. This drug reduces elevated plasma glucose level and improves insulin resistance perhaps by stimulating the activity of glucose transporter in cell. Troglitazone belongs to thiazolidinedione family and a specific ligand for PPARɣ [73]. Troglitazone enhances the insulin sensitivity by activating the PPARɣ. Different body parts show higher expression of PPARɣ. PPARɣ is a member of nuclear receptor superfamily and function as a master regulator of adipogenesis. It is highly expressed in adipocyte and induces differentiation of several pre-adipocyte cells. Adipocyte differentiation results in the expression of PPARɣ in fibroblast and myoblast cells [73]. PPARɣ combines with RXRα to constitute a heterodimer which binds with DNA response components in the presence of ligand and helps to modulate the target gene expression. Previous studies suggest that prostaglandin, prostaglandin like molecule and arachidonic acid are metabolite activate PPARɣ [74]. Studies have shown that adipocytes differentiation promoted by enhancer binding protein transporter factor and CCAAT [75]. Troglitazone induces differentiation of adipocytes. Prostate cancer cells exhibit high concentration of PPARɣ as compared to that of normal prostate tissue [76].

PPARɣ belongs to the nuclear receptor superfamily which includes retinoid, thyroid hormone receptors and vitamin D3 each of which is vital for cellular growth and differentiation. PPARɣ is a heterodimer to RXRα and bind to its ligand. Studies have suggested that PPARɣ expressing cells including adipocytes, myoblast, fibroblast, liposarcoma and breast cancer cells induce their terminal differentiation activated by PPARɣ ligands [77]. Potentially, PPARɣ has the ability to lower the blood sugar level and prominently transactivate the target gene [78]. It has been reported that breast cancer and liposarcoma cells are differentiated by PPARY and RXRα agonist. These finding suggest that PPARɣ and RXRα ligand might induce the differentiation of these cells [77]. This evidence suggests that elevated prostate cancer cells are potential target by thiazolidinedione because these prostate cancer cells are also expressed PPARɣ (Figure 4). In addition proliferation of prostate cancer cell is inhibited by RXRα selective retinoid [79]. Troglitazone and retinoid have no synergistic activity but troglitazone itself demonstrated as a powerful anti-proliferator on fast growing androgen independent PC-3 prostate cancer cell [75]. Troglitazone has a powerful necrotic effect on fresh human prostate cancer cell. Both have no demonstrable activity on normal human prostate cells. Troglitazone may act as a promising adjunct in treatment of prostate cancer when taken together [76]. Western blot and RT-PCR data show that prostate cancer

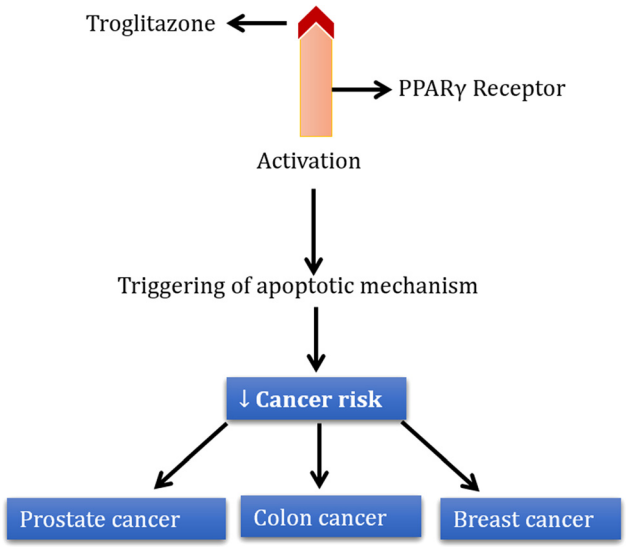


Figure 4: PPARɣ receptors are abundantly expressed on various cancerous cells notably prostate, breast and colon cancer. Trioglitazone acts as an agonist for PPARɣ receptors. Once the receptors are activated following the attachment of agonist (trioglitazone), it induces the apoptosis in cancerous cell.

cells express PPARɣ [80]. It has been reported that PPARɣ and RXR agonist suppress the proliferation of prostate tumor by the induction of differentiation [75]. Like troglitazone, RXR agonist also has anti-proliferating activity against prostate cancer cells especially which is used clinically for treatment of acute promyelocytic leukemia [76]. When troglitazone is used in combination with RXR ligand i. e., LG100268, a mild additional inhibition of cancer cells occurred. Troglitazone alone is more effective against prostate cancer when it is used with ATRA [81]. This evidence shows that troglitazone and ATRA exhibit their anticancer effects against prostate cancer by same mechanism [82].

Conclusion

The findings discussed here in this article indicate that DM is itself a risk factor for the occurrence of cancer. It is valuable model for studying the role of hyperinsulinemia and insulin resistance in tumor development and progression. The tumor promoting activity of T2DM is also attributed to hyperglycemia. The splendid anti-hyperglycemic activity of anti-diabetic drugs such as metformin and troglitazone along with their pronounced effect on important characteristics of metabolic syndrome make them a spectacular therapy for normal and complicated conditions of hyperglycemia and cancer.

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