

Diabetes & its Complications

Anti-Diabetic Drugs & Cancer Risk Challenge

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ABSTRACT

Increasing evidences of cancer development in diabetic patients were reported. Many studies demonstrated a correlation between some anti-diabetic drugs and a higher risk of cancer incidence. The highest incidence was shown in liver cancer and pancreatic cancer then kidney, endometrial, colorectal, non-Hodgkin lymphoma, bladder, and breast cancers. Meta-analysis of cohort studies calculating the relative risk (RR) of all-site or site-specific cancers in diabetic patients were accomplished notifying a different RR according to sex.

Mechanisms suggested by authors were related to diabetes itself whether being complicated or a non-adherence to anti-diabetic medications. Obesity-related hyperinsulinemia acts as a critical link to the increased cancer risk through mitogen pathway activation and the enhanced cellular growth and survival. On the other hand, the influence of anti-diabetic medications itself on cancer has recently gained attention. Studies reported evidences that using metformin, as an insulin sensitizer, may decrease cancer development, progression, and mortality. However, treatment with insulin secretagogues, insulin analogues, thiazolidinediones, and some incretin-based therapies are related to increased incidence of development and mortality related to cancer. Currently there is no sufficient evidence to force withholding of certain anti-diabetic drugs' use on the basis of cancer concern. So, cancer risk assessment is a useful primary prevention tool in selecting a suitable anti-diabetic drug(s).

Identification of the individuals at increased genetic or environmental risks of cancer by diabetes physicians should be done. Web-based tools for collecting and predicting individual risks of certain cancers and familial syndromes are easily accessible. Individuals with a high likelihood of having an inherited syndrome should be seriously considered for referral to the cancer genetics professional for further work-up. Special attention should also be paid to potentially modifiable cancer risk factors regarding a healthy lifestyle.

Nevertheless, to reduce the cancer risk associated with anti-diabetic medications' use, treatment with metformin is recommended throughout the course of the disease as long as it is medically acceptable. Also, strong efforts to reduce excess of body weight should be taken. The selection of other anti-diabetic classes as an add-on treatment to metformin is based on cancer risk assessment and review of cohort studies and met-analyses reports on their associated cancer RR.

Keywords

Diabetes, Cancer risk, Anti-diabetic drugs, Cancer risk assessment.

Introduction

Diabetes ranks in the top ten causes of disability worldwide and undermines productivity and human development [1]. As diabetes prevalence continues to rise worldwide, it aroused public health concerns about its morbidity and mortality [2]. According to the International Diabetes Federation, the prevalence of diabetes on

a global scale could reach 530 million people in 2030 [1,3]. This global epidemic of people with type-2 diabetes is largely due to population growth, aging, urbanization, obesity and physical inactivity [4,5]. Glycemic control in patients with DM is associated with significantly decreased rates of microvascular (retinopathy and nephropathy), neuropathic complications and reduction in the risk of cardiovascular morbidities [3,4].

The association between diabetes and cancer was described as far

back as 1885 [2]. Since the first few reports on increased incidence of cancer in insulin-treated type-2 diabetic patients, there are ongoing debates regarding the association of insulin use with cancer. Accordingly, the American Diabetes Association and the American Cancer Society reviewed a number of issues regarding the association between diabetes and cancer, including diabetes treatment and cancer risk [6].

Diabetes has been recognized as a key factor contributing to the development of solid organ malignancies [2]. The strongest cancer association to type-2 DM in both sexes involves those of the liver and pancreas, creating a risk dilemma [2,7]. Descriptive clinical studies confirmed the increased prevalence of hepatocellular carcinoma (HCC) in patients with diabetes, as well as, an increased prevalence of diabetes in patients with HCC [8].

In Egypt, HCC is the second most common cancer in men and the 6th most common cancers in women. Since, approximately 80% of HCCs develop in cirrhotic livers, a rising incidence had been reported in Egypt mostly due to high prevalence of viral hepatitis and its complications. However, this incidence is boosted by the emerging association between DM, cirrhosis and HCC; as according to WHO statistics in 2008, it was estimated that 7.4% of Egyptian females and 7% of Egyptian males above the age of 25 years have elevated blood glucose [9,10].

Common modifiable risk factors for cancer are related to obesity and dietary habits. Central obesity has been linked to breast, colorectal, liver, and endometrial malignancies. Dietary choices high in carbohydrates load and saturated fat and low in fiber accompanied by reduced physical activity also increase the risk for type-2 DM and malignancy, particularly for the colon, endometrium and breast. Habits: tobacco and excess alcohol usage are linked to cancer and also worsen diabetes complications [11].

Anti-diabetic drugs and cancer risk

Both comparative and cohort studies were done to investigate the relationship between anti-diabetic pharmacotherapy and cancer incidence and mortality due to cancer [12]. Using statistical regression analysis metformin use showed reduced cancer risk, while elevated risk associated with insulin use was significant only in univariate regression analysis. Insulin and sulfonylurea derivatives in monotherapy were associated with significantly higher cancer risk compared to metformin monotherapy, while in combination with metformin this risk was non-significant [13]. So, it is recommended, to minimize cancer risk associated with antidiabetic medications' use, metformin should be continued as long as medically acceptable and it should be combined with insulin or SU to neutralize risk associated with using either of the latter drugs in monotherapy [13].

Metformin as a mitochondrial energy modulator through reversible inhibition of NADH dehydrogenase (mitochondrial complex I) of the respiratory chain by repressing efficient coupling of the redox and proton transfer domains resulting in suppression of ATP production [14]. Compared to normal cells, cancer cells appear

to have a greater glucose uptake, even when oxygen is present. Otto Warburg hypothesized that cancer was a metabolic rather than a genetic problem [15]. Cancer cells exhibit alterations in mitochondrial metabolism due to increased oxidative stress, when positron emission tomography was used to locate glucose dependent cancers in the decision for the use anti-cancer drug-glucose conjugate selective delivery. As certain tumors function and thrive purely on glucose. Hence, disruption of glucose dependent energy production leads to cancer cell apoptosis [14,15].

Adenosine monophosphate-activated protein kinase (AMPK) is a fuel-sensing enzyme that is activated in shortage of energy. The AMPK activation stimulates fatty acid oxidation, enhances insulin sensitivity, alleviates hyperglycemia and hyperlipidemia, and inhibits pro-inflammatory changes [24]. Cell growth and proliferation are energetically demanding, and AMPK may act as an "energy checkpoint" that permits growth and proliferation; thus, it was reported to play a role in linking metabolic syndrome and cancer. The identification of a complex containing the tumor suppressor Liver kinase B1 (LKB1) as the critical upstream kinase required for the activation of AMPK by metabolic stress represented the first clear link between AMPK, metabolism and cancer [2,6,16,17].

Metformin triggers multiple pathways exerting anticancer activities which are mediated through AMPK-dependent and independent pathways [18]. The activity of a tuberous sclerosis complex-2 (TSC2) is modulated by AMPK, TSC2 together with TSC1 form a tumor suppressor complex that inhibits mTORC1. The latter regulates protein synthesis and cell survival by directly activating two important targets involved in this process, such as S6 kinase and translation initiation factor 4E binding protein [19].

Furthermore, activation of AMPK by energy shortage reprograms cellular metabolism and enforces a metabolic checkpoint on the cell cycle. Loss of such a checkpoint could lead to unrestrained cell growth [16].

At gene level, AMPK stimulates cell cycle arrest through p53/p21 axis and the metabolic reprogramming induced by metformin seems to be p53 dependent. On the other hand, metformin inhibits the PI3K/Akt/mTOR signaling pathway in an AMPK-independent way by modulating Rag GTPase activity. It prevents DNA damages through the modulation activity of checkpoint homolog kinase-2 [18]. Besides AMPK critical roles in regulating growth and reprogramming metabolism, it has been connected to other cellular processes such as autophagy, apoptosis, and cell polarity [19,20].

Pioglitazone, being a peroxisome proliferator activated receptor gamma (PPAR- γ) agonist from Thiazolidinediones (TZDs), it increases insulin sensitivity by regulating the expression of a variety of genes involved in carbohydrate and lipid metabolism. By increasing hepatic and peripheral insulin sensitivity, pioglitazone inhibits gluconeogenesis and ameliorates peripheral glucose uptake. Moreover, it decreases the adipocyte production of several mediators causing insulin resistance, such as TNF- α and

resistin [21]. Similar to metformin, pioglitazone-induced AMPK activation in various tissues was addressed in several studies and was determined to be a direct process independent from PPAR- γ activity [22-25]. This might be due to increased expression of adiponectin with its downstream signals that activate AMPK through increasing the AMP/ATP ratio [26]. Pioglitazone is known to enhance circulating adiponectin levels 2–4 fold. TZDs function by inducing transcription of adiponectin via PPAR γ . They have also been found to enhance secretion of folded adiponectin by inhibiting ERp44 and upregulating Ero1-La and DsbA-L. Interestingly Androgen blockers have also been proven to be effective at increasing HMW adiponectin and can be used in cases of prostate cancers [27].

Pioglitazone treatment results in a redistribution of fat from the metabolically deleterious visceral adipose tissue to the more inert subcutaneous (SC) fat depots. Therefore, in light of the antidiabetic effects of TZDs, which occur in the presence of both an increase in and distribution of adipose mass, studies were performed to better understand the nature of the TZD-induced adipose remodeling [28]. So it can be hypothesized that TZDs can reverse diabetes esp. early diagnosed and further studies are essential for the development of a more selective and safe PPAR- γ agonist.

Studies of the association between pioglitazone and bladder cancer have been contradictory [27,28]. The IRIS [Insulin Resistance Intervention after Stroke] trial in 2016, found an increased number of new bladder cancers in the pioglitazone group compared with the placebo group 12 (0.6%) vs. 8 (0.4%) but the difference was not statistically significant. A 10-year observational follow-up study, the PRO-active trial in 2016 reported that pioglitazone users had a 35% decreased risk of bladder cancer and a 47% increased risk of prostate cancer compared with placebo recipients. However, rosiglitazone has not been associated with substantial differences in cancer risk [29,30].

Sulfonylureas (SUs) as insulin secretagogues, they increase insulin level, and activate the IGF-1/IGF-1R pathway, hence were hypothesized to have possible pro-cancerous mechanism. (2,31) Nevertheless, previous studies on SUs were supporting an anti-cancerous but no specific mechanism was identified. These KATP channel closers differ in their anti-oxidant potential; that varies from interference with reactive oxygen species (ROS) production, increase of plasma antioxidants, and free radical scavenging. The anti-oxidant potential, is thought to decrease the ROS-mediated damage in the host cells, which constitutes a part of its cancer control mechanisms; as oxidative stress is known to activate apoptosis signaling pathways subsequent to K⁺ efflux [33].

It was reported that gliclazide and glibenclamide were related to a 35% reduced liver cancer risk, whereas, glipizide was related to a 16% increased cancer risk [32]. However, data on glimepiride associated risk is scarce in literature, in spite its wide use among SUs class of antidiabetic drugs. Differences in cancer risk among sulfonylureas have been suggested and warrant further research [31,33-37].

Incretin based therapies: Dipeptidyl peptidase 4 inhibitors (DPP4i) increased risk of acute pancreatitis and pancreatic cancer associated with DPP4i; nevertheless, controversies over this relationship were reported in more recent studies. Furthermore, laboratory findings have raised the possibility that DPP4i can accelerate tumor metastasis [31,38,39]. Experimental studies suggest Glucagon-like peptide 1 receptor (GLP 1R) signaling promotes intestinal growth, and GLP 1R agonists may promote colonic tumorigenesis. No observational studies have been performed to address this potential relationship [31,39].

Insulin preparations

Observational studies have shown no increased risk of breast cancer in patients treated for diabetes with human insulin [31,40]. Insulin glargine use has been associated with an increased breast-cancer risk in some studies that were later criticized methodologically [41]. No increased risk of breast cancer has been detected in trials of insulin analogues, but the follow-up durations are limited [42].

Physiological concentrations of insulin show no measurable binding to the IGF-1R both in vitro and in vivo. Whereas, soluble human insulin normally binds to IR-A and B. The former signals its mitogenic and anti-apoptotic signaling, while IR-B is associated with cell differentiation and metabolic effect. It had been hypothesized that imbalance of metabolic and mitogenic actions may occur due to an increased binding affinity or duration of long-acting insulin analogs for IGF-1R that predominantly activate the mitogenic signaling [43].

Other antidiabetic agents

Gaps in our knowledge exist with the use of α glucosidase inhibitors, meglitinide, colesevelam, and sodium glucose transporter 2 inhibitors in relation to cancer risk or prognosis [31].

Cancer risk assessment

Cancer risk assessment tools (RAT) are important cancer primary prevention tool used in screening. They are variable among countries due to different risk factors whether being genetic, environmental, and dietary or habits-related. Hence, there are specific country designed RATs ideally done at primary health care level and depends on screening for abnormal symptoms related to cancer especially for individuals with back ground hereditary susceptibility or had an exposure risk to develop cancer due to certain viral infections, smoking, precancerous lesions and recently are for diabetic patients and obese individuals [44-51].

These RATs are either check-listed algorithm in a certain screening form and the absolute risk is manually calculated or are web-based online calculators with special forms to each sex [47,50]. Following risk calculation there are safety netting measures to follow and timely refer the patient to a higher level of health care for confirmatory laboratory assessment by biomarkers and an expert opinion [48].

Besides the use of anti-diabetic drugs to attain euglycemia and prevention of complications in diabetic patients. They are also

used in non-diabetic patients as in polycystic ovarian disease and ketosis enhancement during ketogenic diet [52-54]. Although the assumed diabetes-cancer associated risk is less in these conditions as hyperinsulinemia or insulin resistance isn't yet fully developed, cancer risk assessment is also needed in these conditions.

Anti-diabetic drugs selection in cancer patients

A hypothetical patient with obesity, type 2 diabetes mellitus (T2DM), and breast cancer is depicted [31]. Treatment for early stage breast cancer is commenced on the background of dual antidiabetic therapy with metformin and a sulfonylurea (SU). Further dysglycaemia leads to metformin, thiazolidinedione (TZD), and a dipeptidyl peptidase 4 inhibitor (DPP4i) triple therapy for T2DM, with continuation of adjuvant hormonal therapy for breast cancer. When liver metastases are diagnosed and hyperglycaemia worsens, metformin and TZD are withdrawn; chemotherapy and irradiation are then administered as anti-cancer therapy, and long-acting (LA) insulin is prescribed to achieve better glycaemic control. Following the diagnosis of brain metastases, the patient is given steroids, necessitating the addition of short-acting (SA) insulin to antidiabetic therapy (with DPPi withdrawal) [31].

Conclusion

Nevertheless, to reduce the cancer risk associated with anti-diabetic medications' use, treatment with metformin is recommended throughout the course of the disease as long as it is medically acceptable. Also strong efforts to reduce excess of body weight should be taken. The selection of other anti-diabetic classes as an add-on treatment to metformin is based on cancer risk assessment using RATs and review of cohort studies and met-analyses reports on their associated cancer relative risk.

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