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Review article

Antidiabetic drugs and risk of cancer

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ABSTRACT

Antidiabetic drugs are an important group of medications used worldwide. They differ from each other in the mechanisms of lowering blood glucose as well as in adverse effects that may affect the course of the treatment and its efficacy. In recent years, new drugs have been discovered in order to improve the maintenance of proper blood glucose level and to reduce unwanted effects of these drugs. Their growing administration is related to the increasing incidence of diabetes observed in all countries in the world. Epidemiological data indicate that diabetes increases the risk of cancer, as well as the risk of death linked with neoplasms. It is still unknown whether this is an effect of antidiabetic drugs or just the effect of diabetes itself. In recent years there have been numerous investigations and meta-analyzes, based on both comparative and cohort studies trying to establish the relationship between antidiabetic pharmacotherapy and the incidence and mortality due to cancer. According to their findings, most of antidiabetic drugs increase the risk of cancer while only few of them show antitumor properties. Different mechanisms of action of glucose-lowering drugs may be responsible for these effects. However, most of the published studies concerning the influence of these drugs on cancer incidence were designed with some limitations and differed from each other in the approach.

In this review, we discuss the association between antidiabetic drugs used in monotherapy or polytherapy and cancer risk, and consider potential mechanisms responsible for the observed effects.
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Contents

Abbreviations: ATP, adenosine triphosphate; BMI, body mass index; CI, confidence interval; DDDs, defined daily doses; DNA, deoxyribonucleic acid; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; Egr-1, early growth response-1 transcription factor; FDA, Food and Drug Administration; GLP-1 agonists, glucagon-like peptide-1 agonists; HR, hazard ratio; IGF-1R, insulin-like growth factor 1 receptor; IR, insulin receptor; IU, international unit; mTOR, mammalian target of rapamycin; OR, odds ratio; PPAR γ, peroxisome proliferator-activated receptor gamma; *p*, *p*-value (probability value); RR, relative risk; SC, subcutaneous injection; SGLT2 inhibitors, sodium/glucose cotransporter 2 inhibitors; SIR, standardized incidence ratio; T2DM, type 2 diabetes mellitus; TZDs, thiazolidinediones.

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Introduction

Diabetes is a serious disease in which cardiovascular pathology, retinopathy, diabetic nephropathy, neuropathy and other conditions may occur. Proper glycemic control is the best prevention that slows down the progression of disease and development of associated complications [1,2]. Diabetes effective treatment has become possible since the discovery of insulin in the 1920s. While oral glucose-lowering drugs are recommended for type 2 diabetes treatment, insulin is a basic medication for type 1 diabetes and it is also used in diabetes type 2 when oral drugs are not sufficient or in some particular conditions such as pregnancy, perisurgical time or acute states, e.g. myocardial infarction. Several groups of drugs are used in monotherapy or in polytherapy of diabetes, including insulin and insulin analogs, insulin secretagogues (sulfonylureas, meglitinides, GLP-1 agonists, DPP-4 inhibitors), insulin sensitizers (biguanides, thiazolidinediones), and drugs with other mechanisms of action (alpha-glucosidase inhibitors, SGLT2 inhibitors). Although they help to maintain proper blood glucose level, their side effects may limit the use of those drugs [1,2].

Numerous epidemiological research and meta-analyzes based on both comparative and cohort studies indicate the association between diabetes and the incidence and mortality due to cancer. Elevated cancer risk in type 2 diabetes refers to liver, pancreatic, colorectal, kidney, endometrial and breast cancers [3]. Australian researchers examined the risk of site-specific cancer among people with diabetes (type 1 and type 2) compared with the general population, and linked National Diabetes Registry from 1997 to 2008 with national death and cancer registries. Significantly elevated SIRs were observed for brain, thyroid, esophageal, stomach, colorectal, pancreatic, liver, lung, endometrial and ovarian cancers, and for melanoma in type 1 diabetes while type 2 diabetes was linked with significantly increased SIRs for almost all site-specific cancers (with the highest SIR observed for pancreas and liver) and decreased risks for melanoma and prostate cancer. Elevated cancer risk was observed throughout all follow-up time, but was notably high in 3-month-period after registration [4]. This tendency may suggest the detection bias. Therefore, researchers highlighted the importance of cancer screening among patients with diabetes [3,4]. Moreover, coexistence of cancer and diabetes is related to the elevated risk of all-cause mortality (hazard ratio, HR = 1.41; 95% confidence interval, 95% CI = 1.28–1.55) compared to the presence of cancer without diabetes [5]. Whereas diabetes type 2 primarily refers to elderly patients, an increased cancer risk may also be associated with patient's age. Nevertheless, cohort study conducted by Zendehdel and colleagues showed that the risk of cancer incidence among patients with type 1 diabetes is increased by 20% (standardized incidence ratio, SIR = 1.2; 95% CI = 1.0–1.3), reflected in the elevated risk of stomach (SIR = 2.3, 95% CI = 1.1–4.1), cervical (SIR = 1.6, 95% CI = 1.1–2.2), and endometrial cancers (SIR = 2.7, 95% CI = 1.4–4.7) [6]. However, in recent years another issue has concerned patients and doctors, who would like to know whether this neoplastic tendency is an effect of using specific medications or just the effect of diabetes itself. Identifying glucose-lowering drugs that may affect the risk of cancer has become a very important task. In this paper the relation between antidiabetic drugs and cancer risk is discussed at the base of the animal and human studies, mostly after drugs registration (Table 1).

Insulin and insulin analogs

Insulin is widely used in the treatment of type 1 diabetes and some cases of type 2 diabetes when it is impossible to achieve adequate compensation of carbohydrate metabolism with lifestyle changes and oral antidiabetic drugs or in other conditions such as pregnancy, perisurgical time or sudden acute medical states, e.g. myocardial infarction. The insulin molecule is a polypeptide, consisting of two chains connected by two disulfide bonds. Initially it was prepared from animal pancreas. Currently, *Escherichia coli*, with human insulin gene implanted, synthesizes human insulin which is then purified and used. Insulin analogs are formed by modifications of amino acids in the insulin chain, resulting in changes of stabilization of the molecule and changes of its activities, absorption profile and duration of action. According to the time of action, they are divided into rapid-acting (taken shortly before mealtime, e.g. lispro, aspart, glulisine) and long-acting analogs (controlling glycaemia during sleep and between meals, e.g. glargine, detemir, degludec).

The interesting fact about insulin signaling is the structural and functional relation to insulin receptor (IR) and IGF-1R (insulin-like growth factor type 1 receptor). Insulin-like growth factor 1 (IGF-1) is a stimulator of cell proliferation through IGF-1R and IR [7]. Consequently, stimulation of IR is also associated with cancer cell proliferation. Zhang et al. [8] posed a challenge to prove that downregulation of IR reduces cancer cell proliferation, angiogenesis and lymphangiogenesis. Additionally, IR downregulation displayed antimetastatic properties in an athymic mouse model, even in the IGF1R presence. The authors strongly suggested that IR might be a target in cancer therapy [8]. The mechanisms mentioned above may play a role in neoplasia observed in diabetic patients (Fig. 1).

Despite the large number of patients with type 1 diabetes treated with long-term insulin, the relationship between particular drugs and cancer risk remains elusive due to the lack of good quality research. Gu et al. [9] conducted the study in which 8774 diabetic type 2 patients from the Shanghai Diabetes Registry were enrolled and divided into two cohorts: the human insulin users (n = 3639) and the non-insulin users (n = 5135). According to the study, the overall risk of cancer in patients with type 2 diabetes treated with human insulin was not elevated compared to patients without insulin treatment (adjusted RR = 1.20, 95% CI = 0.89–1.62, p = 0.228). However, the site-specific analysis showed a significantly higher risk of liver cancer in this group (adjusted RR = 2.84, 95% = CI 1.12–7.17, p = 0.028). Moreover, those patients had higher risks of overall mortality (adjusted RR = 1.89, 95% CI = 1.47–2.43, p = 0.0001) and cancer mortality (adjusted RR = 2.16, 95% CI = 1.39–3.35, p = 0.001). The authors underlined obvious limitation of the study, such as lack of randomization, appropriate therapy control, incomplete data (mainly without dose and duration of treatment) and potential confounding factors [9]. Moreover, in 2009 Currie et al. [10] also confirmed that insulin-based therapy increased the risk of colorectal cancer (HR = 1.69, 95% CI = 1.23–2.33) and strongly increased the risk of pancreatic cancer (HR = 4.63, 95% CI = 2.64–8.10) compared to metformin but had no influence on the risk of breast and prostate cancer [10].

The synthesis of insulin analogs was another step forward in diabetes pharmacotherapy. However, the first analog (B10Asp)

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