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SGLT2 Inhibitors and Cancer: is Immunity the Missing Link?

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Abstract

Background. After their introduction to clinical use, several reports related the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors to certain cancer. In this review, we will discuss whether the use SGLT2 inhibitors can increase cancer or, surprisingly, reduce the risk of certain cancers. We will also discuss the proposed mechanisms of inducing or inhibiting cancer by SGLT2 inhibitors with special attention to immunity as a point that needs further consideration. Summary. While some SLGT2 inhibitors might induce cancer in human, others might protect against cancer. Animal results showed some contradiction. None of the clinical studies considered the effect of SLGT2 inhibitors on immunity during assessment of the relationship between SLGT2 inhibitors and cancer. Key messages. It seems that the relationship between SLGT2 inhibitors and cancer is not a class. Further studies should focus whether the interaction between SLGT2 inhibitors and immune system could affect cancer growth.

Introduction

The risk of cancer is elevated in patients with type 2 diabetes [1]. Although the actual mechanisms are yet to be revealed, many factors related to diabetes may play a role in increasing the risk of cancer. Obesity that usually associates type 2 diabetes mellitus is an example [2]. Some anti-diabetic medications by themselves can increase the risk of certain cancers. One example is pioglitazone which was linked to bladder cancer [3]. Another example is sodium–glucose cotransporter 2 (SGLT2) inhibitors [4].

In the kidney, the filtered glucose is reabsorbed again in the proximal tubules via SGLT1 and SGLT2 [5]. SGLT2 accounts for 90% of the glucose reabsorbed from the kidneys while SGLT1 accounts for only 10% [6,7]. SGLT2 inhibitors are a new class of anti-diabetic drugs that reduce plasma glucose levels by inhibiting SGLT2 in the renal tubules. Recently, these drugs are gaining popularity because they can also reduce blood pressure and body weight [8]. Common examples of SGLT2 inhibitors include dapagliflozin, canagliflozin, and empagliflozin. In this review, we will focus on the relation between SGLT2 inhibitors and cancer.

Do SGLT2 Inhibitors Cause Cancer?

The first report that linked the use of SGLT2 inhibitors to induction of cancer was in 2011 [4]. It was reported that dapagliflozin was associated with higher incidents of male bladder cancer and female breast cancer in comparison to control diabetic patients of the same age. For either cancer types, 9 cases were reported in comparison to one case in the control arm [4]. The 9 cases of bladder cancer were reported on dapagliflozin out of 5,478 patients while the only reported case in the control arm was out of 3,156 patients [4]. However, these results were not replicated in animals. An experimental study that exposed mice and rat to a high dose (100-fold human dose) of dapagliflozin for up to 2 years found no increase tumor incidence or urinary bladder preneoplastic lesions [9]. On the contrary to dapagliflozin, canagliflozin did not increase the overall incidence of bladder, breast and renal cancers in a pooled analysis of eight clinical trials [10]. However, experimental settings gave variable results. Long-term exposure to canagliflozin at doses up to 14-fold human dose did not increase the incidence of neoplasms or preneoplastic lesions in mice [11]. Clinical trials on empagliflozin reported an increase in the risk of bladder cancer [12]. Away from individual SGLT2 inhibitors, a study on SGLT2 knockout mice compared with wild-type mice did not find increased hyperplasia or neoplasia in the urinary bladder mucosa, urogenital tract or kidney although mice had significant glucosuria [9].

Focusing on the clinical aspect, several studies and clinical trials since 2011 have been conducted to clarify whether SGLT2 inhibitors are associated with increase cancer risk [10,13]. One

meta-analysis suggested that lack of proper diagnosis prior to randomization might explain the increased risk of cancers rather than a causal relationship [14]. Another recent meta-analysis reported 580 incidences of cancer among 34,569 people with type 2 diabetes. The study found that, SGLT2 inhibitors were not significantly associated with an increased risk of overall cancer. However, they found that SGLT2 inhibitors might increase the cancer risk in obese participants (BMI ≥30 kg/ m2) while age and sex were irrelevant. In addition, SGLT2 inhibitors, especially empagliflozin, was found to increase the risk of bladder cancer [13]. Most incidences of bladder cancer were identified from one trial.12 Interestingly, the originally accused SGT2 inhibitor, dapagliflozin, in addition to canagliflozin did not significantly increased risk of bladder cancer. Moreover, canagliflozin might be associated with reduction of gastrointestinal cancers [13]. The study did not detect any increase in breast cancer risk with the use of SGLT2 inhibitors. Nevertheless, the authors warned that the results of their meta-analysis are not conclusive since the duration of most of the clinical trials was not long enough. The low number of incidences was another point to consider before reaching final conclusion [12].

The mechanisms underlying the probable elevated risk of bladder cancer associated with SGLT2 inhibitors remain unclear. It was suggested that diabetes and obesity are, by themselves, risk factors for bladder cancer [1,2]. The inflammatory cytokines, inflammation and generation of free oxygen species by hypertrophied adipose tissue can enhance cancer cells proliferation [15]. Another proposed mechanism is inhibition of SGLT2 function with or without the resultant glucosuria or urinary tract infections [10]. However, it was found that SGLT2 knockout mice did not show any increase in hyperplasia or neoplasia in the urinary bladder mucosa, urogenital tract or kidney over the 15 months of observation although glucosuria was significant.9 This indicates that neither glucosuria nor loss of SGLT2 function could explain the increased cancer risk. Using glucose-free diet in another study, it was concluded that malabsorption of glucose could be accused as a mechanism to explain the ability of canagliflozin to induce tumors in rats [16,17]. The authors suggested that such mechanism do not take place in human. Nevertheless, it seems that the relation between some SGLT2 inhibitors and cancer is not "class effect". Individual drugs might act indirectly to affect cancer development in certain species.

Do SGLT2 Inhibitors Protect against Cancer?

In the meta-analysis conducted by Tang et al. [13]. they reported that canagliflozin might be associated with reduction of gastrointestinal cancers. In one experimental study using mouse model of human non-alcoholic steatohepatitis, it was found that canagliflozin attenuated hepatic steatosis and significantly reduced the number of liver tumors after one year of treatment.17 Similarly, canagliflozin inhibited cellular proliferation and survival of lung and prostate cancer cells. It also enhanced the ability of chemotherapy and ionizing radiation to inhibit clonogenic survival [18].

The mechanisms by which canagliflozin can inhibit cancer cell growth remain unclear. In the study conducted by Villani [18]. authors found that canagliflozin, but not dapagliflozin, successfully inhibited cancer cell growth because only canagliflozin was capable of inhibiting mitochondrial respiration. By inhibiting complex-I supported respiration, canagliflozin inhibited mitochondrial respiration, which is critical for antiproliferative actions. In a different way, Shiba [17]. suggested that canagliflozin reduced the number of liver tumors by attenuating the development of nonalcoholic steatohepatitis, reducing oxidative stress and expanding healthy adipose tissue.

Another proposed mechanism explaining the cancer-suppressing effect of canagliflozin depends on its affinity to glucose transporter GLUT1. Canagliflozin can effectively inhibit GLUT1 [19]. GLUT1 is expressed in prostate cancer cells [20]. It would be expected that, by inhibiting GLUT1, depriving cancer cells from glucose can play a crucial role in cancer cell survival. However, inhibition of glucose uptake in prostate cancer cells was found to be insufficient for inhibition of cellular proliferation [21]. In a different way, the cancer-suppressing effect of canagliflozin could be attributed to its affinity to both SGLT1 and SGLT2. In comparison to dapagliflozin, canagliflozin has a higher affinity for inhibiting SGLT1 [22]. SGLT1 is mainly expressed in the gastrointestinal tract and SGLT2 is highly expressed in the kidneys and, to a lesser extent, in the gastrointestinal tract [23]. In humans, SGLT1 is overexpressed in many cancers [24,25]. Inhibition of SGLT1 sensitizes prostate cancer cells to treatment with EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor [24]. However, such theory needs validation.

SGLT2 Inhibitors, Immunity and Cancer

The ability of SGLT2 inhibitors to interact with the different components of the immune system and, hence, affect cancer development is a possibility yet to be discovered. Unfortunately, most of the conducted clinical trials did not consider the effect of SGLT2 inhibitors on immunity. Most of the data comes from animal models and suggested a significant anti-inflammatory effect of SGLT2 inhibitors [26-28]. However, most of these studies did not explain whether the anti-inflammatory effects are the result of the specific activity of SGLT2 inhibitors or just a secondary effect to correction of hyperglycemia. Immune cells rely on glucose consumption in order to sustain their pro-inflammatory program [29]. In non-diabetic models, empagliflozin and dapagliflozin still exhibit anti-inflammatory effects under normal blood glucose level [30,31]. It might be possible that SGLT2 inhibitors inhibit inflammation by both glycemia-dependent and glycemia-independent mechanisms. SGLT2 inhibitors may indirectly exert their anti-inflammatory effect via affecting oxidative balance, hemodynamics, the renin–angiotensin system (RAS) activation and obesity-related

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inflammation; as reviewed by Yaribeygi [32]. Whether this anti-inflammatory effect of SGLT2 inhibitors could induce, prevent or repress cancer is yet to be determined. Initially, it could be expected that inhibiting inflammation might indicate negative affection on immunological response to cancer cells. However, SGLT2 inhibitors reduce inflammation and oxidative stress in adipose tissue [17]. Hypertrophy of adipose tissue increases M1 macrophages. These cells secrete inflammatory cytokines, enhance low-grade inflammation and generate free oxygen species, therefore, lead to genetic instability and cancer cells proliferation.15 By reducing inflammation and oxidative stress and enabling "healthy adipose tissue", SGLT2 inhibitors may have a potential to reduce cancer risk [17,33]. On the other side, Xu [17]. found that canagliflozin exerts anti-inflammatory effects by promoting autophagy in immune cells. Further studies are required to specifically determine what kind of immune cells are affected by canagliflozin. Thus, we could expect the overall effect of this drug on cancer growth. For example, autophagy in myeloid-derived suppressor cells has been linked to suppression of antitumor immunity [34]. Promoting autophagy in such cells is expected to enhance tumor growth.

Conclusion

Further studies are required to confirm whether SLGT2 inhibitors can affect tumor growth in human. Focusing on the interaction between SLGT2 inhibitors and immune system might clarify the current conflict. Nevertheless, it seems that, whether induction or inhibition of cancer, SLGT2 inhibitors effects won't be a class effect and each drug in the class should be evaluated separately.

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