Diabetes and cancer; is there a relationship?

Fatemeh Sadat Aleabtahi¹, Banafsheh Yalameha¹, Ali Hasanpour Dehkordi²*

¹Nickan Research Institute, Isfahan, Iran
²Social Determinants of Health Research Center., School of allied medical sciences, Shahrekord University of Medical Sciences, Shahrekord, Iran

Abstract

Diabetes and cancer are known as two of the most common diseases with significant impacts on the health and well-being of people throughout the world. Epidemiologic evidence has shown that diabetic patients are highly vulnerable to the risk of cancer. There are common risk factors in diabetes and cancer including age, obesity, dietary, physical activity, smoking and alcohol consumption. It has been demonstrated that diabetes imposes a significant impact on cancer through several mechanisms including hyperinsulinemia, hyperglycemia and chronic inflammation. Therefore, understanding the mechanisms involved in the occurrence of diabetes and cancer and their relationship can provide new strategies for the effective prevention, diagnosis and treatment of these diseases.

Introduction

Diabetes and cancer are known as two of the most common diseases with significant impacts on the health of people throughout the world. The prevalence of these diseases is increasing even in developing countries (1). Many risk factors are expressed for type 2 diabetes (T2D) and cancer that some of them are common including obesity, sex, physical activity, age, diet, alcohol, and smoking (2). Epidemiologic studies have shown that diabetic patients are highly vulnerable to the risk of cancer (2,3). In addition, clinical reports of over 50 years have confirmed the simultaneous incidence of diabetes and cancer in patients (4). It has been demonstrated that diabetes enhances cancer through different mechanisms such as hyperglycemia, hyperinsulinemia, and inflammation (5). According to the study, the intensity of obesity can be associated with a higher risk of prostate cancer and subsequently, death in obese men than men with normal weight (6). It has been presented that the metabolic factors as such hyperinsulinemia and obesity can prevent the prompt diagnosis and proper treatment of cancers including prostate cancer. Diabetes can increase cancer mortality rate, since, a study on the 5-year survival rate of breast cancer has displayed that diabetic-cancer patients were exposed to a higher mortality rate than non-diabetic cancer patients (7,8). However, more researches are needed to clarify the precise relationship between diabetes and cancer, accordingly, the present study aimed to investigate this matter.

Methods

For the present study, Web of Science, PubMed/Medline, Embase, Scopus, Directory of Open Access Journals (DOAJ), EBSCO, and Google Scholar were searched using keywords of cancer, diabetes, obesity, hyperinsulinemia, hyperglycemia, insulin, insulin analogs, insulin-like growth factor 1 and inflammation.

Common risk factors in diabetes and cancer

Age

Older patients are more prone to diabetes and cancer. However, other factors including epidemic obesity and T2D may affect the risk of cancer (9, 10).

Gender

The mean age of exposure to diabetes is higher in men than in women (11). Studies have exhibited that diabetes is associated with...
the risk of all-site and some site-specific cancers (12-14). Besides, it has extremely been evident that diabetic women are more in the risk of stroke (15), coronary diseases (16) and dementia (17) than men. According to the findings of a systematic review and meta-analysis study, the highest observable mean score of gender-specific relative risk (RR) for diabetes-induced fatal/non-fatal cancers was respectively 1.27 in women and 1.19 in men. The highest observable mean score of RR for renal, oral, gastric and leukemic cancers was significantly witnessed in diabetic women than diabetic men while diabetic women presented a lower mean value for hepatic cancer than diabetic men (18). However, some other studies have indicated that there is no statistically significant relationship between cancer and gender in diabetic patients. Cancer in diabetic women may contribute to the poor regulatory mechanism of glucose compared with diabetic men (19,20). Additionally, women are not only less cared (19,20) but also use glucose-lowering medications less than men (21). In general, women are more likely to develop insulin resistance and subsequently at a higher exposure to hyperinsulinemia than men. Hyperinsulinemia increases cancerous cellular proliferation by stimulating insulin receptors directly and insulin-like growth factor 1 (IGF-1) indirectly (3). Consequently, diabetes is a risk factor for cancer in both genders (women higher than men). The significance of gender is highly apparent in determining the effect of diabetes on the incidence, prevention, and treatment of cancer (18). Nonetheless, further studies are required to investigate the relationship between diabetes and cancer based on gender differences.

Obesity

Amongst various cancer types, cancers of the breast (in postmenopausal women), colorectal, endometrial, pancreatic, esophageal adenocarcinoma, renal, hepatic and gallbladder are mostly known as obesity-associated cancers. Obesity may enhance the mortality rate of prostate cancer (6). Moreover, a study has displayed that there is a significant relationship between obesity and the prevalence of T2D and insulin resistance (22).

Weight loss reduces the outbreak of diabetes and returns euglycemia in most patients with T2D. It also can diminish the risk of gestational diabetes (23). The relationship between weight loss and cancer has not been sufficiently investigated however, weight loss, may be the latent sign of cancer. It has been found that obese women with a history of weight loss surgery are less prone to cancer than obese ones without surgery. In contrast, no statistically significant relationship has been observed between bariatric surgery and cancer in men (24). It has been indicated that adipocyte cells produce interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) that lead to the expression of cell proliferation, angiogenesis, apoptosis inhibition, and increased C-reactive protein (CRP) (a risk factor for some cancers) (25, 26).

Dietary

Diets including low red meat and processed foods as well as fruit, vegetables, whole grains, and fiber-rich food may have a protective effect against T2D and improve insulin sensitivity. Energy-dense and sugary food results in weight gain and obesity. According to the American Cancer Society, the World Cancer Research Fund, and the American Institute for Cancer Research, the consumption of the aforesaid food should be limited (27-29).

Physical activity

The relationship between increased physical activity and decreased risk of cancer is still uncertain. However, some studies have represented that physical activity may ascend the survival rate of cancers such as breast (30) and colorectal (31). It has been illustrated that physical activity reduces insulin resistance, TGF-1 level, and estrogen even without losing weight. A study has also determined that moderate-intensity physical activities, like a 30-minute walking (5 times per week), can decrease the risk of T2D progression (32-34).

Smoking and alcohol

According to some studies, smoking is an independent risk factor for diabetes that also acts as a deterrent agent for diabetes treatment. According to the National Cancer Institute, smoking can cause pancreas, stomach, lung, mouth, throat, and esophagus cancers (35-37). Excessive alcohol use is another risk factor for diabetes. In addition, it has been shown that the occurrence of oral cancer is 6 times more in alcoholic people (38).

Possible biological relationship between diabetes and cancer

It seems that diabetes imposes a significant impact on cancer through several mechanisms including hyperinsulinemia, hyperglycemia and chronic inflammation.

The insulin and insulin-like growth factor axis

Most cancer cells express IGF-1 and insulin receptors (IR). Insulin receptor isoform A (IR-A) can stimulate insulin-mediated mitogenesis and defective cells in IGF-1 receptors (39). Moreover, IR is capable of cancer cell proliferation and metastasis. Concerning high glucose absorption in cancer cells that is independent of insulin binding, the activating effect of IRs on neoplasm cells may be more associated with the survival and mitogenesis of cancer cells than increase glucose absorption by these cells (40).

Signaling pathways activate several cancer phenotypes such as cellular proliferation, protection against apoptosis, invasive and metastatic stimuli that can potentially stimulate the growth of cancer cells. It has also been specified that insulin and IGF-1 induce normal cells to the progression of cancer cells (41). Hyperinsulinemia may increase carcinogenicity directly by affecting IGF-1 in the
circulation and cancer cells (42). The carcinogenic and antiapoptotic activities of IGF-1 are higher than those of insulin (43), meaning that it can act as the stimulant of precancerous and cancerous cells growth expressing the IGF-1, insulin and hybrid receptors (44).

Several studies have found that IR overexpression associated with breast cancer prognosis (45, 46). Although these results may be conflicting, but are consistent with other hormone-dependent metabolic pathways in breast cancer (47). In addition, the relationship between obesity, diabetes, and cancer can be directly perceived by insulin and IGF axes mechanisms (48). Increased insulin may affect the synthesis of other hormones related to cancers. Hyperinsulinemia is most probable to increase the synthesis of adrenal hormones and ovarian androgen in premenopausal women. It also increases testosterone bioavailability in women that related to the risk of some cancer. Increased endogenous sex steroid is highly associated with the high risk of endometrial and postmenopausal breast cancers in addition to other cancers (49).

**Hyperglycemia**

Glucose can mediate the complexity of the interaction between diabetes and cancer. A recent overview of Warburg theory and energy supply of cancer cells has shown that the energy supply of most cancers depend on ATP, produced by glycolysis. Nevertheless, glycolysis, for ATP generation, requires more glucose for the intended energy supply compared with the process of oxidative phosphorylation. Also, untreated hyperglycemia is likely to facilitate cancer progression (50). There is no precise information on the relationship between cancer and the dose-response effect of glucose (51). Concerning the molecular heterogeneity of cancers, it cannot be ignored that there are some types of hyperglycemia-related cancers providing the chance of finding an appropriate treatment for diabetes and hindering the progression of cancer. However, data generally suggest that IR activation may be a more important variable than hyperglycemia for determining tumor development (3).

**Inflammation cytokines**

T2D and obesity may be effective in cancer development by activating other metabolic pathways. Adipose tissue is an active endocrine organ that produces free fatty acids, IL-6, TNF-α, monocyte chemoattractant protein, plasminogen activator inhibitor-1 (PAI-1), leptin, and adiponectin, each of which may play a crucial etiological role in cancer transformation or progression (52). The role of these molecules has identified in some cases. For instance, the plasminogen system is associated with breast cancer by affecting PAI-1 expression (53). Furthermore, induction of signal transducer and activator of transcription protein (STAT) pathway using such cytokines as IL-6 not only increases proliferation, survival, and invasion of cancer cells but also suppresses host antitumor immunity (54). Studies on energy balance have supported the epidemiological outcomes of the relationship between obesity and cancer deaths. Certain cancers become more invasive due to overeating. Therefore, the limitation of calorie intake reduced the cancers invasive (55-57). In fact, it has revealed that dietary-caused changes in IL-6 and insulin may mediate the effect of diet on cancer and can also determine tumor differences based on tumor behavior depending on the specific signals of metabolic pathways (58).

**Effect of antidiabetic drugs on cancer**

Metformin (MET) is a biguanide that is widely applied to lower blood glucose of patients with T2D (59). In-vivo studies have shown that MET inhibits the proliferation of cancer cells and impedes colony formation by suppressing a part of the cell cycle (60, 61). MET utilization related to the reduced risk of different types of cancers, especially pancreatic, hepatic and colon cancers (62). Furthermore, MET reduces the progression of breast cancer in rodents (63). The results of a study exhibited that MET has a higher pathological response in patients with early-stage breast cancer receiving neoadjuvant therapy (64). Mechanically, activation of AMP-activated protein kinase (AMPK) in cancer cells by MET inhibits cellular proliferation and suppresses lipogenic enzymes to decrease fatty acid availability for tumor cells. Moreover, AMPK reduces pro-inflammatory cytokines such as IL-6, TNF-α, IL-8 and vascular endothelial growth factor (VEGF) by its anti-inflammatory property. Other mechanisms of action of MET in cancer cells include reduction of leptin, insulin, IGF-1 and elevation of adiponectin (65, 66). It may selectively exterminate the stem cells through suppressing NF-kB and phosphorylation of STAT3 and improve the effect of regimen on breast cancer (67). Additionally, it is possible that MET impedes proliferation, migration and self-renewal of ovarian cancer cells by inhibiting sphingosine kinases 1 (SPHK1) (68).

Thiazolidinediones (TZDs) are known as peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists that lead to hypoglycemia and decreased insulin resistance in patients with T2D (69). Some studies have displayed that TZDs possess anti-carcinogenic effects through PPAR-γ activation that arrest cell cycle, induce apoptosis, inhibit angiogenesis and modulate differentiation (70). It has been indicated that different types of TZDs such as rosiglitazone, pioglitazone, and rosiglitazone can use as a treatment adjunct for cervical cancer (71).

Sulfonylureas and rapid-acting glinides, as secretagogues, release insulin by binding to beta-cell receptors. Sulfonylureas reduce A1C, also induce hypoglycemia. Research has reported that diabetic patients treated with the sulfonylureas were more vulnerable to cancer or cancer mortality rate than those treated with MET (72-75).
Incretin-based therapies

Medications such as exenatide (%50 structurally similar to glucagon-like peptide 1 (GLP-1)) and liraglutide (analog of human GLP-1) both are considered as agonists binding to GLP-1 receptors and known as incretin-based therapies. These medications increase or replicate the effect of gut-derived incretin hormones (e.g. GLP-1). These hormones ameliorate glucose-dependent insulin secretion, reduce postprandial glucagon and postponed gastric emptying. It has been indicated that liraglutide maximizes the risk of medullary thyroid cancer (MTC) in rats and mice models. It also promotes calcitonin levels in human serum. Dipeptidyl peptidase-IV inhibitors (DPP-IV) block the GLP-1-degrading enzyme. Animal studies have demonstrated that DPP-IV increases the proliferation of beta cells. These medications have not yet presented any significant effect on human cancers (76).

As the 1st- and 2nd-line therapies of T2D, both GLP-1 agonists and DPP-IV inhibitors are the most interesting area of researches. The number of patients with increased risk of acute pancreatitis, pancreatic cancer, and thyroid cancer is limited in clinical trials to be a concerning matter (77). In smooth muscle cells, hyperglycemia exhibits mitogenic response by altering IGF-1 signaling (41). Based on cancer treatment policies, patients with pancreatic cancer are more exposed to the risk of diabetes (78). Moreover, cancer patients are highly vulnerable to hyperglycemia during the process of cancer treatment due to their particular dietary, infections, stress, and physical activity level (79). Daniel Morganstein, a Consultant Endocrinologist at Royal Marsden Hospital, found that the cancer patients who receive high-dose steroids are exposed to diabetes. The diabetogenic effect is caused by the high volatility of blood glucose levels in a short-term period. Nevertheless, substances used for cancer patients in chemotherapy are more likely to develop hyperglycemia than steroids (Drugs such as temsirolimus, docetaxel, and everolimus alone or in combination with other elements) (80).

Subcutaneous injection of insulin elevates the ratio of exogenous insulin to endogenous insulin and subsequently fortifies the relationship between hyperinsulinemia and the risk of cancer. Research has shown that insulin glargine may have an adverse effect on the risk of cancer by bounding to IGF-1 receptors. Nevertheless, the strengths and weaknesses of the aforesaid study are yet controversial (81-83). On the contrary, the findings of a 5-year survey on the impacts of insulin glargine versus NPH insulin on cancer found no evidence in the increased risk of cancer progression (84).

The relationship between exogenous insulin, insulin analogs, and cancer; possible mechanisms

Exogenous insulin or insulin analogs have direct effects such as interference of injected ligand with cancer cells that transforms normal cells or prone-to-change cells to cancer cells, as well as indirect effects such as interference in cell surfaces of signaling molecules affected by the insulin injected to the target cells. Considering the direct effects of such ligands, not only should the inclination of exogenous substances to various receptors be heeded but also their pharmacokinetic aspects should be taken into account (85).

Studies have revealed that there are differences between the inclination of human insulin and insulin analogs to binding to IGF-1 receptors. Their findings have also conveyed that insulin glargine is more inclined to IGF-1 receptors and has higher mitogenic ability than human insulin or other insulin analogs (86-88). The affinity of some specific insulin analogs reduces IGF-1 receptors. However, insulin receptors do not cease the proliferation of malignant cells in response to insulin glargine (86). It is hardly possible that insulin and its analogs, which preserve the specificity of the insulin receptor more than the specificity of IGF-1 receptor, have significant mitogenic effects on neoplasm (47, 89).

Recent research has demonstrated that insulin receptors situated on the neoplasm cell may affect neoplastic behaviors. It has remained unrecognized that whether there is a biological difference between the exposure of cancer cells to endogenous insulin alteration in physiological conditions and levels of endogenous insulin in T2D, obesity and after administration of exogenous insulin. Diabetes and hypertension are the main risk factors for colorectal cancer. It has been stated that diabetic patients, especially diabetic men (than women), are more prone to colorectal cancer than healthy individuals (90-95).

However, diabetes can increase the risk of colorectal cancer in women without the effect on their survival. According to the results of studies, the colorectal cancer patients with hypertension treated with bevacizumab were more likely to survive than those without hypertension (96-98). A study showed that metabolic diseases, hypertension, and diabetes are associated with advanced stages of colorectal cancer. In addition, the results of their study indicated that both hypertension and T2D are the most prevalent diseases in patients with colorectal cancer and both have the same impact on the survival of colorectal cancer (99).

Conclusion

Based on conducted studies, it can conclude that diabetes and cancer are recognized as two common diseases worldwide and one each can have a negative impact on the other one. Therefore, understanding the mechanisms involved in the occurrence of diabetes and cancer can provide new strategies for the effective prevention, diagnosis and treatment of these diseases.

Authors’ contribution

FSA participated in the literature review and prepared the primary draft by FSA. BY and AHD edited the manuscript. All authors read and signed the final paper.
Funding/Support
No sources of funding obtained to support the study.

References
30. Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan


68. Rattan R, Graham RP, Maguire JL, Giri S, Shridhar V. Metformin...
77. doi: 10.1111/dob.13178.
81. Gerstein HC. Does insulin therapy promote, reduce, or have a neutral effect on cancers? JAMA. 2010;303(5):446-7.