Exploration of Endocrine and Metabolic Diseases

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Diabetes and cancer: two epidemic diseases requiring an opposite therapeutic approach to target cells

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Abstract

Diabetes and cancer are two chronic metabolic diseases with ever-increasing incidence rates worldwide. These disorders can often occur together, as diabetes presents an important risk factor for cancer and some cancers could in turn lead to diabetes. In this perspective article, many more commonalities between diabetes and cancer are highlighted, including the role of lifestyle and environmental factors in the pathogenesis, the presence of a rather long latency period before clinical diagnosis of invasive disease, as well as the ultimate progression to diabetic complications or malignant metastases. Moreover, both of these devastating disorders still lack curative treatment options, whereas several currently approved antidiabetic and anticancer drugs have been originally derived from different natural sources. However, while in the case of diabetes, the main therapeutic goal is to maintain the pancreatic islet mass by preserving β-cells survival, the major purpose of cancer therapy is to kill malignant cells and reduce the neoplastic mass of solid tumors. It is expected that both diabetes and cancer, two systemic diseases with epidemic proportions, would be managed more effectively through an integral approach, considering many different aspects related to their pathogenesis, including also lifestyle changes and dietary modifications.

Keywords

Diabetes, cancer, prevalence, pathogenesis, therapy, dietary modifications

Introduction

Diabetes mellitus (diabetes) and cancer represent two chronic, complex, and potentially fatal diseases [1]. As chronic diseases, both conditions develop (mostly) slowly, last a long time, and are progressive, incurable, and life-limiting [2, 3]. Moreover, it is currently well-accepted that diabetes is a risk factor for the development of cancer [1, 4]. Several types of malignancies have been indeed found to develop more commonly in patients with diabetes, including cancers of the liver, pancreas, and endometrium, but also the colon and rectum, breast, and bladder [5]. On the other hand, some cancers could in turn lead to diabetes, probably mainly as a result of the applied anticancer therapies, such as chemotherapy, radiotherapy,

immunotherapy, androgen deprivation therapy, and administration of steroids [4, 6–9]. Actually, about eight percent to eighteen percent of patients with malignant disorders have been estimated to have also diabetes, being associated with a significantly enhanced risk of cancer mortality [4]. Based on this relationship, it can be supposed that there is much more common between these two dreadful diseases. Therefore, in this perspective article, some important aspects of the pathogenesis and therapy of diabetes and cancer are closely examined.

Major similarities between diabetes and cancer

First of all, both diabetes and cancer are reaching epidemic proportions, revealing an ever-increasing incidence rate worldwide. According to the data of the International Diabetes Federation, there were approximately 537 million adults (20–79 years) living with diabetes in 2021, whereas the total number of diabetics is projected to rise to 643 million by 2030 and 783 million by 2045 [10]. An estimated 19.3 million new cancer cases (with almost 10.0 million cancer deaths) occurred in 2020 and the global cancer burden is expected to increase to 28.4 million by 2040, meaning a 47% rise from 2020 [11].

Diabetes is generally classified into type 1 diabetes mellitus (T1DM, juvenile-onset diabetes mellitus) and T2DM (adult-onset diabetes mellitus). While T1DM (comprising 5–10% of all cases) results from an autoimmune attack on pancreatic β-cells and has a strong genetic component, the development of T2DM (90–95% of all cases) has been associated with a sedentary lifestyle, unhealthy dietary pattern, obesity, smoking, urbanization, and air pollution [12, 13]. Type 3c (pancreatogenic) diabetes has also been recently described, as occurring because of diverse exocrine pancreatic diseases, such as chronic pancreatitis and pancreatic cancer [14, 15]. Rather similarly, only about five percent to ten percent of all cancer cases have their roots in genetic defects, whereas the remaining 90–95% are attributed to a variety of lifestyle and environmental factors [16]. These data clearly indicate that the majority of cases of both diabetes and cancer would be preventable by appropriate lifestyle changes. Moreover, as the risk of both diseases increases with age, these chronic devastating disorders can be considered as age-related diseases.

The pathogenesis of diabetes (T2DM) involves chronic hyperglycemia, insulin resistance, and alterations in pancreatic β-cells size and function. The rise in blood glucose levels is the primary stimulus for insulin secretion. In insulin resistance, β-cells in the islets of Langerhans compensate for the defects in insulin action by secreting more insulin into the bloodstream. T2DM only develops when β-cells are unable to release adequate amounts of insulin to compensate for the reduced insulin sensitivity. T2DM is therefore related to a substantial decline in the mass and function of β-cells, whereas insulin resistance can be considered as a latency period of diabetes (prediabetes). Signs of β-cells dysfunction are indeed detected to arise after several years of insulin resistance [17–20]. Cancer is also associated with a long-term latency period, being generally diagnosed 10–20 years after the initial exposure to a carcinogen that induces malignant transformation, providing a prolonged timeframe for early intervention with chemopreventive agents [21, 22]. Moreover, the development and progression of both diabetes and cancer are closely related to chronic inflammation, as diverse types of proinflammatory mediators play an important role in the deterioration of these conditions [23, 24]. As the final stage, diabetes can progress to several micro- and macrovascular complications affecting numerous organs, decreasing the quality of life of patients and increasing the rate of mortality. The most common diabetic complications include nephropathy, retinopathy, neuropathy, and cardiovascular diseases [25]. The majority of patients with cancer lose their lives due to metastasis of primary tumors to distant organs through a dynamic multi-step process [26]. These findings clearly show that both diabetes and cancer should be considered as systemic diseases undergoing local complex interactions with diverse surrounding cells, but affecting also the whole body through developing multiorgan complications/distant metastases under the control of systemic regulation.

Despite the devastating nature of both diabetes and cancer, no curative therapeutic options are still available for the clinical management of either of these disorders. Diabetes (T2DM) is mostly controlled by arranging a healthy lifestyle and dietary modifications combined with the administration of antidiabetic drugs for the lowering of blood glucose levels through various different mechanisms [17]. The major

modalities for cancer treatment involve surgical resection, cytotoxic chemotherapy, radiotherapy, and targeted therapies [26]. However, no effective standard strategies for fighting against the development of diabetic complications and malignant metastases have been established yet, although these are the actual life-threatening steps of diabetes and cancer, making both diseases dreadful and devastating [26, 27]. Interestingly, more than sixty percent of the currently used anticancer drugs were originally derived from different natural sources, including various plant extracts, marine organisms, and microorganisms. For example, vincristine, vinblastine, and paclitaxel were initially purified from plants, whereas actinomycin, bleomycin, and anthracyclines were first isolated from different microbial strains [28, 29]. Natural products have been an important source for the development of novel medications also against diabetes, as the first-line used oral hypoglycemic drug metformin was originally derived from the French lilac, while acarbose was initially isolated from *Actinomycetes* species [17, 30]. Moreover, the diversity of natural products has remained an abundant resource for the identification of novel effective antidiabetic and anticancer agents also for the future.

Differences in therapeutic principles in affecting target cells

As the development of diabetes is associated with the destruction of pancreatic β-cells and a decrease in islet mass, while cancer is characterized by the formation of a new transformed cell mass (neoplasm), the pharmacological approaches to these two conditions are quite opposite. The ultimate aim of the management of diabetes is to maintain an adequate β-cell mass by preserving β-cells survival and function, whereas the purpose of cancer treatment involves the killing of malignant cells and eradication of neoplastic tissue of solid tumors. Progression of β-cell impairment is at least partially due to enhanced production of reactive oxygen species (ROS), induced by excessive amounts of glucose (glucotoxicity), but also saturated fatty acids (lipotoxicity). The generated oxidative stress can gradually result in β-cells apoptosis with a decrease in their mass and function via modulating a variety of cellular signaling cascades, thereby contributing to the pathogenesis of diabetes (T2DM) [17–19]. Therefore, overcoming hyperglycemia as well as its associated oxidative stress may protect the integrity of β-cells. The intake of an antioxidant-rich diet has been indeed demonstrated to be beneficial for improving the parameters indicative of diabetes [19, 20]. On the contrary, apoptosis is an important mechanism for regulating the destruction of cancer, whereas the overproduction of ROS may be involved in causing the damage and death of malignant cells through stimulating different apoptotic pathways, ultimately leading to a decrease in tumoral mass [31]. Therefore, agents leading cancer cells to apoptosis, but leaving normal healthy tissues unharmed, might be important in combating diverse types of malignancies.

Challenges emerging from the comparative approach

The comparative features of diabetes and cancer, summarized in Table 1, clearly reveal a number of important similarities between these two systemic metabolic diseases. However, such an approach also points to some challenges requiring further careful consideration. For example, on the one hand, it is well-accepted that diabetes is an important risk factor for developing cancer and some cancers could lead to diabetes, probably due to applied treatments. On the other hand, dietary modifications (called also diabetes diet) have been agreed to play a decisive role in keeping diabetes under control, combined with the administration of hypoglycemic drugs. This, in turn, raises the question of why the importance of dietary pattern is still generally ignored in integral cancer therapy in clinical settings. Does the scientific community disregard thereby one substantial aspect in the multi-piece puzzle of the cancer fight?

Table 1. Comparison of the most important characteristics of diabetes and cancer

Characteristics	Diabetes mellitus	Cancer
Prevalence	Epidemic prevalence with an ever-increasing incidence rate	Epidemic prevalence with an ever-increasing incidence rate
Classification	90–95% T2DM (lifestyle-related, mostly in older adults), 5–10% T1DM (probably heritable, juvenile-onset type)	90–95% sporadic (lifestyle-related, in older adults > 50 years of age), 5–10% genetic (heritable type, in younger age)

Table 1. Comparison of the most important characteristics of diabetes and cancer (*continued*)

Characteristics	Diabetes mellitus	Cancer
General feature	Destruction of pancreatic β-cells, decrease in islets mass	Development of malignant cells, formation of neoplasm
Description	Chronic lifelong metabolic disease with insulin resistance as a long-term preceding phase for T2DM (often latent)	Chronic metabolic disease with a long latency period (about 10–20 years) before diagnosis of invasive cancer
	Pathogenesis is closely associated with inflammation	Pathogenesis is closely associated with inflammation
Final stage	Multiorgan complications	Distal metastases
Pharmacological aims in target cells	Pancreatic β-cells: oxidative stress (ROS), DNA damage, and apoptosis	Malignant cells: oxidative stress (ROS), DNA damage, and apoptosis
Treatment options	No curative treatment options were still available. Dietary modification, oral hypoglycemics, and insulin (i.e., drugs lowering blood glucose level). No therapies discovered to prevent diabetic complications	No curative treatment options were still available. Surgery, chemotherapy, radiotherapy, and targeted therapy (i.e., strategies suppressing the primary tumors). No therapies discovered to prevent the formation of metastases
Importance of natural products in drug discovery	The first-line used drug, metformin, was originally derived from French lilac. Acarbose isolated from *Actinomycetes* species	More than 60% of approved drugs are originally derived from different natural products, such as various plant extracts, marine organisms, and microorganisms

ROS: reactive oxygen species; T2DM: type 2 diabetes mellitus

Abbreviations

T1DM: type 1 diabetes mellitus

Declarations

Author contributions

KS: Conceptualization, Methodology, Writing—original draft, Writing—review & editing.

Conflicts of interest

The author declares that she has no conflicts of interest.

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References

1. Habib SL, Rojna M. Diabetes and risk of cancer. Int Scholarly Res Notices. 2013;2013:583786.
2. Pituskin E. Cancer as a new chronic disease: oncology nursing in the 21st century. Can Oncol Nurs J. 2022;32:87–92.

3. Pituskin E, Joy AA, Fairchild A. Advanced cancer as a chronic disease: introduction. Semin Oncol Nurs. 2021;37:151176.
4. Zhu B, Qu S. The relationship between diabetes mellitus and cancers and its underlying mechanisms. Front Endocrinol (Lausanne). 2022;13:800995.
5. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33:1674–85.
6. Hwangbo Y, Kang D, Kang M, Kim S, Lee EK, Kim YA, et al. Incidence of diabetes after cancer development: a Korean national cohort study. JAMA Oncol. 2018;4:1099–105.
7. Jo A, Scarton L, O'Neal LJ, Larson S, Schafer N, George TJ, et al. New onset of type 2 diabetes as a complication after cancer diagnosis: a systematic review. Cancer Med. 2021;10:439–46.
8. Yang K, Liu Z, Thong MSY, Doege D, Arndt V. Higher incidence of diabetes in cancer patients compared to cancer-free population controls: a systematic review and meta-analysis. Cancers (Basel). 2022;14: 1808.
9. Sylow L, Grand MK, von Heymann A, Persson F, Siersma V, Kriegbaum M, et al. Incidence of new-onset type 2 diabetes after cancer: a danish cohort study. Diabetes Care. 2022;45:e105–16.
10. 1 in 10 people are living with diabetes [Internet]. International Diabetes Federation; c2024 [cited 2023 Dec 8]. Available from: https://idf.org/
11. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
12. Redondo MJ, Oram RA, Steck AK. Genetic risk scores for type 1 diabetes prediction and diagnosis. Curr Diab Rep. 2017;17:129.
13. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PLoS One. 2018;13:e0194127.
14. Vonderau JS, Desai CS. Type 3c: understanding pancreatogenic diabetes. JAAPA. 2022;35:20–4.
15. Bhattamisra SK, Siang TC, Rong CY, Annan NC, Sean EHY, Xi LW, et al. Type-3c diabetes mellitus, diabetes of exocrine pancreas - an update. Curr Diabetes Rev. 2019;15:382–94.
16. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008;25:2097–116. Erratum in: Pharm Res. 2008;25:2200.
17. Al-Ishaq RK, Abotaleb M, Kubatka P, Kajo K, Büsselberg D. Flavonoids and their anti-diabetic effects: cellular mechanisms and effects to improve blood sugar levels. Biomolecules. 2019;9:430.
18. Alkhalidy H, Wang Y, Liu D. Dietary flavonoids in the prevention of T2D: an overview. Nutrients. 2018; 10:438.
19. Hajiaghaalipour F, Khalilpourfarshbafi M, Arya A. Modulation of glucose transporter protein by dietary flavonoids in type 2 diabetes mellitus. Int J Biol Sci. 2015;11:508–24.
20. Jasmin, Jaitak V. A review on molecular mechanism of flavonoids as antidiabetic agents. Mini Rev Med Chem. 2019;19:762–86.
21. Nadler DL, Zurbenko IG. Estimating cancer latency times using a Weibull model. Adv Epidemiol. 2014; 2014:746769.
22. Mohammed A, Fox JT, Miller MS. Cancer chemoprevention: preclinical in vivo alternate dosing strategies to reduce drug toxicities. Toxicol Sci. 2019;170:251–9.
23. Hussain T, Tan B, Murtaza G, Liu G, Rahu N, Saleem Kalhoro M, et al. Flavonoids and type 2 diabetes: evidence of efficacy in clinical and animal studies and delivery strategies to enhance their therapeutic efficacy. Pharmacol Res. 2020;152:104629.
24. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity. 2019;51:27–41.

25. Testa R, Bonfigli AR, Genovese S, De Nigris V, Ceriello A. The possible role of flavonoids in the prevention of diabetic complications. Nutrients. 2016;8:310.
26. Ganesh K, Massagué J. Targeting metastatic cancer. Nat Med. 2021;27:34–44.
27. Wang RA, Lu YY, Fan DM. Reasons for cancer metastasis: a holistic perspective. Mol Clin Oncol. 2015; 3:1199–202.
28. Shaik BB, Katari NK, Jonnalagadda SB. Role of natural products in developing novel anticancer agents: a perspective. Chem Biodivers. 2022;19:e202200535.
29. Kanwal N, Rasul A, Hussain G, Anwar H, Shah MA, Sarfraz I, et al. Oleandrin: a bioactive phytochemical and potential cancer killer via multiple cellular signaling pathways. Food Chem Toxicol. 2020;143: 111570.
30. Chen J, Mangelinckx S, Adams A, Wang ZT, Li WL, De Kimpe N. Natural flavonoids as potential herbal medication for the treatment of diabetes mellitus and its complications. Nat Prod Commun. 2015;10: 187–200.
31. Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative stress in cancer. Cancer Cell. 2020;38:167–97.