Review Article

A comprehensive review of diabetes and cancer

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Abstract

Diabetes and cancer are two complicated and common diseases that have received a lot of attention in the fields of medical and public health. The goal of this in-depth review article is to offer a full analysis of the complex connection between cancer and diabetes. The review starts out by exploring

the epidemiological data connecting these two illnesses, underlining the elevated risk of cancer among those with diabetes. The various underlying mechanisms are then explored, including hyperglycemia, insulin resistance, persistent inflammation, and common risk factors including obesity. This article additionally explores how managing diabetes affects cancer outcomes and vice versa. It highlights the value of interdisciplinary care approaches and clarifies the difficulties faced by those who deal with both disorders. The review also emphasizes recent advances in the field, such as the use of anti-diabetic drugs in the treatment and prevention of cancer, as well as the possibility of precision medicine to personalize care for those who have both cancer and diabetes. This comprehensive review highlights the complex interactions between cancer and diabetes and stresses the necessity for a multidisciplinary approach to care, early detection, and management techniques that address both disorders simultaneously. For those who are impacted by these difficult co-morbidities, the changing landscape of research in this area offers promise for improved outcomes and a higher quality of life.

Key words

Diabetes, Cancer, Epidemiology, Diagnostic techniques, Management, Recent advances.

Introduction

Researchers, doctors, and public health specialists have all paid close attention to two pervasive and powerful foes, cancer and diabetes, in the complex web of human health. While each of these chronic illnesses has long been studied separately, there has been a growing interest in recent years to figuring out how they are connected. With a primary focus on elucidating how diabetes, contributes to the onset and progression of cancer, this review article sets out on a comprehensive journey to examine the complex and changing relationship between diabetes and cancer.

Individually, diabetes and cancer pose significant threats to world health [1]. Diabetes, which is largely characterized by dysregulated glucose metabolism, has grown to enormous proportions and is affecting hundreds of millions of people globally [2]. On the other hand, cancer continues to be the largest mortality and morbidity factor worldwide [3]. Cancer is a broad category of disorders characterized by uncontrolled cell growth and proliferation [4]. Despite having different etiologies and pathophysiological mechanisms, a growing amount of research is starting to show that these two health burdens have a complicated and possibly reciprocal relationship.

Numerous studies have linked diabetes to an increased risk of cancer. Moreover, recent findings imply that changes in glucose homeostasis might affect cancer prognosis independently from altering susceptibility to certain forms of cancer [5, 6]. Other hypothesized mechanisms are mostly based on hormonal, inflammatory, and metabolic aspects connected to diabetes, as well as specific diabetes management therapies [7]. Additionally, many anti-diabetic drugs have been linked to varied impacts on the chance of developing cancer. Notably, several cancer forms in diabetic people have been associated to insulin sensitizers including metformin and thiazolidinediones (TZDs). For instance, metformin has been linked to a lower risk of breast cancer and prostate cancer that is HER2-positive [8, 9]. When compared to diabetic people taking metformin, those receiving insulin or insulin secretagogues may have a higher risk of acquiring cancer.

This review essentially acts as a beacon, leading us through the complex labyrinth where diabetes and cancer collide. It highlights the urgent necessity to fully comprehend the relationship between these two deadly adversaries. We want to provide significant insights that can guide clinical practice, research projects, and public health measures targeted at more effectively addressing these two serious health issues by

illuminating the intricate interactions between diabetes and cancer.

Epidemiology

A crucial and ever-present public health issue is the link between diabetes and cancer. In recent years, a significant shift in the epidemiological environment surrounding the link between diabetes and cancer has taken place. The importance of this association between diabetes & cancer is emphasized throughout this comprehensive examination, which digs into the changing epidemiological trends and significant findings that provide insight into it.

The accumulated data from a meta-analysis that included 12 cohort studies shed light on the elevated risk of cancer incidence linked to diabetes. The meta-analysis showed that those with diabetes have a statistically higher chance of developing any type of cancer. For both men and women, the pooled adjusted Relative Risk (RR) was determined to be 1.14 (95% Confidence Interval: 1.06-1.23) [10]. These findings highlight the slight but significant increase in cancer risk that is linked to diabetes. Diabetes showed links with a variety of different cancers, underscoring the complexity of its connection to malignancies. The pancreas, liver, breast, colorectal, urinary tract, gastric, and female reproductive malignancies stand out among these. These correlations suggest that diabetes may have a variable impact on various cancer types, demanding a complex strategy for comprehending and treating these relationships. The meta-analysis synthesized information from earlier studies on the relationships between diabetes and site-specific cancer in order to present a thorough overview. **Table - 1** provides a concise summary of these findings, highlighting the various levels of risk that diabetes poses for various cancer locations.

Table - 1: Meta-analysis results of cohort studies indicating the association of cancer with diabetes.

No. of cohort study	Cancer	RR (95%CI)	RR (95%CI) female	RR (95%CI) male	Ref.
11	Gastric	1.20 (1.08-1.34)	1.24 (1.01-1.52)	1.10 (0.97-1.24)	Yoon et al, 2013 [58]
11	Kidney	1.39 (1.09-1.78)	1.47 (1.18-1.73)	1.28 (1.10-1.48)	Bao et al, 2013 [59]
11	Non-Hodgkin's lymphoma	1.21 (1.02-1.45)	1.24 (0.97-1.58)	1.13 (0.96-1.34)	Castillo et al, 2012 [60]
15	Endometrium	1.81 (1.38-2.37)	1.81 (1.38-2.37)	NA	Zhang et al, 2013 [61]
18	Liver	2.01 (1.61-2.51)	1.66 (1.14-2.41)[1]	1.96 (1.71-2.24)[1]	Wang et al, 2012 [62]
20	Breast	1.23 (1.12-1.34)	1.23 (1.12-1.34)	NA	De Bruijn et al, 2013 [63]
25	Prostate	0.92 (0.81-1.05)	NA	0.92 (0.81-1.05)	Zhang et al, 2012 [64]
29	Bladder	1.29 (1.08-1.54)	1.28 (0.75-2.19)	1.36 (1.05-1.77)	Zhu et al, 2013 [65]
30	Colon-rectum	1.27 (1.21-1.34)	1.23 (1.13-1.33)[1]	1.25 (1.17-1.33)[1]	Jiang et al, 2011 [66]
35	Pancreas	1.94 (1.66-2.27)	1.60 (1.43-1.77)[1]	1.70 (1.55-1.87)[1]	Ben et al, 2011 [67]

Diabetes and various kind of cancer

There is strong evidence from epidemiological research that diabetes, especially Type 2 diabetes, increases the chance of developing many types of cancer [11]. This relationship is intricate and involves a number of variables, including insulin resistance, hyperinsulinemia, persistent inflammation, and metabolic disturbances. Notably, people with diabetes, especially Type 2, have a higher risk than people without the illness of getting a variety of malignancies. While there are differences between men and women in certain cancer types, diabetes and cancer risk remain generally linked. Diabetes and several well-known cancers have a stronger relationship than others, including pancreatic, liver, colorectal, and breast cancer. Even prediabetes increases the chance of developing cancer, highlighting the significance of controlling blood sugar levels even before full-blown diabetes develops. Studies have revealed a correlation between greater cancer mortality and elevated fasting blood sugar, even when it is within prediabetic ranges, underlining the possible influence of modestly elevated blood sugar on cancer risk [12]. Along with cancer screening and preventative efforts to detect cancer early and limit consequences, managing diabetes through dietary and lifestyle modifications, medications, and routine check-ups is essential. The importance of a comprehensive healthcare strategy that covers both diabetes control and cancer prevention in at-risk people is highlighted by these findings. Individual risk factors and outcomes, however, can differ, necessitating individualized examinations and advice from healthcare experts.

Lung cancer

In the USA, lung cancer is the second most common cancer in both men and women and a major contributor to cancer-related mortality [13]. Diabetes did not have a negative impact on the 5-year overall survival rate, according to a case-controlled study that looked at cancer survival in lung cancer patients with and without the disease. Patients without diabetes had a 5-year survival rate of 29%, compared to 20% for those with diabetes, indicating that diabetes did not have a negative effect on lung cancer survival [14].

Gastric cancer

Research on the relationship between stomach cancer risk and mortality and diabetes (DM) has produced contradictory results. A meta-analysis of 22 cohort studies with 8,559,861 participants found that males with diabetes had a higher risk of developing stomach cancer [15]. A similar prospective study in Japan discovered that men with diabetes had a 61% higher risk of developing cancer. However, conflicting findings on the risk of cancer in women have been documented. Another meta-analysis found that diabetes women had an 18% higher risk of developing stomach cancer than diabetic males did [16] In several studies, elevated fasting serum glucose and diabetes were regarded as separate risk factors for gastric cancer [17]. Gastric cancer may result from immune system dysfunction and an unbalanced energy metabolism, both of which have been linked to hyperglycemia. While numerous research and meta-analyses have found substantial differences between diabetic and non-diabetic people, other studies and analyses have found a variety of outcomes, some of which have found no connection between diabetes and the risk of stomach cancer in either gender.

Pancreatic cancer

Ductal adenocarcinoma (DPAC), a kind of pancreatic cancer, is the fifth most common cancer-related death in developed nations and the thirteenth most common cancer worldwide [18]. Diabetes or decreased glucose tolerance are associated with about 80% of pancreatic cancer incidences [19]. People with diabetes had a 94% increased risk of developing pancreatic cancer, according to a recent meta-analysis of 88 studies [20, 21]. Diabetes and pancreatic cancer have a complicated relationship, with poor glucose regulation likely influencing the development of cancer. Asian researches show that diabetics

have a higher mortality risk for pancreatic cancer. According to studies, type 2 diabetes triples the risk of pancreatic cancer [22, 23, 24]. Contradictory observations imply that type 2 diabetes may be a cause, not an effect, of pancreatic cancer, despite several ideas that link the disease to asymptomatic pancreatic cancer.

Hepatic cancer

Several studies have found a strong link between diabetes and an increased risk of liver cancer. For instance, a US study discovered that diabetics had a 2.8-fold increased chance of developing hepatocellular carcinoma (HCC) in comparison to non-diabetics [25]. Similar findings were seen in Greece, where people with diabetes had a 1.86-fold increased risk of developing liver cancer [26]. Even after controlling for conditions like alcoholism and viral hepatitis, this association between diabetes and HCC has continuously been shown in past studies. According to certain research that particularly examined the many causes of HCC, diabetes increases the risk among those who have hepatitis B virus (HBV), hepatitis C virus (HCV) infection, or alcoholic cirrhosis [27]. However, contradictory data have been found, indicating that diabetes may independently raise the risk of HCC. The correlation between diabetes, chronic hepatitis, and HCC risk has been studied in China and Europe with various degrees of success [28, 29]. The complex underlying mechanisms that connect diabetes and the risk of developing HCC may include elements like low insulin levels and hyperglycemia, which can impair viral response and hinder the eradication of HCV, ultimately causing fibrosis and cirrhosis in people with Type 2 diabetes and HCV [30, 31, 32, 33]. In order to completely comprehend this intricate interaction, more study is required.

Kidney cancer

Kidney cancer has been more common recently, increasing dramatically. Risk factors for Type 2 Diabetes Mellitus (T2DM) and Renal Carcinoma include hypertension, obesity, and smoking. There is still no definite connection between diabetes and kidney cancer, despite numerous studies showing that people with diabetes are more prone to acquire cancer at multiple sites. However, crucial information demonstrating that people with diabetes had a noticeably higher risk of kidney cancer than those without diabetes was supplied by a meta-analysis carried out by Larsson and Wolk in 2011 that included nine cohort studies [34]. However, research connecting diabetes with kidney cancer has produced conflicting results, particularly in regards to gender disparities. Surprising findings emerged from a recent research of a sizable cohort in the US, including over 117,000 women and almost 49,000 men, looking at the risk of diabetes and renal cell carcinoma (RCC). Compared to non-diabetic women, women with diabetes had an increased chance of developing RCC, while no significant connection was seen in men. This shows that, compared to men, women who have T2DM have an increased chance of developing RCC [35].

Possible biologic links between diabetes and cancer risk

Hyperglycaemia

In comparison to hyperinsulinemia (excess insulin), hyperglycemia, or elevated blood sugar levels, has historically been viewed as a secondary cause in the development of cancer [36]. However, a number of studies have found a link between hyperglycemia and a higher risk of cancer [37, 38] For instance, insulin-deficient hyperglycemic mice showed an increase in the number and size of liver tumors as well as decreased apoptosis when compared to insulin-sufficient mice in animal models predisposed to tumors. This syndrome was reversed by insulin therapy. It's interesting to note that research has shown Type 1 Diabetes Mellitus (T1DM), which is characterized by hyperglycemia, might inhibit the growth of tumors. This suggests that, at least in cases of insulin shortage, hyperglycemia may not always promote tumor growth.

According to recent study, tumors continue to eat a lot of glucose regardless of blood glucose

levels [39]. This has been further corroborated by a meta-analysis, which found that better glycemic management did not always lower cancer risk in diabetes people [40]. This shows that hyperglycemia may independently increase the chance of developing cancer, and further study is required to determine the proportional contributions of insulin and glucose to the growth of cancer.

The "indirect effects" and "direct effects" of hyperglycemia on cancer risk can be divided into two categories [41]. Through the stimulation of the synthesis of circulating growth factors (including insulin and IGF-1) and inflammatory cytokines, acts at other organs might indirectly affect tumor cells. On the other hand, direct impacts have an immediate influence on tumor cells by boosting invasion and migration, promoting proliferation, causing mutations, and altering signaling pathways that are connected to cancer. For instance, it has been demonstrated that elevated glucose levels promote the Wnt/-catenin signaling pathway, a crucial route linked to cancer. In spite of hyperinsulinemia, adipokines, or inflammation, this is made possible by enabling the nucleus retention and accumulation of transcriptionally active –catenin [42].

Insulin resistant

Increased levels of circulating insulin are caused by insulin resistance, which is frequently seen in Type 2 Diabetes. Diabetes increases the chance of developing cancer, and cancer cells frequently exhibit high insulin and IGF-1 receptors, indicating a key function for the insulin/IGF axis in this relationship [43]. The relationship between diabetes and cancer has been extensively researched using hyperinsulinemia, a sign of insulin resistance. By directly interacting with the insulin receptor or indirectly by raising levels of circulating IGF-1, it may have an impact on the onset of cancer.IR-A and IR-B are the two IR isoforms that mediate insulin signaling. IGFs and insulin are both recognized by IR-A, but IR-B mainly controls glucose homeostasis [44, 45]. By interacting with IR-A and raising hepatic production of IGF-1, elevated insulin levels can drive cell proliferation by further activating the IGF-1 receptor. The majority of fetal tissues and tumor cells express IR-A and IGF-1 receptors [46, 47].

Studies demonstrating that down-regulating IRs in particular cells lowers tumor growth and inhibits metastasis demonstrate the independent role of the insulin receptor (IR). The proliferation of breast cancer cells has also been linked to inhibiting the IGF-1 receptor. Additionally, hyperinsulinemia raises levels of bioactive IGF-1 by lowering levels of IGF binding protein-1 [48, 49].

After interacting with their ligands, IRs or IGF-1 receptors activate a number of downstream signaling pathways. The PI3K/Akt/mTOR and Ras/MAPK/ERK1/2 pathways, which are important in the proliferation and carcinogenesis of cancer cells, are two key pathways. Additionally, the oncogenic -catenin signaling inhibitor is rendered inactive by the PI3K/Akt signaling pathway, which results in the stimulation of -catenin signaling. Chemotherapy resistance and this mechanism have both been linked to cancer stem cells. These processes emphasize the significance of insulin resistance and hyperinsulinemia in the complex interaction between diabetes and the risk of developing cancer.

Chronic inflammation

Chronic inflammation plays a crucial role in the nuanced interaction between cancer and diabetes. A chronic pro-inflammatory condition brought on by poorly controlled diabetes is characterized by high levels of inflammatory substances such interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-), and C-reactive protein. Genetic instability and an elevated risk of cancer are linked to ongoing inflammation [50, 51]. The proven ability of non-steroidal anti-inflammatory medicines to lower the incidence of several malignancies lends evidence to this association.

There are a number of elements at play, but the precise mechanisms underpinning how chronic inflammation encourages cancer in diabetes people are not entirely understood. Reactive oxygen species produced during oxidative stress can harm lipids, proteins, and DNA, which starts the process of carcinogenesis [52, 53]. Chronic inflammation and oxidative stress are strongly related. High levels of TNF-a, which activate nuclear factor-kappa B (NF-B), a crucial regulator of inflammation, are also linked to chronic inflammation. Cancer cell growth and survival, angiogenesis, metastasis, immune system inhibition, and reactions to hormones and chemotherapy are all regulated by NF-B. Chronic inflammation and oxidative stress over an extended period of time enhance the likelihood that vulnerable cells will develop into cancerous transformation [54, 55]. This intricate interplay emphasizes how crucial it is to comprehend and control diabetes-related chronic inflammation in order to lower the risk of developing cancer [56, 57].

Implications for medical practice

Lifestyle Interventions

Changes in lifestyle can help manage diabetes and lower the chance of developing cancer.

Cancer Screening for Diabetes Patients

Due to their increased risk of getting particular types of cancer, patients with preexisting diabetes, especially Type 2 Diabetes (T2DM), should undergo routine cancer screening. Combining a nutritious diet with regular exercise and maintaining a healthy weight are three lifestyle choices that may help lower your chances of developing diabetes and some malignancies. A joint statement from the American Diabetes Association and the American Cancer Society supports this strategy. Individuals with T2DM should undertake cancer screening tests that have shown benefits in detecting malignancies, such as breast, colon, and endometrial cancer, to improve prognoses and early detection. In comparison to the general population, these screenings ought to start earlier in at-risk populations. These cancer screening techniques must, however, be based on current recommendations and guidelines. It's important to note that even while it's clear that people with diabetes need cancer screening, precise guidelines for diabetes-related cancer screening still need to be developed and improved. Implementing thorough screening programmes for this demographic can considerably aid in the early detection of cancer and better patient outcomes.

Managing Diabetic Patients with Cancer

Diabetes management in people with a cancer diagnosis at the same time is a difficult task. Diabetes may have a detrimental effect on both the risk of developing cancer and the results of cancer treatment. It is clear that co-morbidities have a significant impact on how clinically successful cancer patients are. Therefore, co-morbid illnesses should receive special attention from healthcare professionals who treat cancer patients with Type 2 Diabetes (T2DM). A rigorous and comprehensive strategy is required to adequately manage diabetes in individuals receiving cancer treatment. Patients with cancer who have poor glycemic control have a significantly higher risk of morbidity and mortality. As a result, controlling hyperglycemia becomes a crucial part of providing care for individuals who also have cancer and diabetes. It is crucial to keep an eye out for signs of both hyperglycemia (high blood sugar) and hypoglycemia (low blood sugar). Diabetes patients and their loved ones should be watchful in seeing these signs and obtaining proper medical attention as once when they do. An aggressive glycemic management strategy is essential for hospitalized patients with acute concurrent cancer and diabetes problems. This proactive approach seeks to enhance blood sugar levels and the general outlook for people dealing with both illnesses.

Impact of Anti-Diabetic Treatments

Different pharmacological types are used to treat diabetes; some of these treatments work to replace or improve insulin's ability to lower blood sugar levels, while others target concomitant problems including obesity. Insulin sensitizers like metformin and TZDs (thiazolidinediones) are key players in this group of medications. Metformin, a commonly prescribed drug for Type 2 Diabetes (T2DM), has drawn interest for its conceivable anticancer properties. Emerging data from studies, including both human trials and preclinical research, has suggested that metformin may have a preventive effect against cancer. The use of metformin in individuals with or at risk for diabetes was related with a clinically meaningful 39% lower risk of cancer compared to people who did not use metformin, according to a meta-analysis of 17 randomized controlled studies.

In some cancer cell lines, metformin has also shown a capacity to reduce cell growth and trigger apoptosis (cell death). Although metformin has demonstrated promise in lowering the risk of many malignancies, a new retrospective cohort research found that its usage did not enhance survival in people with advanced pancreatic cancer. Furthermore, depending on the particular cancer type, different associations have been shown between metformin use and cancer risk. It has not been connected to a higher risk of prostate cancer, but it may be linked to a lower risk of colon, liver, pancreatic, or breast cancer.

On the other hand, thiazolidinediones (TZDs) have displayed a mixed profile in terms of cancer risk. A possible cancer risk has been raised by some investigations, specifically in relation to pioglitazone and bladder cancer. In other studies, they have also been linked to a preventive effect against colorectal, lung, and breast malignancies.

Conclusion

This extensive research has revealed a complicated relationship that goes much beyond simple coexistence at the junction of diabetes and cancer. The alarm for increased vigilance in this demographic has been raised by the epidemiological evidence that diabetic patients have a higher risk of cancer. The investigation of underlying mechanisms has uncovered a web of interrelated elements, from DNA damage brought on by hyperglycaemia to the complex relationship between insulin and inflammation in the development of cancer. Obesity and other shared risk factors have complicated the situation even further, emphasizing the significance of lifestyle changes. The review has also highlighted the reciprocal effects of these disorders on one another. Both treating cancer in people with diabetes and managing diabetes in cancer patients involve special obstacles. It is impossible to stress the importance of multidisciplinary care teams working together to improve treatment outcomes. New research offers hope for a better future. Novel diabetes drugs have the potential to treat and prevent cancer. With the help of precision medicine, medicines may be tailored to the special requirements of patients with co-morbidities, opening the door to more efficient and manageable treatments. In conclusion, this review emphasizes how important it is to see diabetes and cancer as connected enemies in the field of health. There is optimism that as knowledge grows and research progresses, we will not only create methods to better the lives of people impacted by these disorders but also those who co-occur with them. Although the road ahead may be complicated, it is lit up by the hope for advancement and the dedication to providing comprehensive, patient-centered care.

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