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Updates in Diabetes Control in Cancer Patients Receiving Cytotoxic Drugs Management: A Systematic Review

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Abstract

Background/Objectives*:** Diabetes is frequent among cancer patients. Diabetes and cancer co-occurrence may result in a worse prognosis and complications in cancer patients. This systematic review aims to investigate the impact of glycemic control in patients having both cancer and diabetes. ***Methods*:** PubMed, Web of Science, Science Direct, and Google Scholar were systematically searched to include the relevant literature. Rayyan QRCI was used throughout this systematic approach. ***Results/ Interpretation: A total of thirteen studies with 13550 patients were included in this review. The reported follow-up duration ranged from 2 to 12 months. Cancer patients with diabetes are more likely to get infections, be hospitalized, and require chemotherapy reductions or discontinuation. Having cancer with comorbid diabetes affects diabetes self-management and results in poor glycemic control. Applying clinical pharmaceutical programs to raise awareness about compliance with diabetic medication along with cancer treatment was found to have positive outcomes. Evidence-based practice recommendations or policies should be developed that advocate assessing diabetes patients' glycemic state at the time of cancer diagnosis.

Keywords: Diabetes, Cancer, Cytotoxic drugs, Chemotherapy, Systematic review.

INTRODUCTION

Cancer and diabetes are two of the major causes of death in the world today, and their prevalence is rising [1]. Diabetes patients are more likely to acquire cancer, specifically malignancies of the breast, colon, lung, prostate, and pancreatic [2]. Approximately 18% of all cancer patients have diabetes at the time of their diagnosis [3]. Diabetes can be found in up to 30% of cancer patients, depending on the type of cancer [4-6].

Diabetes has been found to be six times more common in cancer patients than in the general population. Diabetes patients are likely to be encountered by professionals dealing with cancer patients. As a result, health-care practitioners must understand how diabetes affects cancer-treatment regimens and outcomes, particularly the significance of glycemic management [7].

The number of studies investigating the association between cancer and diabetes has significantly increased over the last decade, demonstrating that academics and health-care professionals are becoming more aware of the challenges connected with the concurrent management of these two complex, chronic disorders. The American Diabetes Association and the American Cancer Society collaborated on a paper on the association between diabetes and cancer in 2010 [8].

Many cancer chemotherapy regimens contain glucocorticoids, which can cause diabetes or worsen pre-existing diabetes. Other treatments, such as androgen-deprivation therapy (ADT) with luteinizing hormone-releasing hormone agonists for prostate cancer, have been related to an increased risk of T2D development, presumably due to insulin sensitivity loss [9]. ADT use in patients with pre-existing T2D and prostate cancer led to deteriorating glycemic control and higher insulin requirements over 2 years [10].

Chemoradiation can cause hyperglycemia [11]. Hyperglycemia has been linked to platinum-based chemotherapy (e.g., cisplatin), 5-fluorouracil-based chemotherapy, [12] mTOR (mammalian target of rapamycin) kinase inhibitors (e.g., everolimus), and

ABL (Abelson murine leukemia) kinase inhibitors (e.g., nilotinib).

In the absence of strong RCT evidence of the potential benefits of treating hyperglycemia in cancer patients, a pragmatic approach to glycemic control in diabetic cancer patients should be considered. This systematic review aims to investigate the impact of glycemic control in patients having both cancer and diabetes.

METHODOLOGY

This systematic review followed established standards (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, or PRISMA) [13].

Study Design and Duration

This was a systematic review conducted between April and May 2023.

Search Strategy

A thorough search of four major databases, including PubMed, Web of Science, Science Direct, and Google Scholar, was done to find the relevant literature. We limited our search to English and took into account the specific requirements of each database. The keywords listed below were transformed into PubMed Mesh terms and used to locate related studies; "Diabetes," "Glycemic control," " Hyperglycemia," "Hyperinsulinemia," "Cancer," "cytotoxic drugs," and "chemotherapy." "The Boolean operators "OR" and "AND" matched the required keywords. Among the search results were publications with full English language, freely available articles, and human trials.

Selection Criteria

We considered the following criteria for inclusion in this review:

- Study designs that investigated the impact of glycemic control in patients having both cancer and diabetes.
- Only adult patients (> 18 years).
- Studies conducted in the last 20 years.
- English language.
- Free accessible articles.

Data Extraction

Rayyan (QCRI) was utilized to detect duplicates in the output of the search strategy [14]. To assess the relevance of the titles and abstracts, the researchers narrowed the combined search results using a set of inclusion/exclusion criteria. The reviewers thoroughly read each paper that met the inclusion criteria. The authors discussed other conflict settlement methods. The permitted study was uploaded utilizing a data extraction form that had previously been created. The authors extracted data about the study titles, authors, study year, country, participants, gender, follow-up duration, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for Data Synthesis

Summary tables were created to provide a qualitative overview of the outcomes and study components contained using data obtained from relevant research. Following data extraction for the systematic review, the most effective technique for utilising data from the included study articles was selected.

Risk of Bias Assessment

The quality of the included studies was assessed using the ROBINS-I risk of bias assessment approach for non- randomized trials of treatments [15]. Confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and selection of the reported result were among the seven themes examined.

RESULTS

Search Results

A total of 844 study articles resulted from the systematic search, and 134 duplicates were deleted. Title and abstract screening were conducted on 710 studies, and 595 studies were excluded. 115 reports were sought for retrieval, and only 25 articles were not retrieved. Finally, 90 studies were screened for full-text assessment; 56 were excluded for wrong study outcomes, and 21 for the wrong population type. Thirteen eligible study articles were included in this systematic review. A summary of the study selection process is presented in Figure 1.

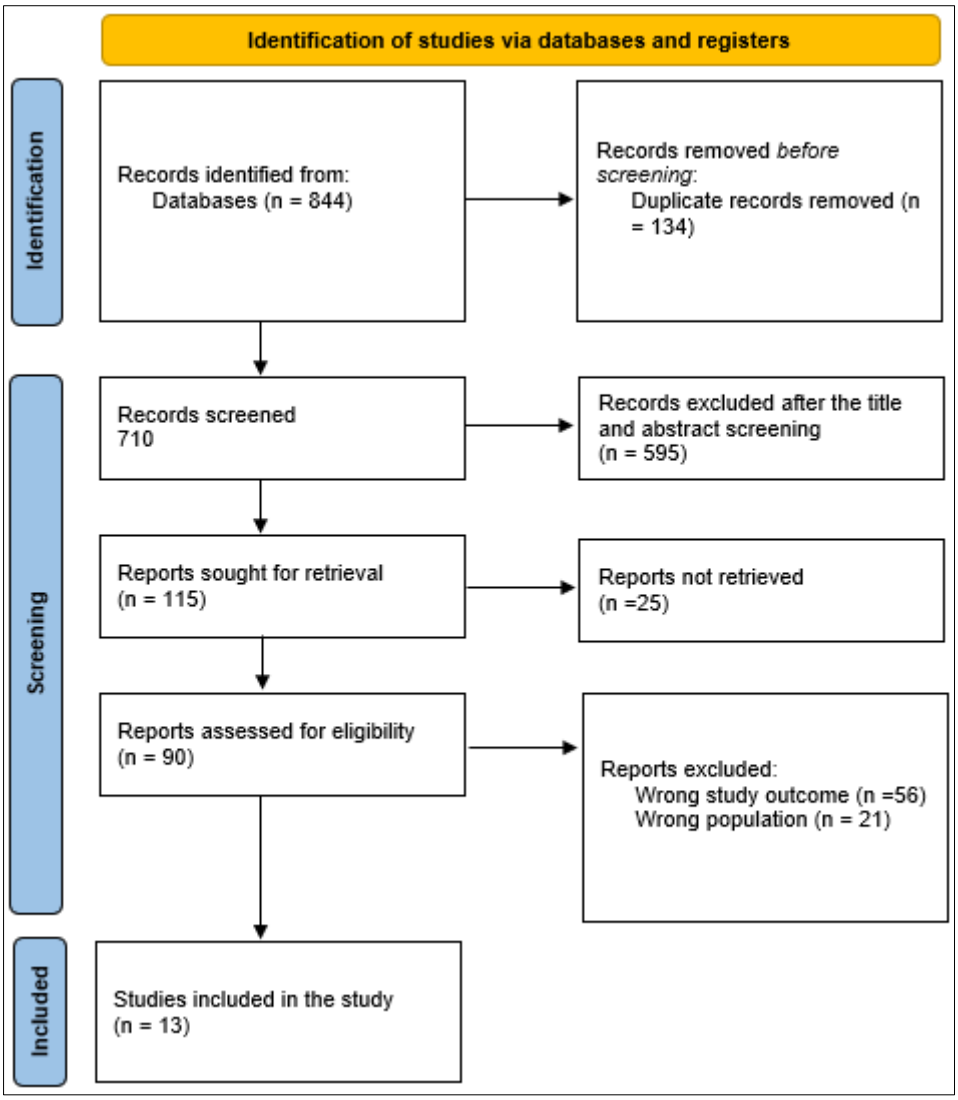

Figure 1: PRISMA flowchart summarizes the study selection process

Characteristics of the Included Studies

Table 1 includes the socio-demographic characteristics. Our results included thirteen studies with a total of 13550 patients. Six studies were conducted in the USA [16, 20, 22, 24, 25, 27], two in India [21, 23], one in Japan [17], one in France [18], one in Turkey [19], one in China [26], and one in Greece [28]. Six studies were retrospective in nature [18, 21, 23-26], three were cohort studies [22, 27, 28], two were prospective studies [16, 19], one was a qualitative descriptive study [17], and one was an exploratory study [20].

Table 2 presents the clinical characteristics. The reported follow-up duration ranged from 2 to 12 months.

All of the included studies reported that the level of glycemic control, when a person begins cytotoxic cancer treatment, appears to relate to the incidence of an adverse event, getting an infection and/or being hospitalized during treatment [16-28]. One study reported that diabetes was twice as common in cancer patients as in non-cancer controls. Having cancer with comorbid diabetes affects diabetes self-management and results in poor glycemic control [17, 19, 20]. Al-Taie *et al.*, applied a comprehensive clinical pharmacy service with one-on-one interviews to provide greater self- management information, raise awareness to take medication regularly as prescribed, optimize therapy and drug management, and provide better care for diabetes and cancer. This resulted in a significant drop in HbA1c, a significant increase in medication adherence, and a significant improvement in diabetic self-care behaviours such as diet awareness, blood glucose self-monitoring, and foot care. Furthermore, when compared to the control group, patients in the intervention group reported less decline in many QoL functions [19].

Because of the potential of infection and hematological damage associated with cytotoxic chemotherapy, oncologists should be extra cautious about diabetes in cancer patients. First, they should

ensure glycemic control and, if necessary, change diabetic therapy. Second, given the danger of diabetes decompensation with corticosteroids, their usage should be thoroughly assessed, and dose decrease should be considered [18].

Table 1: Socio-demographic characteristics of the included participants

Study	Country	Study design	Participants	Age	Males (%)
Hershey & Hession, 2017 [16]	USA	Prospective cohort	18	63	8 (44)
Terao, 2023 [17]	Japan	Qualitative descriptive	16	40s - 70s	7 (43.8)
Mailliez *et al.*, 2023 [18]	France	Retrospective	609	60.0 ± 12.2	217 (35.6)
Al-Taie *et al.*, 2020 [19]	Turkey	Prospective RCT	100	60.98 ± 8.99	36 (36)
Hershey *et al.*, 2012 [20]	USA	exploratory	37	64.5 ± 9.5	16 (43.2)
Attili *et al.*, 2007 [21]	India	Retrospective	114	44.8 ± 13.6	NM
Yao *et al.*, 2015 [22]	USA	Cohort	2707	74.4	635 (23.46)
Storey *et al.*, 2022 [23]	India	Retrospective	6851	55.2 ± 11.88	NM
Zylla *et al.*, 2019 [24]	USA	Retrospective	1781	59.5 ± 13.4	721 (40.5)
Phillips *et al.*, 2023 [25]	USA	Retrospective	243	NM	NM
Zeng *et al.*, 2020 [26]	China	Retrospective	200	59.2 ± 10.1	157 (78.5)
Kleckner *et al.*, 2022 [27]	USA	Cohort	674	52.8±10.5	0
Lavdaniti *et al.*, 2021 [28]	Greece	Cohort	200	NM	NM

Table 2: Clinical characteristics and outcomes of the included studies

Study	Follow-up (months)	Main outcomes	ROBIN-I
Hershey & Hession, 2017 [16]	3	The level of glycemic control, when a person begins cancer treatment, appears to relate to the incidence of an adverse event, getting an infection and/or being hospitalized during treatment, and the greater likelihood of having chemotherapy reduced or stopped. Clinicians who work with patients who have pre-existing diabetes and are taking chemotherapy for a solid tumour malignancy must be mindful of how the patient's glycemic level at the start of treatment may affect successful treatment completion.	Moderate
Terao, 2023 [17]	NM	Patients with diabetes having chemotherapy for the first time must balance "the management of blood glucose level and side effects according to the patient's physical condition," while continually trying for "mental balance." Patients with diabetes who are taking chemotherapy make efforts to self-manage their blood glucose levels as well as chemotherapy-related side effects, despite their bewilderment regarding their abnormally high blood glucose levels and the additional adverse effects of their medication.	Moderate
Mailliez *et al.*, 2023 [18]	NM	Diabetes increases the incidence of severe adverse events within 90 days of initiating chemotherapy in cancer patients. Because of the potential of infection and hematological damage associated with cytotoxic chemotherapy, oncologists should be extra cautious about diabetes in cancer patients. First, they should ensure glycemic control and, if necessary, change diabetic therapy. Second, given the danger of diabetes decompensation with corticosteroids, their usage should be thoroughly assessed, and dose decrease should be considered.	High
Al-Taie *et al.*, 2020 [19]	3	A comprehensive clinical pharmacy service with one-on-one interviews was implemented to provide greater self-management information, raise awareness to take medication regularly as prescribed, optimize therapy and drug management, and provide better care for diabetes and cancer. This resulted in a significant drop in HbA1c, a significant increase in medication adherence, and a significant improvement in diabetic self-care behaviours such as diet awareness, blood glucose self-monitoring, and foot care. Furthermore, when compared to the control group, patients in the intervention group reported less decline in many QoL functions.	Moderate
Hershey *et al.*, 2012 [20]	2	Cancer treatment and cancer-related symptoms may have a negative impact on diabetes self-management behaviours in diabetic people	

Study	Follow-up (months)	Main outcomes	ROBIN-I
		undergoing chemotherapy. Diabetes self-management education that targets the "cause" rather than merely the "source" of the problem is needed to enhance health outcomes in patients with diabetes and cancer.	High
Attili *et al.*, 2007 [21]	NM	Diabetes is linked to an increase in mortality and poor response rates. This mechanism is most likely unaffected by glycemic control, concomitant diseases, or the therapy strategy employed to control diabetes. They discovered no statistically significant increase in complication rates in diabetes patients. The relatively good glycemic control in the current study could explain this clinical paradox: all of the diabetics in the current investigation have near-normal blood sugar levels throughout.	Moderate
Yao *et al.*, 2015 [22]	6 m	Diabetes management care for cancer patients dropped following diagnosis, regardless of where their cancer surgery was performed. This is an example of a missed opportunity to connect diabetic cancer patients to diabetes care, particularly among patients treated in major comprehensive cancer centers. This study establishes benchmarks for measuring advances in comorbidity management among cancer patients.	Moderate
Storey *et al.*, 2022 [23]	12	Comorbid T2D has a negative impact on health-related outcomes and resource utilization in breast cancer survivors. These findings point to the need for clinical practice guidelines to assist doctors in managing diabetes among BCS across the cancer trajectory, as well as coordinated models of treatment to reduce health-care resource utilization. More research is needed to investigate the implications of diabetes in BCS, as well as to design and evaluate strategies to enhance outcomes and reduce resource utilization.	High
Zylla *et al.*, 2019 [24]	12	They discovered that hyperglycemia, regardless of diabetes status, was linked to lower survival and higher infection/admission rates. However, baseline HbA1c levels were not related to clinical outcomes or healthcare utilization in patients with established diabetes. This could imply that baseline average glucose is not a predictor of results, but that diabetes and/or poorly controlled diabetes during active cancer treatment contributes to poor outcomes.	Moderate
Phillips *et al.*, 2023 [25]	NM	Diabetes and glycemic management may have an impact on the health outcomes of NMBC patients. More research is needed to validate these findings and to discover the best monitoring and management options for NMBC patients with diabetes and/or poor glycemic control during cytotoxic chemotherapy.	High
Zeng *et al.*, 2020 [26]	NM	Based on the observed prolonged progression-free survival (PFS), adequate glycemic control appeared to be a favourable prognostic factor in T2D patients with advanced non-small cell lung cancer (NSCLC) receiving first-line platinum-based doublet chemotherapy. Because improved blood glucose control may improve chemotherapy efficacy without causing additional side effects, it should be given special consideration in these patients.	Moderate
Kleckner *et al.*, 2022 [27]	NM	Diabetes was twice as common in cancer patients as in non-cancer controls. Diabetes was also linked to cancer-related fatigue in female breast cancer patients before, during, and after chemotherapy treatment, even after correcting for demographics, clinical features, and lifestyle factors. If these findings are correct, glycemic management during cancer treatment may minimize the burden of both acute and long-term cancer-related fatigue. Future study is required to explain the causes of fatigue so that metabolically focused treatments can be developed.	High
Lavdaniti *et al.*, 2021 [28]	NM	Diabetes appears to have a negative impact on certain areas of quality of life in cancer patients who have undergone chemotherapy, and this may be modified by the length of diabetes and whether or not glycemic control has been attained.	Moderate

DISCUSSION

All of the included studies in this systematic review addressed that the level of glycemic control, when a patient starts cytotoxic cancer treatment, is related to the incidence of an adverse event, getting an infection and/or being hospitalized during treatment [16-28]. Glycemic management is one theory explaining the difference in outcomes between cancer patients with and without diabetes. However, few researchers have looked into the significance of glycemic management in the outcomes of cancer patients with diabetes. Several chemotherapeutic drugs and corticosteroids routinely used to treat side effects in cancer patients have been linked to an increased incidence of hyperglycemia in people without diabetes [29]. Diabetes patients undergoing chemotherapy are more likely to prioritize their cancer treatment over managing their diabetes, increasing their risk of poor glycemic control during this important period, according to research [20]. Furthermore, when chemotherapy is being administered, oncologists and patients' primary care physicians may not focus on diabetes management [20, 30]. Despite this lack of focus, glycemic control levels can have a significant impact on the outcomes of cancer patients with diabetes.

We also found that having cancer with comorbid diabetes affects diabetes self-management and results in poor glycemic control [17, 19, 20]. This detrimental impact on self-management activity performance is consistent with the literature. The more symptoms an individual has, and the overlapping or competing consequences of these symptoms, the worse their performance of self-management activities. According to the analysis of the open-ended questions, one of the factors that affected one's ability to execute diabetic self-management activities was the influence of symptoms [31-33].

In our review, Al-Taie *et al.*, applied a comprehensive clinical pharmacy service with one-on-one interviews to provide greater self-management information, raise awareness to take medication regularly as prescribed, optimize therapy and drug management, and provide better care for diabetes and cancer. This resulted in a significant decrease in HbA1c, an increase in medication adherence, and a significant improvement in diabetes self-care behaviours such as diet awareness, self-monitoring of blood glucose, and foot care. Furthermore, patients in the intervention group reported reduced deterioration in numerous QoL functions when compared to the control group [19]. Poor adherence to recommended medications is another major impediment to appropriate care, potentially increasing the risk of complications, hospitalization, and mortality [34]. Diabetes self-care activities have been shown to enhance glycemic control, reduce complications, and improve patients' quality of life [35].

Because of the potential of infection and hematological damage associated with cytotoxic chemotherapy, oncologists should be extra cautious about diabetes in cancer patients. First, they should ensure glycemic control and, if necessary, change diabetic therapy. Second, given the danger of diabetes decompensation with corticosteroids, their usage should be thoroughly assessed, and dose decrease should be considered [18].

Although past research suggests that having both cancer and diabetes leads to worse outcomes, evidence is limited and many essential factors have yet to be researched. According to this systematic review, the bulk of studies focused on general HRQoL and physical function, with little emphasis dedicated to mental health.

Furthermore, a qualitative study has revealed that diabetes patients who get cancer prioritize cancer care over diabetes care [20]. Self-management is widely investigated among diabetes patients, and a prior literature review and meta-analysis found that self-management interventions can improve blood glucose levels, increase knowledge and self-efficacy, and perhaps lower healthcare utilisation costs [36]. It is critical that both patients and doctors understand the necessity of self-management of various chronic conditions. It is critical that patients be able to use their resources, feel in charge of their lives, and address difficulties as necessary. As a result, we believe that patient empowerment and enhancing self-management behaviour are relevant issues to investigate in future studies including patients with multiple chronic conditions [37].

CONCLUSION

Cancer patients with diabetes are more likely to get infections, be hospitalized, and require chemotherapy reductions or discontinuation. While it has been suggested that glycemic management increases the likelihood of these adverse outcomes, few research articles investigated this possibility. Having cancer with comorbid diabetes affects diabetes self-management and results in poor glycemic control. Applying clinical pharmaceutical programs to raise awareness about compliance with diabetic medication along with cancer treatment was found to have positive outcomes.

RECOMMENDATIONS

Evidence-based practice recommendations or policies should be developed that advocate assessing diabetes patients' glycemic state at the time of cancer diagnosis. Survivorship care plans should include suggestions for ongoing diabetes and cancer management, assessment, and therapy. To provide the best level of quality of life during this period, such plans must meet all of the patient's health-care

demands. As the patient progresses from survivorship to end-of-life care, diabetes management discussions with the patient and family should cover when and how to reduce the frequency of glucose monitoring and diabetes medications.

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