Review Article

Glycemic Excursion, Adverse Drug Reactions, and Self-Management in Diabetes Patients Undergoing Chemotherapy: A Literature Review

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ABSTRACT

The purpose of this study was to identify the state of self-management in patients with diabetes who underwent chemotherapy, by referring to fluctuations in glycemic excursion and adverse drug reaction. We conducted a literature search in May 2021 using PubMed, CINAHL, and Ichushi-Web databases with "Cancer AND Diabetes AND Chemotherapy" as keywords. Based on our criteria, 25 articles were selected, and a review matrix sheet was created for the analysis of fluctuations in glycemic excursion and any adverse drug reaction to diabetes in patients undergoing chemotherapy. Substantial increases and unpredictable fluctuations in glycemic excursion were observed in these patients. In addition, an increase or change in the treatment dose was prevalent. Primarily, peripheral neuropathy and infection were reported as common adverse drug reactions. The risk of adverse drug reactions was especially high for patients with diabetes undergoing chemotherapy; furthermore, among this cohort, the detrimental effects were more likely to exacerbate into a severe condition that required special attention. Almost inevitably, the implementation rate of diabetes self-management programs decreased on the 8th week after the commencement of chemotherapy. Considering the findings of large individual differences in fluctuation in this cohort, tailored assistance that is appropriate for each patient's chemotherapy regimen or blood glucose level is of paramount importance. Support of patient self-management to achieve stable blood glucose levels and thus prevent adverse drug reactions was a key component in the successful completion of chemotherapy and improved patient outcomes for this group of special needs patients.

Key words: Adverse drug reaction, chemotherapy, glycemic excursion, patients with both cancer and diabetes, self-management

Introduction

Worldwide, the number of patients with both diabetes and cancer has been increasing.[1,2] In Japan, the leading cause of death among patients with diabetes from 2001 to 2010 was malignant neoplasm, accounting for about 38% of all cases.[3] In the United States, malignant neoplasms are the second leading cause of death in patients with diabetes,

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accounting for approximately 20% of all cases.[4] Thus, malignant neoplasms are the leading cause of death in patients with diabetes. Since 90% of patients with diabetes are suffering from type 2 diabetes mellitus,[5] it is reasonable to speculate that patients with both cancer and complications of type 2 diabetes mellitus are similarly on the rise. It is critical for type 2 diabetes mellitus patients to improve their daily lifestyle habits and maintain stable blood glucose and blood pressure levels to prevent the onset and worsening of diabetes-related complications and atherosclerotic diseases.[6,7] However, improving lifestyle habits is not only difficult to change but also affects interpersonal relationships, work, and roles. Therefore, even if the need is known, it is difficult to put it into action.[8-10] For this reason, self-management of patients with type 2 diabetes is focused on behavior change, motivation, and self-efficacy.[11] In contrast, the introduction of self-management programs, appropriate for the specific treatment of tumors based on their location, is crucial for patients with cancer.[12,13] As a result, when patients with diabetes are diagnosed with cancer and undergoing chemotherapy, they are forced to manage both diabetes and chemotherapy side effects, which increases the difficulty and complexity of self-management. Previous studies have reported that patients with diabetes undergoing chemotherapy experienced a decrease in self-management of diabetes 8 weeks after the start of chemotherapy.[14] Moreover, patients experienced more glycemic variability and dietary changes during treatment compared to before cancer treatment.[15] Diabetes mellitus has been shown to negatively affect the quality of life of physical and mental functions of patients undergoing chemotherapy.[16] As shown above, chemotherapy in patients with type 2 diabetes mellitus leads to difficulties in self-management and deterioration of patients' quality of life.

Especially for patients with diabetes who underwent chemotherapy, corticosteroids (steroids) used for antiemetic[17] and allergy prevention[18] can cause hyperglycemia.[19] This risk of hyperglycemia or hypoglycemia associated with chemotherapy is alarming, particularly because accidents involving disorders of consciousness due to hyperglycemia or bone fracture owing to falls caused by hypoglycemia have been reported, and some of these cases can indeed be fatal.[20] Clearly, controlling blood glucose levels during chemotherapy is a matter of life or death to patients with both cancer and diabetes. Physical weariness,[21] susceptibility to infection,[22] or diabetic neuropathy[23] manifest simultaneously with adverse drug reactions to chemotherapy; this further exacerbates patient health and makes the continuation of chemotherapy difficult. Thus, the self-management of blood glucose levels and adverse drug reactions to chemotherapy become a key component of the safe completion of chemotherapy for patients with diabetes. Despite its relevance and effect on patient outcomes, the self-management issues concerning fluctuation in blood glucose levels or adverse drug reaction to chemotherapy of patients with diabetes have largely been overlooked. Therefore, the purpose of the present literature review was to illuminate the state of self-management among patients with diabetes undergoing chemotherapy in relation to fluctuation in their blood glucose levels or adverse drug reactions.

Methods

We used PubMed, CINAHL, and Ichushi-Web databases to conduct a literature search in May 2021 with the following keywords: "Cancer AND Diabetes AND Chemotherapy." We did not establish any specific year range for this search. Out of 16,992 articles returned in our search, 953 articles were selected based on the following criteria: A peer-reviewed, original article published in an academic or professional journal of English or Japanese language whose participants were 19 years of age or older. After reading abstracts from 953 articles, 928 articles that did not report on patients with diabetes undergoing chemotherapy were excluded, which left us with 23 articles. After adding two articles found in-person, a total of 25 articles remained for analyses: 17 articles in English and 8 articles in Japanese [Figure 1]. A review matrix sheet with a table that listed the following items and topics was created to analyze the content and trend involving self-management, fluctuations in blood glucose levels, and adverse drug reactions to chemotherapy: The date of publication, survey country, research design, the purpose of the study, the type of study, attributes, cancer type, cancer stage, chemotherapy treatment plan (regimen), usage of steroids during chemotherapy, classification of diabetes mellitus, blood glucose, or glycated hemoglobin (HbA1c) levels, and the manifestation of adverse drug reactions. The first author (N.T) extracted the references for analysis, and then discussed and confirmed with the co-researcher (K.S) whether the extracted references were appropriate for analysis.

Results

Research overview of patients with diabetes undergoing chemotherapy

The overwhelming majority of the study designs were quantitative: 22 studies out of 25. Observational studies were the most common, with 14 cases. The study focus was as follows: Fluctuations in blood glucose levels during chemotherapy (n = 6), adverse drug reaction to chemotherapy (n = 13), and patient self-management (n = 6). The types of cancer observed in most participants were a

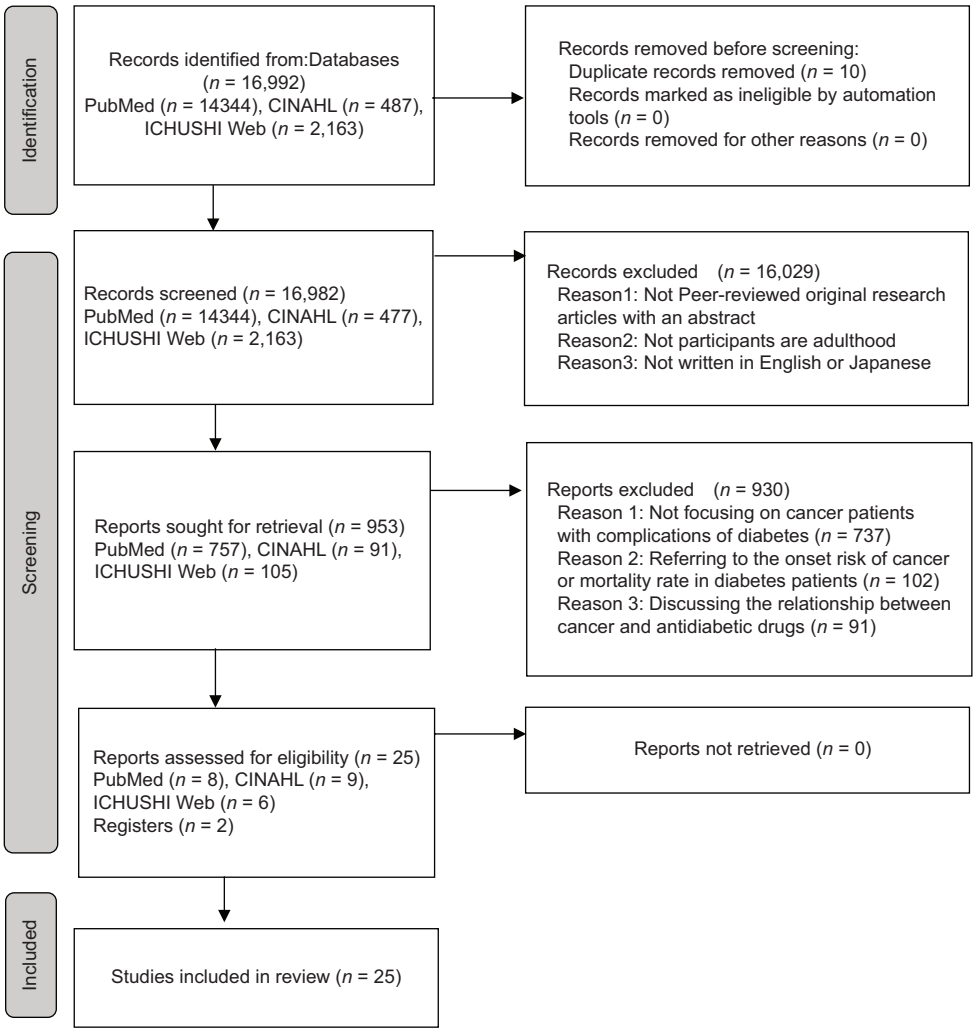

Figure 1: Sampling process

combination of solid carcinoma and hematologic cancer. For those studies that specified the tumor location, four out of fourteen concerned breast cancer. On the other hand, the locations of tumors in other studies were diverse. Regarding cancer stage, studies that included stages I to IV ($n = 9$) and I to III ($n = 3$) were common. Only two studies specified one specific type of chemotherapy regimen while others either made no statement or involved a combination of various regimens. Most studies did not provide details of diabetes type, or blood glucose, or HbA1c levels. Participants were predominantly older: The average age of the participants from 18 studies was 60 years or older. The scale of the studies varied widely ranging from four to 14,000 participants; of 24 studies, 19 studies were small, with <100 participants [Table 1].

Fluctuations in blood glucose levels of patients with diabetes undergoing chemotherapy

All the participants in the reviewed studies had used steroids during chemotherapy. The highest recorded levels of blood glucose during chemotherapy were over 300 mg/dl.[37,44] The surge in blood glucose levels occurred within a few hours of anticancer drug treatment, peaked at approximately 10 h, and dropped after 24 h.[44] The mean fasting blood glucose level was significantly increased from 131.4 ± 37.2 mg/dl before treatment to 163.8 ± 52.3 mg/dl before breakfast on the day after treatment ($P < 0.01$).[39] Hyperglycemia was detected in 80% of the 40 patients during the first course of chemotherapy and 60% during the fifth course.[35] The achievement rate of glycemic control goals by steroid type was 54% for dexamethasone and 87% for prednisolone among 40 patients, with dexamethasone being significantly lower than prednisolone ($P < 0.05$).[37] Significant positive correlations were identified (blood glucose: $r = 0.697$; HbA1c: $r = 0.712$; $P < 0.01$) between cumulative doses of dexamethasone and the increase in the levels of blood glucose and HbA1c. When cumulative doses of dexamethasone reached over 150 mg, significant increases in blood glucose and HbA1c levels were identified ($P < 0.01$).[37]

Table 1: Characteristics of reviewed studies

First author (publication year)/ survey country	Research design	Number of participants	Average age or median (years)	Type of cancer	Cancer stage	Average blood glucose level (mg/dl) or HbA1c (%)	The state of steroid medication	Regimen	State during chemotherapy
Kunitake *et al*., (2020)[24]/Japan	Qualitative	6	52.7	Pancreatic, biliary	I～IV	7.3	NR	GEM, GS, NabPTX	Patients were trying to grasp their own bodies as diabetic more than before the onset of cancer Patients had been living a blood glucose conscious life while continuing their chemotherapy Patients continued to use their diets to control their blood glucose levels while on chemotherapy Patients were experiencing difficulties in living a diabetes-conscious life while continuing chemotherapy
Kikuchi and Fujino (2020)[25]/Japan	Qualitative	7	67.1	Colon	NR	7.6	NR	XELOX, FOLFIRI, XELOX + Bev	Patients were experiencing numbness in their fingertips and could not take their blood glucose readings, so they had to retake the blood glucose test
Molassiotis *et al*., (2019)[26]/Hong Kong, Singapore, UK	Observational	37	54.2±9.2	Solid tumor	I～IV	NR	NR	Taxanes, platinum, combined	Diabetes showed a trend ($P<0.05$) with sensory CIPN only Those with history of neuropathy had a higher risk for CIPN
Zylla *et al*., (2019)[27]/ USA	Observational	330	64.6	Solid tumor, hematological tumor	I～IV	7.1% ±1.4%	Available (details unknown)	NR	At least one glucose test >300 mg/dl, and a higher HbA1c When limited to infection-related admissions, patients with diabetes had nearly 8% higher rates of admission No significant differences were seen when analyzing patients with diabetes in different HbA1c categories There was no association between cancer stage, age, or gender on the rate of new onset/chemotherapy infections
Gaballah *et al*., (2018)[28]/Egypt	Observational	54	50.1±11.5	NR	NR	NR	NR	Cisplatin, oxaliplatin, paclitaxel, docetaxel	A significant correlation was noted between the presence of diabetes and incidence of CIPN About 63% of the patients who developed CIPN had a positive history of diabetes ($P<0.01$) With oxaliplatin, no factor affected the occurrence or grade of CIPN
Lega *et al*., (2018)[29]/ Canada	Cohort	4955	66.8	Breast	I～III	NR	NR	NR	Among woman with Stage III breast cancer, in whom chemotherapy is considered guideline-adherent treatment, those with diabetes were slightly less likely to receive chemotherapy than those without diabetes
Goebel *et al*., (2016)[30]/USA	Qualitative	5	59.4±6.5	Breast, colon, lymphoma	NR	NR	NR	NR	The nurse and oncologist groups discussed that their patients were able to focus on only one disease at a time, which usually was cancer Some patients believed that their providers "didn't worry about (their) sugar at all," so they, too, did not have to be concerned about their diabetes Specifically, fatigue interfered with regular exercise, while nausea and vomiting interfered with nutrition, and altered sleep cycles prevented the maintenance of regular schedules Patients said that following a diet was particularly difficult because they "were not supposed to have (the food they wanted) with their diabetes" "The lady had chemo so she was having difficulty swallowing .(so) she couldn't actually swallow her diabetes pills" "I didn't have neuropathy that bad before I started cancer treatment. Now it's bad" "The peripheral neuropathy can really mix and confuse the picture of what's going on. Sometimes, having the patient put the two together can create a confusing timeline as to what caused it"

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First author (publication year)/ survey country	Research design	Number of participants	Average age or median (years)	Type of cancer	Cancer stage	Average blood glucose level (mg/dl) or HbA1c (%)	The state of steroid medication	Regimen	State during chemotherapy
Kus *et al*., (2016)[31]/ Turkey	Observational	81	NR	NR	NR	NR	NR	Taxanes	Patients receiving the taxane and platinum combination arm were evaluated independently. Neuropathy developed in 81.8% of diabetic patients ($P<0.05$) In the taxane-only therapy group ($n=270$), neuropathy development was observed in 45.5% ($n=96$) of non-diabetic and 52.5% ($n=31$) of diabetic patients ($P<0.05$) In the taxane and combination group, 34.6% of diabetic patients developed neuropathy of > Grade 2 ($P=0.001$) Diabetic patients having a duration of >5 years showed high incidences of neurotoxicity
Park *et al*., (2015)[32]/ Republic of Korea	Observational	79	61.8±12.1	Solid tumor	I～IV	NR	NR	Alkylating agents, antimetabolites, anthracyclines, etc.	The decision tree analysis identified underlying diabetes and the alkylating agent regimen as the greatest risk factors for infections in patients undergoing chemotherapy In the subset of subjects with diabetes or combination of diabetes and hypertension, the likelihood of infection was 25.3%
Hershey and Pierce (2015)[33]/USA	Exploratory	41	64.6±9.5	Solid tumor, hematological tumor	I～IV	NR	NR	NR	Patients who had diabetes experienced increased severity only for appetite and nausea Patients started with moderate fatigue that tended to increase slightly
Higo *et al*., (2015)[34]/ Japan	Observational	34	61.9±4.6	Solid tumor, hematological tumor	NR	7.1%±0.8%	NR	NR	Levels of self-efficacy were significantly higher ($P<0.01$) for diabetes patients who responded "completely agree" than "somewhat agree" to a questionnaire item that stated "I would like to focus on treatments for both cancer and diabetes because both diseases are curable"
Brady *et al*., (2014)[35]/Japan	Observational	40	61	ALL, lymphoma	NR	220.6 mg/dl (blood glucose level during fasting)	Dexamethasone (40 mg) by mouth daily for four consecutive days	Hyper- CVAD	All the patients who were on metformin and/or an oral secretagogue continued on their oral regimen with the addition of insulin during steroid treatment At least one glucose value<70 mg/dL, which accounted for 1.3% of all recorded glucose values. No severe hypoglycemia (blood glucose level, <40 mg/dL) was observed The average insulin dose received by patients per cycle was 1-1.3 units/kg Analysis of insulin dosage on demographic and clinical characteristics showed higher doses in patients with higher body mass index Hyperglycemia occurred in 80% of glucose measurements in Cycle 1 compared with 60% of Cycle 5 measurements; this was statistically significant

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First author (publication year)/ survey country	Research design	Number of participants	Average age or median (years)	Type of cancer	Cancer stage	Average blood glucose level (mg/dl) or HbA1c (%)	The state of steroid medication	Regimen	State during chemotherapy
Hershey *et al*., (2014)[14]/USA	Exploratory	41	64.0±9.6	Solid tumor, hematological tumor	Early and late	NR	NR	NR	When compared with baseline, cancer patients with diabetes performed significantly fewer self-management activities for diabetes after a minimum of 8 weeks of chemotherapy Symptom severity was significantly higher after a minimum of 8 weeks of chemotherapy when compared with baseline Number of years with diabetes (r=0.52), total number of medications (r=0.38), level of DSE (r=0.67), level of OE (r=0.41), and baseline diabetes self-management (r=0.75) Individuals who had diabetes longer, had higher levels of DSE, and had higher levels of performance of diabetes self-management activities at baseline also had higher levels of self- management after a minimum of 8 weeks of chemotherapy Living arrangements, total number of years with diabetes, total number of medications, baseline self-management, DSE, and level of symptom severity at baseline and 8 weeks were all noted to be significant (P<0.05) predictors of diabetes self-management after a minimum of 8 weeks of chemotherapy This decrease in the performance of self-management activities may be due to the increase in symptom severity
Takenaka *et al*., (2013)[36]/Japan	Observational	6	63	Head and neck	II～IV	NR	NR	TPF, DC	Tube feeding and the presence of diabetes were both independent significant predictors of febrile neutropenia
Dote *et al*., (2013)[37]/ Japan	Observational	40	72.5	Hematological tumor	NR	NR	Prednisolone, 40 mg/day; dexamethasone, 19.8 mg/day	Anthracycline and cytarabine, CHOP, etc.	The sliding scale, used as a measure against hyperglycemia after steroid prescription, indicated that the control of blood glucose levels was difficult The rate of achieving the goal for blood glucose control was significantly lower for the dexamethasone administered group than the prednisolone administered group (P<0.05) Prominently high level of hyperglycemia (above 300 mg/dl) was detected Even with the small dosage of prednisolone, there were cases that required an active increase in the insulin prescription
Vincenzi *et al*., (2013)[38]/Italy	Exploratory	29	<60 or>60: 50%	Colon	NR	NR	NR	FOLFOX4	Diabetic patients did not show a higher incidence of peripheral neuropathy when compared with non-diabetic patients Grade 2-3 neurotoxicity was observed in 55% of the diabetic population
Tanimoto *et al*., (2013)[39]/Japan	Observational	20	64.0±12.1	Gynecologic	I～IV	At the commencement of chemotherapy, 6.97%; At the completion or termination of chemotherapy, 6.59%	Used by 95% of patients	Taxanes and Platinum, CPT11 and Platinum, etc.	The treatment plan for diabetes had to be changed during chemotherapy for four patients (20%) due to the challenge associated with blood glucose control 5 patients (25%) received nonperiodic insulin injections due to hyperglycemia Blood glucose level significantly increased before breakfast on the day after chemotherapy (163.8±52.3 mg/dl) compared to the blood glucose level during a fasting period (131.4±37.2 mg/dl) before chemotherapy There were no reports of hypoglycemic attack during chemotherapy in all cases

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First author (publication year)/ survey country	Research design	Number of participants	Average age or median (years)	Type of cancer	Cancer stage	Average blood glucose level (mg/dl) or HbA1c (%)	The state of steroid medication	Regimen	State during chemotherapy
Uwah *et al*., (2012)[40]/USA	Observational	15	60.2	Colon	NR	NR	NR	Oxaliplatin-induced	Patients with diabetes developed neuropathy at a significantly lower mean cumulative dose of 388 mg/m2 From the fifth cycle of chemotherapy, patients with diabetes showed a higher chance of developing OXIPN than patients without diabetes
Hershey *et al*., (2012)[16]/USA	Action research	76	NR	Breast, colon. Lung, other	NR	NR	NR	NR	Patients with and without diabetes aged ≤59 years had similar levels of mental health. Mental health improved in patients with diabetes aged 60-69 years, but declined in patients with diabetes and cancer >70 years The presence of diabetes negatively impacted physical function and mental health in patients undergoing chemotherapy
Tsuda *et al*., (2012)[41]/Japan	Observational	7	53.2±10.7	Breast	NR	NR	NR	FEC, CE, AI	It was speculated that diabetes patients undergoing paclitaxel chemotherapy were at high risk of developing grade ≥3 peripheralnerve disorder
Wuketich *et al*., (2012)[42]/Vienna	Cross-sectional research	168	66-75, 50.8% 76-80, 49.2%	Solid tumor	I～IV	NR	NR	Gemcitabine, taxanes, oxaliplatin, etc.	Of all nondiabetic patients, 5.9% showed symptoms of chemotherapy-induced oral mucositis versus 6.9% in the diabetes mellitus group ($P<0.05$)
Fujii *et al*., (2012)[43]/ Japan	Observational	14	61.6±7.2	Solid tumor	I～IV	NR	Dexamethasone cumulative dose after: 3 months, 46.4 mg; 6 months, 91.7 mg; 12 months, 157 mg	GEM, FOLFOX, FOLFIRI, etc.	The blood glucose levels of diabetes patients with cancer who were administered dexamethasone for 12 months were significantly higher ($P<0.05$) than those for diabetes patients who had received diabetic treatment for more than 1 year without a history of anti-cancer and steroid therapies including dexamethasone A significant positive correlation was identified between a 12 montha cumulative dose of dexamethasone and the change in blood glucose and HbA1c levels over 12 months ($P<0.01$) When a cumulative dose of dexamethasone exceeded 150 mg, the capacity of variation in blood glucose or HbA1c levels over a 12 months period was positively significant Although the type or dosage of antidiabetic drug were adjusted for approximately half of the patients, levels of blood glucose and HbA1c increased with the cumulative dose of dexamethasone Changes in the treatment plan such as the unit change in insulin, increase in the dosage of internal medicine, or introduction of different type of insulin were made for 4 patients (28.6%)
Saito *et al*., (2011)[44]/Japan	Observational	4	67.7±9.6	Gynecologic	I～IV	NR	Dexamethasone 6.6 mg or 19.8 mg	Paclitaxel, carboplatin, docetaxel, and carboplatin	Blood glucose level was heightened by dexamethasone even for those patients with excellent blood glucose control before chemotherapy A significant increase in blood glucose levels was identified in all cases after the administration of dexamethasone ($P<0.05$) Peak blood glucose levels were observed about 10 h after the intravenous administration of dexamethasone Increases in blood glucose level due to dexamethasone were transitory; they became apparent a few hours after administration, but then decreased after 24 h

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First author (publication year)/ survey country	Research design	Number of participants	Average age or median (years)	Type of cancer	Cancer stage	Average blood glucose level (mg/dl) or HbA1c (%)	The state of steroid medication	Regimen	State during chemotherapy
Srokowski *et al.*, (2009)[45]/USA	Cohort	14,414	66-75, 50.8% 76-80, 49.2%	Breast	I~III	NR	NR	Anthracyclin, Taxane, etc.	32.7% of patients with diabetes were hospitalized In the multivariable analysis, diabetes was associated with increased odds of hospitalization for any cause; hospitalization for chemotherapy toxicity; and hospitalization for infection or fever, neutropenia, or anemia
Pinder *et al.*, (2007)[46]/USA	Cohort	6145	73.2	Breast	I~III	NR	NR	Anthracycline	Diabetes emerged as a highly significant predictor of a subsequent diagnosis of congestive heart failure

GEM: Gemzar, NabPTX: Nab-Paclitaxel, GS: Gemzar and TS-1 combination, FOLFIRI: Fluorouracil, folinic acid, irinotecan, XELOX: Capecitabine, L-OHP, XELOX+Bev: Capecitabine, L-OHP, Bevacizumab, CIPN: Chemotherapy-induced peripheral neuropathy, CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisolone, FOLFOX: Leucovorin, fluorouracil, oxaliplatin, FOLFOX4: 5-fluorouracil, leucovorin, oxaliplatin, Hyper-CVAD: Hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy, CPT11: Irinotecan, ALL: Acute lymphocytic leukemia, DSE: Diabetes self-efficacy, OE: Outcome expectancies, TPF: Docetaxel, cisplatin, fluorouracil, DC: Docetaxel carboplatin, FEC: Fluorouracil, epirubicin, cyclophosphamide, CE: Cyclophosphamide, epirubicin, AI: Aromatase inhibitor, OXIPN: Oxaliplatin-induced peripheral neuropathy, NR: Not reported

Regarding hypoglycemia, that focused on type 2 diabetes mellitus patients who received Hyper-Cyclophosphamide Doxorubicin Vincristine and Dexamethasone Chemotherapy (Hyper-CVAD) to counter hypoglycemia, demonstrated that while blood glucose levels of several patients decreased to 70 mg/dl or lower, it did not fall <40 mg/dl.[28] Furthermore, no studies to date report on patients who developed hypoglycemia who received similar treatment.[39]

In response to fluctuations in blood glucose levels during chemotherapy, increased doses of oral antidiabetic and insulin preparations were administered and nonperiodic insulin injections were given.[37,39,43,44] Twenty percent of the patients' treatment plans were modified during chemotherapy.[39] Type 2 diabetes mellitus patients who received Hyper-CVAD were administered with 1.2–1.3 units of insulin per 1 kg of body weight, and this dose was increased when the patients were overweight.[35] A sliding scale method which determines the dosage of insulin based on blood glucose levels was used for patients who received periodic insulin doses.[39] The treatment plan for approximately half of the patients was changed by adjusting the dosage or type of antidiabetic drug; as the cumulative dose of dexamethasone[43] was increased in these patients, levels of their blood glucose and HbA1c rose correspondingly. Even with a small dose of prednisolone, some cases required an active increase in insulin dose.[37]

Adverse drug reaction to patients with diabetes undergoing chemotherapy

There were 13 studies on side effects seen in patients with diabetes undergoing chemotherapy, the main ones were as follows: Peripheral nerve disorder, 6 cases; infectious, 3 cases; oral mucositis and heart failure, 1 case; nonspecific, 2 cases.

Peripheral nerve disorder

In studies with more than 50 patients, patients with a medical history of diabetes comprised approximately 60%–80% of those patients who manifested peripheral nerve disorder. [28,31] In particular, 52% of patients with diabetes for <5 years and 75% of patients with diabetes for more than 5 years developed peripheral nerve disorder. The incidence of peripheral nerve disorder was higher among patients with diabetes with the duration of five or more years than for those counterparts with <5 years ($P < 0.01$).[31] On the other hand, a study with <30 patients reported that there was a nonsignificant correlation between the presence of diabetes and clinical grading of peripheral nerve disorder.[38] The degree of symptoms ranged from Grade 2 to Grade 3 in the Common Terminology Criteria for Adverse Events[31,38,41] and the symptoms progressively worsened after each chemotherapy treatment.[30,33] However,

studies with fewer than 30 patients, reported that there was a nonsignificant correlation between the presence of diabetes and clinical grading of peripheral nerve disorder.[38] It was difficult to distinguish whether the peripheral nerve disorder was caused by worsening diabetes or the side effects of chemotherapy, and some patients were confused.[30]

Moreover, the likelihood of symptom emergence was significantly higher after the fifth course for patients with diabetes who received chemotherapy with oxaliplatin.[40] The only symptom of peripheral nerve disorder that emerged was sensory neuropathy.[36]

There were no significant differences in the occurrence of peripheral nerve disorder between patients with or without diabetes when taxane-only chemotherapy was applied.[31] Regimens that were significantly more likely to occur in patients with diabetes were those that included taxanes and platinum, FOLFOX4 (5-fluorouracil, leucovorin, oxaliplatin), and oxaliplatin.[31,38,40] The cumulative dose of oxaliplatin at the onset of symptoms was 388 mg/m^2; even with a small dose, peripheral nerve disorder emerged in patients with diabetes.[40]

Infection

In a study of patients who received intravenous chemotherapy with steroids, the probability of new infection was increased by 68% in those patients with diabetes compared to counterparts without diabetes. In addition, the rate of hospitalization for infection during the 1st year after initial chemotherapy was 37.0% in patients with diabetes and 29.2% in patients without diabetes, within 1 year after receiving their first chemotherapy, the admission rate to the hospital was about 8% higher for patients with diabetes ($P < 0.01$).[27] Alkylating agent chemotherapy was the primary factor contributing to infectious disease in these patients.[32] The highest onset of risk factors was observed in diabetes with high blood pressure or tube feeding.[32,36] None of the following were associated with the onset of infectious disease: HbA1c level, cancer stage, age, and gender.[27]

Oral mucositis

Chemotherapy-induced oral mucositis occurred in 5.9% of patients without diabetes and 6.9% of patients with diabetes, with significantly more patients with diabetes developing the disease compared to patients without diabetes ($P < 0.05$).[42]

Other side effects or adverse drug reactions

Patients with diabetes tend to develop severe anorexia, nausea, and physical weariness.[33] In a study that investigated patients' symptoms during chemotherapy using The Symptoms of Illness Checklist, which consists of 33 items, symptoms during chemotherapy in patients with diabetes were significantly more severe 8 weeks after the start of chemotherapy compared to before.[14] Among patients aged 66 years or older receiving adjuvant chemotherapy for breast cancer, more patients with diabetes were hospitalized outside the treatment period (32.7%) and patients without diabetes (25.1%) ($P < 0.01$). The reasons for hospitalization were infection, neutropenia, and anemia.[45] Diabetes was a predictor for the onset of heart failure for those patients with breast cancer undergoing chemotherapy.[46]

Self-management for patients with diabetes undergoing chemotherapy

Some patients with diabetes undergoing chemotherapy responded that they wished to concentrate on treatment for both cancer and diabetes[34] although other patients solely focused on cancer treatment simply because "killing two birds with one stone" was not feasible.[29,30] Self-management of diabetes among patients with diabetes undergoing chemotherapy who developed solid tumors was investigated with the Self-care Inventory-Revised (SCI-R), which examines patients' attitudes toward adherence to self-care recommendations regarding diabetes, and the results showed that patients with diabetes' self-management of diabetes decreased significantly 8 weeks after the start of chemotherapy ($P < 0.01$).[14] Hindering factors included: Physical weariness, nausea, change in the sleep cycles, degrees of severity in symptoms, and unavailability of advice from medical staff about dietary intake with diabetes in mind.[14,30] Specifically, physical weariness and nausea prevented optimal dietary intake and implementation of exercise therapy. Other obstacles included: Hyperphagia due to steroids, the fact that the patient was recommended to eat anything regardless of fluctuations in blood glucose, and the challenge associated with oral administration of hypoglycemic agents when suffering from nausea.[30] Some patients had difficulty in performing self-monitoring of blood glucose because of peripheral neuropathy.[25] This naturally raised a question regarding the traits of patients whose implementation rates for diabetes self-management were high even at 8 weeks into chemotherapy. The profile of such patients included: Disease duration for diabetes was long, self-efficacy and levels of expected outcome were high, control of blood glucose levels after chemotherapy were excellent, and the number of prescribed drugs was few.[14,30] The differences in SCI-R by cancer site were not clarified.[14]

Discussion

Research trend concerning patients with diabetes undergoing chemotherapy

Most of the studies on patients with diabetes during chemotherapy were related to the frequency and severity

of symptoms of adverse effects of chemotherapy, especially peripheral neuropathy and infection. However, most of the studies did not analyze the frequency and severity of side effect symptoms for each chemotherapy regimen received by the subjects. The risk of emetic and peripheral nerve disorder differs depending on the type of anticancer drug used.[47,48] Therefore, a regimen-specific analysis is needed in the future. The only study of glycemic variability was in patients with diabetes undergoing chemotherapy with steroids. Because of the variety of steroids administered and the lack of clarification of the status of blood glucose control before chemotherapy, future studies are needed to standardize the conditions of the subjects and to include the status of blood glucose control before chemotherapy in the survey items.

Fluctuations in blood glucose levels of patients with diabetes undergoing chemotherapy

Multiple studies show that blood glucose levels in patients with diabetes increase more than 300 mg/dl after undergoing chemotherapy.[37,44] Elevated blood glucose levels have the potential to detract from the beneficial effects of chemotherapy.[49] Furthermore, when blood glucose levels exceed 250 mg/dl, the risk of diabetic ketoacidosis, an acute complication of diabetes, is increased, thereby causing dehydration and a reduction in blood pressure.[50] Moreover, if such elevated blood glucose persists, it could lead to other complications of diabetes.[51] Thus, the prevention of elevated blood glucose levels is of paramount importance for patients with diabetes undergoing chemotherapy. Despite its relevance to the treatment of this group of special needs patients, there is no consensus on the appropriate glycemic control target for patients with diabetes undergoing chemotherapy.[52] Therefore, accurate blood glucose control, responsive to the unique fluctuation of blood glucose levels of each patient, is indispensable.

Another challenge for patients with diabetes undergoing chemotherapy lies in the common inclusion of the steroids prednisolone and dexamethasone.[53] There is a clear difference between prednisolone and dexamethasone's half-life in the blood, at 2.5 h and 3.5 h, respectively.[54] Therefore, the remaining effect of elevated blood glucose from the previous day makes the control of blood glucose levels challenging, especially when therapy includes a daily administration of dexamethasone.[43] To respond to this challenge, the identification of patient-specific steroids and assessment of their blood glucose level fluctuation before the commencement of chemotherapy should never be overlooked.

Other strategies for minimizing fluctuation in blood glucose levels during chemotherapy include increasing the dose of oral antihyperglycemic agent and insulin or scheduling extra administration of insulin. However, by performing such strategies, it is apparent that the risk of hypoglycemia will also be magnified. Nevertheless, the extant literature, containing a small sample size of fewer than 40 patients, reports either mild cases of hypoglycemia in a few patients[35] or no hypoglycaemia.[39] Due to these missing details, for those drugs with an antihyperglycemic effect used in the aforementioned studies, further acquisition of data concerning hypoglycemia during chemotherapy is warranted.

Side effects that emerged in patients with diabetes undergoing chemotherapy

Compared to patients without diabetes undergoing chemotherapy, some studies show that patients with diabetes undergoing chemotherapy are more likely to manifest peripheral nerve disorder.[28,31,40] Peripheral nerve disorder is a notable side effect that warrants the undivided attention of all medical staff involved in the treatment of patients with diabetes undergoing chemotherapy. Peripheral nerve disorder is highly likely if hyperglycemia persists.[55] Furthermore, because steroids are involved in chemotherapy, patients with diabetes are prone to developing hyperglycemia during this treatment.[56] Consequently, the time at which the steroid is introduced becomes the turning point, when peripheral nerve disorder is induced in patients with diabetes.

The following secondary physical disabilities or symptoms are likely to occur in patients with diabetes who develop peripheral nerve disorder: Inability to perform grip actions or actions in minute detail, aching pains caused by cold stimulation, and instability while walking.[57] Such development of peripheral nerve disorders, particularly in patients with diabetes, that are caused by chemotherapy raise a variety of concerns. First, the risk of not being able to conduct blood sugar determination or perform insulin self-injection becomes pronounced due to a weakened grasp on a blood glucose meter or tools used for insulin self-injection. Second, patient distress could soar from the cold stimulation-induced pain they experience every time they disinfect themselves with alcohol when conducting blood sugar determination. Thirdly, owing to their poorer gait while standing or walking, caused by peripheral nerve injury in the lower extremity, the risk of falling during exercise rehabilitation increases; fear of this may prevent such patients from participating in rehabilitation.

These concerns all point to the need for assistance in self-management against peripheral nerve disorder for patients with diabetes, especially from an early stage of chemotherapy. Several studies[31,38,40] demonstrate that the severity of symptoms is likely to be heightened when patients with diabetes undergoing chemotherapy receive

a regimen comprising a combination of taxane and the platinum anticancer drugs, FOLFOX4, and oxaliplatin. These drugs are known to induce the development of peripheral nerve disorder.[58] It is therefore essential for medical professionals to carefully assess the presence of peripheral nerve disorder before the commencement of chemotherapy or the introduction of those drugs. How symptoms of peripheral nerve disorder manifest in patients with diabetes at an early stage of chemotherapy and how the severity of their symptoms affect the quality of their daily lives, along with their self-management, must be clarified through a systematic assessment. This is crucial, because, when compared to patients without diabetes, patients with diabetes undergoing chemotherapy are more susceptible to infection.

Self-management of patients with diabetes undergoing chemotherapy

Literature shows that patients with the following characteristics demonstrate superior self-management of diabetes while undergoing chemotherapy: A longer diabetes disease duration,[14,30] high self-efficacy for blood glucose control, well-managed blood glucose levels before chemotherapy, and a lower number of drugs per prescription. This underscores the importance of patient support that acknowledges the patient's record and their ability for blood glucose control. Still, owing to the limited number of currently available studies, the real state of self-management among patients with diabetes undergoing chemotherapy is yet to be investigated. Further studies addressing the management of the side effects of chemotherapy and blood glucose level control in patients with diabetes undergoing chemotherapy should provide a basis for developing appropriate support programs of self-management for this group of special needs patients.

Limitations

Although this review makes an important contribution to our understanding of fluctuations in blood glucose levels in each regimen of chemotherapy for patients with diabetes, the overview gained from the literature was limited by missing details in diabetes or cancer information. This prevented us from assembling a meta-analysis of changes in blood glucose levels for each chemotherapy regimen or the effect of various doses of steroids on blood glucose levels. In addition, we could not determine at which phase of chemotherapy the symptoms appeared because there was no information on the observation period, although the symptoms appeared differently with time. Finally, there remains the possibility that not all cases have been considered since our review only focused on papers written in English or Japanese languages.

Conclusions

Patients with diabetes undergoing chemotherapy were given increased doses of hypoglycemic agents or additional doses of hypoglycemic agents to control their blood sugar because of hyperglycemia. Compared to patients without diabetes, patients with both cancer and diabetes are burdened with a higher risk of developing side effects of chemotherapy, particularly peripheral nerve disorder and infectious diseases; both unwanted side effects are more likely to become severe among patients with diabetes than those without. The fact that infectious diseases could prove fatal and that peripheral nerve disorders tend to worsen, lead to a substantial deterioration in patient quality of life. This underscores the importance of timely support for this rapidly emerging group of special needs patients with cancer. Unequivocally, there is an urgent need for a support program based on systematic research that clarifies strategies for the control and self-management of blood glucose levels and adverse drug reactions in patients with diabetes undergoing chemotherapy. Such an endeavor would assist this group of special needs patients who are suffering from two of the most prevalent modern diseases: Diabetes and cancer.

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Conflicts of interest

There are no conflicts of interest.

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