

Evaluation of Blood Glucose Levels in Patients having Chemotherapy Treatment in Combination with Corticosteroids: A Prospective Cohort Study

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Research Article

Keywords: Cancer, Chemotherapy, Hyperglycaemia, Corticosteroids, Diabetes

Posted Date: October 19th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10912205/v1>

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Steroid-induced hyperglycaemia (SIH) is common in patients having chemotherapy treatment with concomitant corticosteroids. However, longitudinal evaluation of blood glucose levels (BGL) during treatment in patients with and without pre-existing diabetes has received limited investigation in routine clinical care.

The purpose of this study was to assess the prevalence of diabetes at the start of treatment, prevalence of SIH during treatment and incidence of steroid induced diabetes (SID) in patients having chemotherapy treatment with concomitant corticosteroids.

Methods

148 patients receiving chemotherapy with corticosteroids measured BGLs on the day after the first chemotherapy treatment. For patients who continued chemotherapy, BGLs were also measured at 6 weeks and 12 weeks. Glycated haemoglobin (HbA1c) was measured at baseline and 12 weeks.

Results

Forty-one patients (28%) had a diagnosis of diabetes at baseline. About one third of participants had SIH at each time point and was more prevalent in those with baseline diabetes. Demographic characteristics including age, gender and BMI were no different between patients with and without SIH. Twelve percent of the non-diabetic patients demonstrated SID at 12 weeks after commencing treatment.

Conclusions

SIH is common in patients having chemotherapy treatment with adjuvant corticosteroids, but more prevalent in patients with baseline diabetes. SID is a potential complication beyond the completion of treatment in this patient cohort. Nurse-led BGL monitoring and management should be developed as a universal comprehensive care strategy for patients having chemotherapy treatment combined with corticosteroids.

Clinical Trial Number: not applicable

Introduction

Corticosteroids are potent anti-inflammatory and immunosuppressive agents that mimic the action of the body's glucocorticoid hormones [1]. These medications are commonly administered to patients having cancer-related chemotherapy treatment to manage nausea and other related adverse effects [2]. However, administration of steroids commonly raises blood glucose levels (BGLs) of people with pre-existing diabetes and can induce hyperglycaemia in those with no previous history of diabetes [3]. Hyperglycaemia can exacerbate the side-effects of chemotherapy treatment including polyuria,

polydipsia, blurred vision and fatigue [4, 5]. When left untreated, hyperglycaemia has been shown to negatively impact quality of life, and life expectancy in this patient cohort [6, 7].

The incidence of SIH in patients without diabetes receiving chemotherapy with corticosteroids is variable across treatment facilities and cancer types. In early-stage breast cancer, 67 percent of patients having chemotherapy with dexamethasone developed SIH during treatment [8]. In other cancer types, SIH has been reported in 59 percent of patients with brain cancer, 49 percent of patients with prostate cancer and 43 percent of patients with non-Hodgkin lymphoma [9, 10]. Diabetes is a common co-morbidity in patients who develop cancer [11]. Consequently, strategies to monitor BGLs in patients with pre-existing diabetes is an important element of the management of this patient cohort during chemotherapy treatment [12].

Previous studies have reported that up to 20 percent of patients having chemotherapy treatment with corticosteroids may go on to develop steroid-induced diabetes [4, 13]. Consequently, monitoring and responding to changes in BGLs over the duration of chemotherapy treatment is an important component of patient management. In patients with diabetes, monitoring BGLs is standard practice which would continue during chemotherapy treatment. However, this is less likely to be the case for patients without diabetes where there is often no consistent approach to BGL monitoring during chemotherapy treatment [14]. Consequently, BGL monitoring may be implemented based on clinician preference, or in response to symptom reporting [15].

Despite the high prevalence of hyperglycaemia in patients having chemotherapy with corticosteroid treatment, there has been relatively limited longitudinal evaluation of BGLs over the duration of treatment. While the risk factors for developing type II diabetes are well recognised, the risk factors for developing hyperglycaemia during chemotherapy treatment are less well known. In patients with a range of cancer types, Yoo et al [16] identified a higher BMI and previous history of diabetes as risk factors for SIH during chemotherapy with corticosteroids, but not the corticosteroid dose. In patients with breast cancer, SIH has been associated with being over 50 years, hypertension, lymph node metastasis and higher BMI [17]. While corticosteroid dose and duration of exposure may increase the risk of developing hyperglycaemia in this patient cohort, these associations have received limited prospective evaluation [18].

Steroid-induced hyperglycaemia is a side-effect of chemotherapy that is often overlooked due to factors including lack of awareness among clinical staff, misinterpretation of hyperglycaemic symptoms or clinical prioritisation [3, 19]. Current clinical guidelines on medication management in cancer care in Australia contain limited reference to BGL monitoring or management of hyperglycaemia for patients having chemotherapy treatment [20]. The purpose of this study was to evaluate changes in BGL in patients with and without diabetes having chemotherapy in combination with corticosteroids, to determine the prevalence of SIH during treatment and incidence of SID. A further objective was to compare the demographic characteristics of patients who had SIH compared to those who had BGLs

below the SIH threshold. Finally, the presence and severity of symptoms commonly associated with hyperglycaemia was compared in patients with and without SIH.

Methods

This prospective observational study was conducted in a 20-chair private hospital Cancer Centre in Perth, Western Australia. The study was approved by the institutional Human Research Ethics Committee (#2029).

Eligible participants were adults with histologically confirmed cancer who were commencing chemotherapy treatment with associated administration of corticosteroid medication. All patients provided written informed consent to participate in the study. Three Cancer Centre nurses were responsible for participant recruitment and data collection, during both their usual work hours and additional hours allocated to the project.

Baseline demographic information including participant age, gender, BMI and history of diabetes was collected prior to the first chemotherapy treatment. Laboratory tests for diagnosis of diabetes (HbA1c) were performed before chemotherapy treatment, and at 12 weeks after treatment commenced.

All participants were provided with a blood glucose meter and associated equipment, and instruction on how to measure BGLs. Participants were instructed to measure BGLs two hours after each meal on the day after treatment and record the results on a data record sheet. The highest of the three measurements on each day was used for the analysis. Concurrently, participants recorded the presence and severity of symptoms commonly associated with hyperglycaemia including thirst, frequency of urination, fatigue and blurred vision. Each symptom was rated as “didn’t notice it at all”, “slightly”, “moderately” or “severely”. Blood glucose levels and symptom reporting were repeated using the same methodology at six weeks and 12 weeks for participants who were still having chemotherapy treatment. The threshold for hyperglycaemia (random blood glucose) was set at 11.1mmol/L consistent with the Royal Australian College of General Practice guidelines [21].

Corticosteroid dose was recorded as the cumulative dose (in mg) administered with chemotherapy (intravenous and/or oral) and oral doses taken on the morning following chemotherapy, prior to BGL monitoring.

Data Analysis

Participant demographics were summarised as proportions for categorical variables, and descriptive statistics for continuous variables. Between group comparisons were conducted using chi-squared tests for categorical variables and unpaired t-tests for continuous variables. For statistical comparisons, the criterion for statistical significance was set at $p < .05$.

Results

Between March 2023 and Feb 2024, 227 patients were invited to participate in the study. Seventy-nine patients declined participation and 148 patients provided written consent to participate. Fifteen patients did not complete any BGL measures and were excluded from the study. One hundred and twenty-seven patients completed the baseline BGL testing. At 6 weeks 97 patients remained on chemotherapy treatment and completed the six-week BGL test, and 65 patients remained on treatment and completed BGL testing at 12 weeks.

The average age of study participants was 63.9 years (range 30 to 88 years). There were 41 participants (28%) with pre-existing diabetes at baseline (type 1, type 2 or diabetes related to pancreatic cancer). Of these, 39 self-identified diabetes and two were found to have type 2 diabetes from baseline HbA1c $\geq$ 6.5%. Participants were receiving chemotherapy for a variety of cancers, with the majority being breast (n = 41), pancreatic (n = 24), colorectal (n = 22), prostate (n = 13) and lung (n = 12).

Most participants received Dexamethasone only (91%, n = 135), some received Hydrocortisone and Dexamethasone (9%, n = 13) and one patient was prescribed Prednisolone only.

Hyperglycaemia was detected in 36 participants (31%) at baseline (range 11.1mmol/L to 28.6mmol/L). At six weeks SIH was detected in 30 participants (31%) (range: 11.1mmol/L to 23.9mmol/L). At 12 weeks SIH was detected in 18 participants (28%) (range: 11.1mmol/L to 17.2mmol/L). At each time-point, hyperglycaemia was significantly more prevalent in patients with pre-existing diabetes (Table 1).

Table 1

Prevalence of SIH in the patient cohort at each time point for patients with- and without diabetes

Time point	Patients who recorded at least one BGL	Prevalence of SIH (all patients)	Patients with pre-existing diabetes	Patients without pre-existing diabetes	p
baseline	127	36 (31%)	17/41 (41%)	19/86 (22%)	< 0.05
6 weeks	98	30 (31%)	17/26 (65%)	13/72 (18%)	< .001
12 weeks	63	18 (28%)	8/15 (53%)	7/48 (15%)	< .01

Table 2 summarises the demographic characteristics of participants with and without SIH. There was no significant difference between groups in relation to gender (p = 0.82), age (p = 0.52) or BMI (p = 0.08).

Table 2
Demographic characteristics of patients with and without baseline SIH

Male	Steroid-induced hyperglycaemia	No Steroid-induced hyperglycaemia
	n = 26	n = 35
Female	n = 24	n = 42
Mean (SD) age	63.5 (11.1) years	64.0 (12.0) years
Mean (SD) BMI	29.4 (5.3) kg/m ²	27.7 (5.4) kg/m ²

There was no clear association between corticosteroid dose and SIH at each study timepoint, with high BGLs recorded at some of the lowest steroid doses (Fig. 1).

Sixty-seven participants had a baseline and 12-week HbA1c measurement. Of the 57 participants who did not have diabetes at baseline, seven (12%) had HbA1c measurements above the threshold for type 2 diabetes at 12 weeks (6.5% or higher). At 12 weeks there was a significant positive correlation between the BGL and HbA1c measurements ($r = 0.70$, $p < .001$).

One hundred and seventeen participants completed the hyperglycaemia symptom checklist at baseline, 80 participants at six weeks and 54 participants at 12 weeks. A result was considered symptomatic for ratings of 'moderately' or 'severely' and asymptomatic for ratings of 'didn't notice it at all' or 'slightly'. On 134 occasions symptom reporting was as expected in relation to the BGL measurement such that asymptomatic participants were below 11.1mmol/L and symptomatic participants were above 11.1mmol/L (Table 3). Symptom reporting was not a consistent indicator of present hyperglycaemia. The proportion of participants reporting each of the symptoms recorded is summarised in Table 4. The most reported symptom at each time point was tiredness.

Table 3
Prevalence of significant hyperglycaemia symptoms in participants with and without hyperglycaemia.

Symptomatic	Hyperglycaemia	No hyperglycaemia
	32	72
Asymptomatic	45	102

Table 4
Prevalence of symptoms commonly associated with hyperglycaemia

Thirst	Baseline	6 weeks	12 weeks
	19%	16%	16%
Frequent Urination	22%	20%	16%
Tiredness	56%	63%	64%
Blurred vision	3%	1%	4%

Discussion

In this study of patients starting chemotherapy for a range of cancer types, almost one-third had previously been diagnosed with diabetes. This is consistent with previous observations that diabetes is a common co-morbidity in patients who develop cancer [22]. Corticosteroids administered with chemotherapy have good efficacy but are associated with a range of undesirable side effects including hyperglycaemia. Hyperglycaemia is clinically significant in this patient cohort as it can increase other treatment side-effects, increase the risk of chemotherapy toxicity and dose reductions, and potentially impact chemotherapy treatment outcomes [23]. Consequently, BGL monitoring during chemotherapy treatment with concomitant corticosteroids in patients with and without diabetes, is increasingly recognised as an important comprehensive care practice [12].

An original element of this prospective study was BGL measurement at six week intervals from the start of treatment in order to evaluate glycaemic variability over time. Hyperglycaemia was identified in about 30 percent of patients at each treatment timepoint, but was significantly more prevalent in patients with pre-existing diabetes. The degree of hyperglycaemia experienced by some participants was surprisingly high, with 33 patients (25%) recording BGLs above the guideline-based threshold for commencement of medical management at some time during their treatment [12]. This finding is consistent with studies examining SIH in similar patient populations. Zhu et al [24], reported hyperglycaemia in 25 percent of patients with no history of diabetes having treatment for advanced pancreatic cancer. In women having chemotherapy with corticosteroids for breast cancer, lower-level SIH was identified in 45 percent, and higher level SIH in 22 percent of patients [8]. While the threshold for defining SIH is inconsistent between studies, these findings confirm that SIH is a common side-effect of chemotherapy treatment combined with corticosteroids for common cancer types.

In the present study cohort, there was no difference in age or BMI between patients who developed SIH compared to those who remained euglycaemic. In contrast, older age and higher BMI have previously been reported as risk factors for SIH in patients having chemotherapy in conjunction with corticosteroids [16, 17]. Similarly, steroid dose did not appear to be associated with prevalent hyperglycaemia at any of the study time-points which is consistent with previous observations [16]. Harris et al [10], reported a significant correlation between steroid dose and SIH in patients having chemotherapy treatment, but the

strength of association was low ($r = 0.19$). These findings suggest the traditional risk factors for hyperglycaemia in the general population may be less predictive for SIH in patients having cancer treatment.

Routine BGL testing in patients having chemotherapy treatment is uncommon as hyperglycaemia is often considered transient and given low clinical prioritisation relative to the cancer treatment [3, 8]. In the current study 12 percent of patients without diabetes had HbA1c measurements above the diabetic threshold ($> 6.5\%$) at 12 weeks after starting their chemotherapy treatment. Consistent with this finding, Jeong et al [4], reported an incidence of SID of 22 percent after six months of chemotherapy treatment with dexamethasone and a significant association with the cumulative dexamethasone dose. Prevention of SID in this patient cohort relies on identification of hyperglycaemia, which is commonly based on patient reporting of constitutional symptoms such as thirst, fatigue, polyurea and blurred vision. While symptom reporting has been recommended for hyperglycaemia screening during chemotherapy treatment [12], the current study found reporting of these symptoms as being moderate or severe was a poor indicator of hyperglycaemia. This finding highlights the importance of improved strategies for glycaemic monitoring and control in this patient cohort [25].

Recent clinical guidelines emphasise a deliberate, multi-disciplinary approach to glycaemic control in patients having chemotherapy treatment [12]. The key strategies for patients without diabetes include baseline HbA1c and random plasma glucose (RPG) check, and provision of a capillary blood glucose meter for those at high risk of SIH or with HbA1c above 12mmol/L [25]. Review of RPG should be conducted at each treatment visit to ensure BGL remains $< 10\text{mmol/L}$, and initiate involvement of a credentialled clinical diabetes educator if BGL is $> 12\text{mmol/L}$ on consecutive occasions. For patients with pre-existing diabetes, education from a clinical diabetes educator should include the likely exacerbation of hyperglycaemia during treatment, more frequent BGL testing at home, and regular review of BGL readings and the patient's diabetes management plan. Patients with diabetes should continue to consult with their diabetes care provider, usually in primary care. Implementation of these glycaemic control guidelines requires a clear strategy including patient and nursing staff education, structured patient screening and monitoring, involvement of a diabetes educator in the clinical team and sound documentation procedures [3].

Limitations

Participation bias may have influenced the results of this study as only 65% of patients offered participation agreed to do so. However, this is consistent with the results of a recent scoping review which showed that about 70% of eligible patients agree to participate in cancer research in Australia [26]. The study may have been more attractive to patients with existing diabetes due to concerns about diabetes management during chemotherapy treatment, and experience with BGL monitoring. Not all patients completed three BGL tests on the day after treatment as required by the study protocol. This may have been due to the burden of BGL testing for patients during on-going cancer treatment, or that patients may have missed meals due to the side-effects of treatment such as nausea and loss of

appetite. This study highlights the challenge of longitudinal monitoring of patients having chemotherapy treatment due to the high discontinuation rate which has been previously documented in cancer treatment research [27]. Only 51 percent of patients who commenced the current study were still receiving treatment at 12 weeks.

Conclusion

Almost one-third of patients commencing chemotherapy treatment in this study conducted in an Australian private hospital were diabetic. Steroid-induced hyperglycaemia was identified in about 30 percent of patients at each study time-point and was significantly more prevalent in patients with pre-existing diabetes. Symptom severity reporting was a poor indicator of SIH suggesting active monitoring of BGLs is a preferable screening approach in the clinical setting. Twelve percent of patients without diabetes had HbA1c levels above the diabetes threshold at 12 weeks after starting chemotherapy suggesting SIH is not always transient in this patient cohort. These findings highlight the importance of nurse-led BGL monitoring in the comprehensive care strategy for patients having chemotherapy treatment combined with corticosteroids. Development of screening and treatment protocols led by cancer care nurses for this patient population needs further development in the Australian health care setting.

Declarations

Funding: This study was supported by funding from the St John of God Foundation, Perth, Western Australia

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Author Contributions:

Shona Vigus: Conceptualisation, Methodology, Investigation, Funding acquisition, Writing – Original Draft, Project Administration

Alexis Cranfield: Methodology, Project Administration, Writing - Reviewing & Editing

Stephen Edmondston: Methodology, Investigation, Project Administration, Writing – Original Draft, Formal Analysis

Kynan Feeney: Conceptualisation, Methodology, Funding acquisition, Writing - Reviewing & Editing

Ethical Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the St John of God Health Care Human Research Ethics Committee (Approval #2029)

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

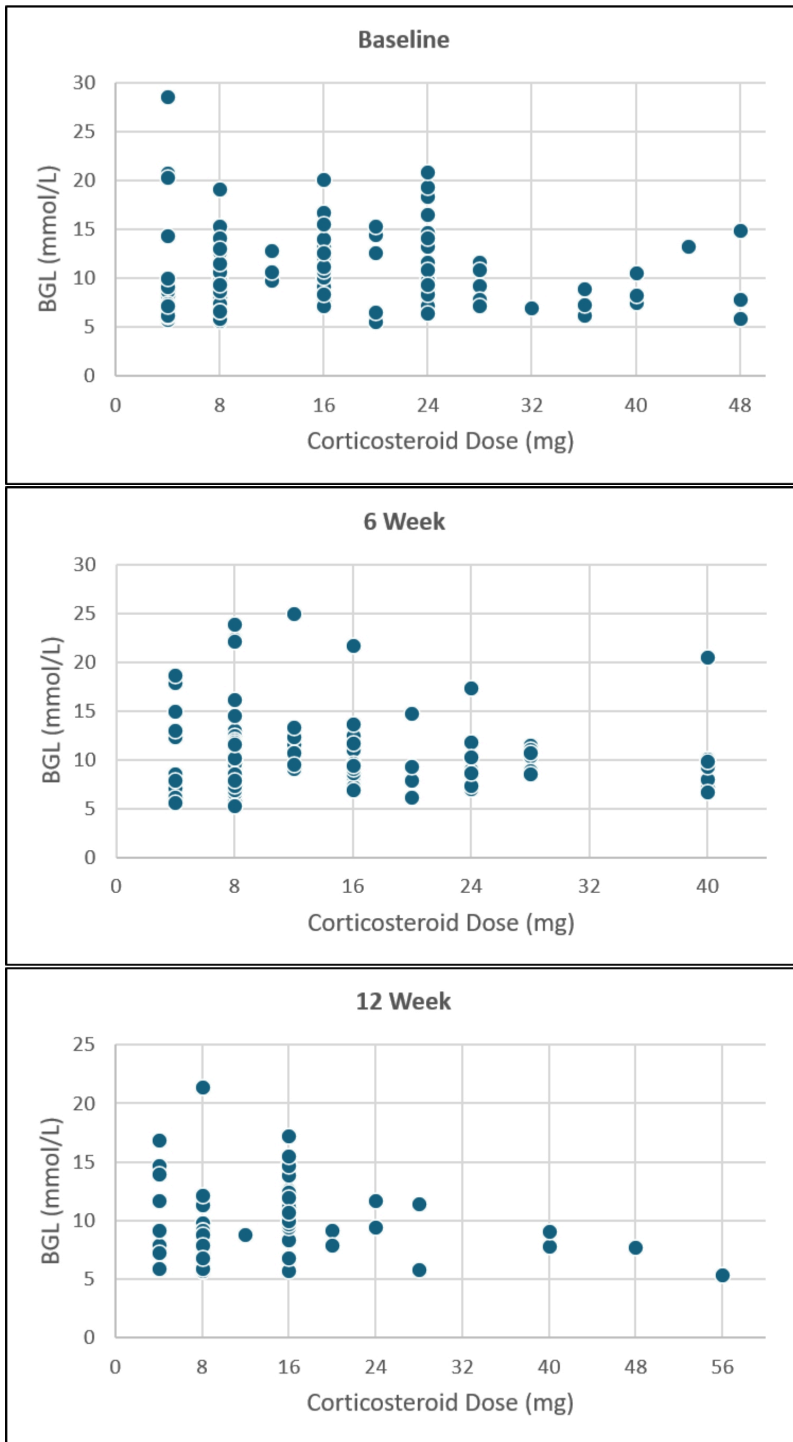


Figure 1

Association between steroid dose and BGL measurement at each study time-point