Endotext

DIABETES MELLITUS IN PEOPLE WITH CANCER

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ABSTRACT

There is increasing evidence of an association between cancer and diabetes mellitus. Patients with type II diabetes are at increased risk of malignancy due to shared risk factors between the two conditions, and people with a diagnosis of cancer may develop new onset diabetes or impaired glycemic control, partly as a result of the systemic anti-cancer treatments (SACT) they receive. Many newer targeted anti-cancer treatments can have off-target metabolic toxicities not seen with conventional chemotherapy agents. Early recognition of diabetes or hyperglycemia in people with cancer can improve outcomes. This chapter aims to summarize these associations, provide an overview of how different SACT modalities can impact on glycemic control, and highlight key recommendations for the management of this complex patient group.

INTRODUCTION

Diabetes mellitus (DM) is a rising global public health emergency, with recent estimates suggesting that over 780 million people globally will be affected by 2045 (1). DM is typically classified into broad categories including type 1 (T1DM), type 2 (T2DM), gestational, monogenic, pharmacologically-induced, endocrinopathy-driven and DM due to pancreatic disease/deficiency (sometimes referred to as type 3c) (2, 3). T2DM is regarded as the most common subtype and is reported to account for over 85% of cases (1). All types of DM can lead to multisystem microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (ischemic heart disease, stroke and peripheral vascular disease) complications, with management of these complications placing a strain upon many health services.

People with a diagnosis of DM are also at higher risk for developing several cancers (4), with reasons for this in part due to shared risk factors between the two, including age, obesity, sedentary lifestyle, and diet (5,6). A recent umbrella review of meta-analyses found that risks of developing most cancers were higher in people with DM compared to those without, with the most convincing evidence seen in breast cancer, intrahepatic cholangiocarcinoma, colorectal cancer, and endometrial cancer. One exception in this study was prostate cancer, where the risk appeared lower in individuals with DM (4). In view of this increased cancer risk in people with DM, some groups even advocate that regular screening for underlying cancer should be part of routine DM assessments (7).

It is estimated that approximately 20% of people with cancer have concurrent diabetes (8). Individuals with cancer are also at an increased risk of developing new onset DM or hyperglycemia, independent of an underlying diagnosis of diabetes, whilst cancer patients with concurrent DM often experience worsening glycemic control (9). Reasons for poor glycemic control in these individuals include complications from systemic anticancer treatments (SACT) along with supportive medications to treat treatment side effects, and symptoms of the underlying malignancy. This chapter aims to summarize the complex relationship between malignancy and DM, particularly the effects of SACT on glycemic control and risk of DM, as well as outlining management guidelines for DM in people with cancer.

DIABETES/HYPERGLYCEMIA AND CANCER OUTCOMES

A number of observational studies have demonstrated that hyperglycemia is associated with poorer overall survival (OS) and increased risk of disease recurrence in a number of malignancies, solid and hematological (10-17), with a number of individual studies, and larger meta-analyses supporting this. One meta-analysis reviewed 12 studies comprising 9,872 people with a diagnosis of cancer without known diabetes. Individuals with hyperglycemia were found to have significantly worse disease-free survival (DFS) (hazard ratio (HR) 1.98, 95% confidence interval (CI) 1.20-3.27) compared to those without, as well as worse OS (HR 2.05, 95% CI 1.67-2.551) (18). A further meta-analysis of 4,241 patients with pancreatic cancer suggested that those individuals with concurrent DM (1,034) have poorer OS (HR 1.16, 95% CI 1.08-1.25) and a higher risk of on-treatment death than those without concurrent DM (19). Furthermore, in a meta-analysis of 8 studies in breast cancer, concurrent DM was found to confer a greater risk of death, and a later stage at presentation, as well as impact on the treatment given (20). People with DM also have a higher prevalence of oral cancers, as well as a higher mortality from these cancers (21).

In addition to this, a number of preclinical studies have suggested that hyperglycemia may specifically attenuate the efficacy of chemotherapy in people with cancer with or without diabetes, which could in part account for these observations (22). For example, hyperglycemia may attenuate chemotherapy-induced reactive oxygen species (ROS) production, which in-turn can diminish the efficacy of treatment (23). In vivo, there are some small series that have demonstrated an association between hyperglycemia and resistance to chemotherapy. A clinical study of 88 people with estrogen-receptor positive breast cancer demonstrated impaired glucose tolerance significantly correlated with disease progression in those patients receiving chemotherapy (24). Furthermore, high blood glucose levels irrespective of an underlying DM diagnosis, were shown to significantly enhance oxaliplatin resistance in individuals with stage III colorectal cancer receiving adjuvant chemotherapy (22). Studies such as these highlight the importance of adequate glycemic control during treatment for cancer to potentially improve outcomes, although these data are mainly from observational studies, with interventional studies lacking.

EFFECT OF DIABETES OR HYPERGLYCEMIA ON QUALITY OF LIFE IN PEOPLE WITH CANCER

Cancer-related symptoms and SACT side effects, such as fatigue, nausea, anorexia and pain can be debilitating to patients. When confounded by symptoms of hyperglycemia, the impact upon an individuals' quality of life can be significant (25). Furthermore, the impact of a cancer diagnosis, as well as treatment and cancer-related symptoms can have major negative impacts on diabetes self-care (26), with data suggesting that adherence to glucose lowering drugs often decreases in individuals following a cancer diagnosis (27). A cancer diagnosis can also have financial and social impacts upon individuals, affecting access to healthy food and outpatient diabetes services, resulting in lower quality of life and a higher symptom burden (28). A systematic review of

10 studies, demonstrated poorer patient reported outcomes (PROs) in those diagnosed with both cancer and DM compared to having either one of these diseases alone (29).

DIABETES AND RISK OF TREATMENT RELATED TOXICITY

People with DM are known to be at higher risk from infections, and undergoing SACT can exacerbate this, resulting in higher rates of infection and hospitalization observed in those with cancer and DM (30, 31). This in turn leads to higher rates of chemotherapy dose reductions and early treatment cessation (28, 32-34). A meta-analysis of 10 observational studies involving 8,688 cases found that the likelihood of developing chemotherapy-induced neutropenia was higher amongst individuals with DM/hyperglycemia than those without (odds ratio (OR) 1.32, 95% CI 1.06-1.64) (31). Chemotherapy-induced neutropenia poses a significant risk for infection and hospitalization in all people with cancer, with an associated rate of morbidity and mortality which is higher in those with raised blood glucose levels (30). In addition to severe hematological toxicity, more severe rates of non-hematological toxicity have also been associated with hyperglycemia during chemotherapy in people with prostate cancer and lymphoma (35). A single-center retrospective analysis found that individuals with cancer and DM who had good glycemic control had no increased risk of treatment-related complications compared with individuals without DM (36), suggesting that optimal glycemic control during SACT could improve tolerability, thereby reducing rates of admission and dose-limiting toxicity.

Conceivably, people with DM may be more prone to neuro- and nephrotoxic agents due to their underlying predisposition conferred by the DM. Indeed, a previous report suggested that taxane-based chemotherapy regimens resulted in a significantly higher rates of peripheral neuropathy in those with DM compared to those without (74.4% vs. 58.5%) (37). There are no convincing data to suggest that a concurrent cancer diagnosis accelerates the risk of diabetic nephropathy or retinopathy.

EFFECTS OF SYSTEMIC ANTICANCER THERAPIES ON GLYCEMIA

Systemic anti-cancer therapies (SACT) encompass a wide range of treatments including cytotoxic chemotherapy, hormone therapy, targeted therapy, and immunotherapy, many of which can impact upon glycemic control directly or as a result of toxicity management or supportive medications which are given alongside treatment. Several anti-cancer agents have been demonstrated to increase the risk of hyperglycemia as summarized in Table 1, and many can do this even in those without a known diagnosis of DM. People receiving SACT are also at risk of developing a new diagnosis of diabetes. One study demonstrated that 11% of people (15/134) undergoing routine chemotherapy met the criteria for a new diagnosis of diabetes (using the diagnostic criteria as per guidelines from the UK National Institute for Clinical and Healthcare Excellence (NICE) and without a previous known diagnosis) based upon HbA_{1c} measurements). The majority of these individuals (73%) had been receiving short course steroids with chemotherapy, and 40% were being treated in the curative/adjuvant setting (38). A second prospective cohort study in 90 people taking glucocorticoids as part of therapy protocols for primary brain tumor or metastases, lymphoma, or for bone marrow transplant, found non-DM range hyperglycemia in 58% and DM-range hyperglycemia in 18.9% (39). These individuals with hyperglycemia are also more likely to present with an emergency admission during cancer therapy than those with normoglycemia (40).

Table 1. SACT used in the Treatment of Cancer Demonstrated to be Associated with Worsening Glycemic Control			
Type of SACT	Drug Examples	**Risk of Diabetes/Hyperglycemia (Range of any grade)**	**Type of diabetes most likely to develop**
Targeted therapy			
mTOR inhibitors	Everolimus (41, 42)	12-50%	T2DM
	Temsirolimus (42)	26%	
PI3K inhibitors	Alpelisib (43)	37%	T2DM
	Idelialisib (44)	28/30%	
EGFR inhibitor	Osimertinib (45)	2%	T2DM
	Panitumumab (46, 47)	1-10%	
Multikinase inhibitor	Sunitinib (48-50)	0-8% Risk of hypoglycemia	Reverses T1/T2DM, but also causes hyperglycemia
	Pazopanib (50)		
Tyrosine kinase inhibitor (TKI)	Nilotinib (51)	6%	T2DM
	Ponatinib (52)	3%	
ALK Inhibitor	Ceritinib (53)	49%	T2DM
FLT3 inhibitor	Midostaurin (54, 55)	7-20%	T2DM
	Gilteritinib (56)	13%	
Monoclonal antibody	Gemtuzumab (anti-CD33) *inpatient use (57)	10%	T2DM
Somatostatin Analogues	Octreotide, Lanreotide (58)	Up to 30%	T2DM, but risk of hypoglycemia
Chemotherapy			
Anti-metabolite	5-fluorouracil (59, 60)	Up to 10%	T2DM
	Pemetrexed (61, 62)	4%	
	Decitadine/Azacitidine (63)	6-33%	
Alkylating agents	Busulfan (64)	66-67%	
Platinum based	Oxaliplatin (65, 66)	4%	
Anthracyclines	Doxorubicin (60, 67)	Up to 10%	
Other	Arsenic trioxide (ATO) (68)	45%	
Immune Checkpoint Inhibitors			
PD-1	Nivolumab (69)	<1%	T1DM
	Pembrolizumab (70)	1-2.2%	
CTLA-4	Ipilumumab (69)	<1%	
	Combination ICP (71)	4%	
Hormone Therapy			

Hormone Treatment	ADT (44, 72)	Risk ratio 1.39 (95% CI 1.27-1.53) n=65,595 cases	T2DM
	Tamoxifen (73)	Diabetes risk adj. odds ratio 1.24 (95% CI 1.08-1.42)	

Abbreviations: ADT = androgen deprivation therapy; ALK – anaplastic lymphoma kinase; ATO – arsenic trioxide; CTLA-4 – cytotoxic T-lymphocyte protein-4; EGFR – epidermal growth factor receptor; FLT3 – FMS-like tyrosine kinase-3; ICP – immune checkpoint inhibitor; TKI – tyrosine kinase inhibitor; mTOR – mechanistic target of rapamycin; PI3K – phosphoinositide-3 kinase; PD-1 – programmed cell death protein-1; T1DM – type 1 diabetes mellitus; T2DM – type 2 diabetes mellitus

Cytotoxic Chemotherapy

Hyperglycemia occurs in between 10 and 30% of people undergoing cytotoxic chemotherapy for malignancy (74), and although often transient during treatment, can persist, or even lead to DM in some people. Poor glycemic control can increase the risk of infections and hospitalization (28, 34), as previously discussed, leading to treatment interruptions and dose reductions, as well as significant morbidity, and even mortality (33). A number of cytotoxic chemotherapy regimens are reported to cause hyperglycemia in people without diabetes, including commonly used drugs such as 5-fluorouracil (5-FU), platinum-based drugs (oxaliplatin, carboplatin, cisplatin) and anthracyclines (doxorubicin, epirubicin) (75). In one cohort study of 422 people receiving 5FU-based chemotherapy regimens for the treatment of early or advanced colorectal cancer, 11.6% (42 people) developed diabetes and a further 11.3% developed impaired fasting blood glucose (FBG) levels. Of the 42 people who developed diabetes, 7 required no treatment, 13 received diet control and physiotherapy only, and 22 received antidiabetic medication (75). In a second cohort of 185 people with head and neck cancer treated with platinum-containing regimens, 3.8% developed type 2 DM, with 3 presenting with hyperglycemic crises (DKA, HHS) (65). One possible contributing factor for developing impaired FBG levels and/or type 2 DM is the concurrent use of corticosteroids in highly emetogenic chemotherapy regimens, but an analysis of type 2 DM following anthracycline use in 3,147 lymphoma patients suggested that the use of these drugs independently increases the risk of T2DM, when data was adjusted for corticosteroid use, comorbidities, age, and gender. A threshold doxorubicin dose of 253mg was identified, below which there was no increased risk of developing T2DM (76). Risk of diabetes from cytotoxic chemotherapy may also increase with age, with one pediatric study suggesting that the risk was higher in acute lymphoblastic leukemia (ALL) patients aged > 10, compared with those < 10 years old (77).

Exact mechanisms of how and why some cytotoxic chemotherapies can lead to hyperglycemia or T2DM remain unclear. Proposed mechanisms include the induction of an inflammatory state which predisposes to hyperglycemia (78) or direct metabolic effects on tissues vital to glucose homeostasis such as skeletal muscles (79).

Oral Targeted Anticancer Agents

Many new targeted cancer therapies inhibit various points in the insulin receptor signaling pathway including the commonly used class of tyrosine kinase inhibitors (TKIs) (80). Reported effects of targeted TKIs on blood glucose metabolism range from the development of metabolic syndrome and diabetes via the blocking of insulin signaling (80), as well as erratic glycemic control and even hypoglycemia in those with pre-existing type 1 or type 2 DM49, (81, 82). In contrast some TKIs may improve glycemic control

suggesting that management of these individuals needs to be individualized with no one-size-fits-all management algorithm. Reversibility of these effects is also unclear, with reported improvements in glycemic control and HbA1c levels following dose reductions or treatment termination (83).

Inhibitors of mTOR (everolimus, temsirolimus or ridaforolimus) have also been shown to impact glycemic control since mTOR is a protein kinase that plays a key role in regulating cell growth as well as lipid and glucose metabolism (84, 85). Meta-analyses looking into these effects have demonstrated significantly higher rates of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia compared with controls (86, 87) In isolated cases, the effects have been severe enough to precipitate DKA (88). To date, studies have not demonstrated either positive or negative associations between treatment response rates and incidence of metabolic complications (89).

As novel targeted agents continue to be introduced to manage a range of cancers, it is expected that metabolic toxicities continue to be reported given the homeostatic function of many of these druggable targets. Whilst some of these agents will provide meaningful benefit in terms of survival for people with advanced cancers, such as the PI3Kα inhibitor alpelisib for PI3KA-mutated metastatic breast cancer (43), glycemic control needs to be at the forefront of the prescriber's mind at initiation, to ensure adequate management of toxicities.

Hormone Therapy

ANDROGEN DEPRIVATION THERAPY

Androgen deprivation therapy (ADT) is recognized as a risk factor for development of diabetes, metabolic syndrome, and cardiovascular disease (72, 90, 91). In a large observational study of over 35,000 men treated for prostate cancer, ADT in the form of gonadotropin-releasing hormone (GnRH) agonists, oral antiandrogens, a combination of the two, or orchiectomy was associated with a significantly increased risk of diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death (90). These findings are supported by other studies, including a meta-analysis of over 150,000 men with prostate cancer receiving ADT (72), with association observed with all forms of ADT, with the weakest association with anti-androgen therapy alone.

ESTROGEN TARGETED THERAPY

Studies examining the effect of estrogen-targeted therapies on the development of diabetes in women with breast cancer are less clear cut. Whilst one retrospective cohort analysis failed to demonstrate a link between tamoxifen use and the development of DM (92), two large population-based studies demonstrated a significant association between tamoxifen use and the development of diabetes in women diagnosed with breast cancer (73, 93); The first of these studies included almost 15,000 Canadian women aged 65 years or older diagnosed with early breast cancer, whilst the second included over 22,000 women in Taiwan aged 20 years and over. Whilst tamoxifen appears to increase the risk of developing DM, aromatase inhibitor therapy does not, with no link found in any of these three studies.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICPi), including cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PDL-1) inhibitors are a sub-class of monoclonal antibody treatments that have revolutionized cancer treatment over the last decade. First approved for use in the treatment of melanoma, ICPi are now recognized as providing a survival benefit across a number of cancers, and are increasingly used in early-stage cancers in the adjuvant setting and also in combination with chemotherapy (94). Whilst clinically effective, ICPi can

lead to a spectrum of immune-related adverse events (IRAEs). Endocrine IRAEs include hypophysitis, thyroiditis, adrenalitis and *de novo* diabetes. The risk of developing de novo diabetes is low, occurring in 0.2-4% of ICPi treated individuals depending on the immunotherapy given (69). The immune checkpoint PD-1 and its ligand PD-L1 have been shown to have an important immune homeostatic function in the pancreas by promoting beta cell maturation and preventing immune-mediated beta cell destruction (95). To date, there is no convincing evidence for a physiological role for CTLA-4 within the pancreas. PD-1 inhibitors, PD-L1 inhibitors, and combination CTLA-4/PD-1 therapy have been demonstrated to precipitate diabetes more commonly than CTLA-4 inhibitors alone. The underlying clinical presentation is akin to type 1 diabetes (70) and believed to be precipitated by inappropriate activation of self-reactive T-cells and destruction of insulin-producing pancreatic islet β-cells. ICP-induced insulin deficiency may lead to new-onset insulin-dependent diabetes or worsening pre-existing type 2 diabetes. Up to 75% of people who develop ICP-induced hyperglycemia/diabetes present with diabetic ketoacidosis (DKA) (96-98). Presentations are frequently acute with a precipitous increase in blood glucose (99). Therefore ICP-induced diabetes can be discriminated from 'standard' type 1 diabetes mellitus, by its tendency towards a faster onset, apparently fulminant course, and high degree of antibody negativity (99). The nomenclature of the condition in the published literature varies mainly between 'type 1 like' to 'fulminant' with there being differences between the presentation of ICPi-induced diabetes and type 1 and fulminant diabetes. Kyriacou and colleagues compared the characteristics of 75 published cases and concluded that there is some overlap with type 1 DM and fulminant DM. However, this was felt to be insufficient overlap for ICPi diabetes to be wholly classified as either type 1 like or fulminant (100). Nevertheless, the recognition that these agents can precipitate rapid beta cell destruction which results in an unusually high number of emergency presentations is key. Treatment of non-endocrine IRAEs is typically with high dose steroids, often for prolonged periods of time. At present, steroids are used in up to a third of people receiving ICPs, further increasing the risk of hyperglycemia, and steroid induced T2DM.

An analysis of the World Health Organizations (WHO) pharmacovigilance database over a 4-year period detected 283 cases of ICP-induced diabetes mellitus, 50.2% of which presented with DKA, and 6% of whom were on concurrent steroids at diagnosis (101). There was a wide variability in duration of ICP treatment, and timing of DM onset, occurring even up to 8 months after cessation of ICP treatment. A systematic review of 90 cases, demonstrated a diagnosis of DM on average after 4.5 cycles of ICP (102). C-peptide levels were usually low or undetectable at diagnosis, islet autoantibodies were positive in 53%, with a predominance of glutamic acid decarboxylase antibodies, and susceptible HLA genotypes present in 65% (102). HbA1c levels were relatively low, consistent with the observed rapid onset of beta cell inflammation. Importantly, an elegant albeit small single-center study, used radiological and biochemical phenotyping to demonstrate that ICPi DM is irreversible (103). This has important clinical implications such that any individual diagnosed with ICPi-induced DM should be counselled around an expected life-long requirement of insulin.

Glucocorticoid (Steroid) Treatment

Glucocorticoids (GC) increase insulin resistance and glucose production and inhibit the production and secretion of insulin by pancreatic beta cells, as well as acting centrally to counteract the appetite-reducing effects of insulin (104). As such they are commonly associated with the development of hyperglycemia and diabetes. GCs have a direct hyperglycemic effect which starts very early after ingestion (105, 106). They typically cause an increase in blood glucose levels 4-8 hours after ingestion leading to a peak blood glucose level between midday meal and evening meal (106, 107). One in ten people not known to have diabetes develop GC-induced diabetes (108) an effect which is

dose dependent (109). The incidence of glucocorticoid-induced hyperglycemia has been shown to occur in up to 30% of individuals without diabetes (110), but could be as high as 50%. The consequences of missing it can lead to significant harm, including the development of Hyperosmolar Hyperglycemic State (HHS), hospitalization, and in extreme circumstances, death. In a single center UK prevalence study 12.8% (120/940) of inpatients were found to be on glucocorticoids, however only 20.5% of these individuals (25/120) had their blood glucose levels measured during admission, demonstrating how infrequently glucose is measured in hospital (111). It is important to ensure that if glucocorticoid (steroid) induced hyperglycemia does occur, it is picked up early.

The use of GCs, is common in advanced cancer, to reduce peri-lesional edema, relieve pain, control nausea, combat fatigue, or boost appetite. For oncological emergencies such as cerebral metastases, superior vena-cava obstruction (SVCO), or metastatic spinal cord compression (MSCC), high dose GC treatment is integral to patient management. Furthermore, GC treatments are the backbone of many hematological cancer treatment regimens, and are often used as supportive anti-emetic medications, or to prevent allergic reactions, in many solid tumor regimens (105), and, as discussed above, the main first-line treatment for the management of ICP toxicity. In one study, the incidence of glucocorticoid-induced diabetes was 20% in those with newly diagnosed gastrointestinal cancer following at least 3 cycles of highly or moderately emetogenic chemotherapy, including dexamethasone as a supportive medication. Furthermore, almost 60% of people in the study exhibited signs of insulin resistance and multivariate analysis showed a significant association between the cumulative dose of dexamethasone and the incidence of corticosteroid-induced diabetes (112). In a separate smaller study of 16 women without diabetes with ovarian or endometrial cancer receiving carboplatin/paclitaxel chemotherapy with dexamethasone as supportive care, almost all experienced elevated interstitial glucose levels with diurnal variation during the first five days of treatment (113). For those who receive prednisolone as part of a treatment regimen for hematological malignancies, rates of steroid-induced diabetes and hyperglycemia have been reported to be as high as 32.5% and 47% respectively, highlighting the scale of this issue (114, 115).

Supra-physiological doses of glucocorticoids approximate to a dose of prednisolone greater than 5mg per day – or an equivalent dose of the alternative synthetic GC (Table 2**)**. With increasing dose of GC, the risk of potential hyperglycemia increases, and in people without pre-existing diabetes, a glucocorticoid dose equivalent of >12mg dexamethasone and longer acting steroids are associated with a greater degree of hyperglycemia (116). As duration of GC treatment increases, it becomes increasingly likely that hyperglycemia may not resolve once the GCs are withdrawn, with those groups at particular risk of developing glucocorticoid induced diabetes, shown in Table 3.

Table 2. Glucocorticoid Dose Equivalent		
Glucocorticoid (steroid)	**Potency (equivalent doses)**	**Duration of action (half-life, in hours)**
Hydrocortisone	20 mg	8
Prednisolone	5 mg	16-36
Methylprednisolone	4 mg	18-40
Dexamethasone	0.8 mg	36-54
Betamethasone	0.8 mg	26-54

Table 3. Risk Factors for Glucocorticoid-Inducted Diabetes
Pre-existing type 1 or type 2 diabetes
Family history of diabetes
Increasing age
Obesity
Ethnic minorities
Impaired fasting glucose or impaired glucose tolerance
Polycystic ovarian syndrome
Previous gestational diabetes
Previous development of hyperglycemia on glucocorticoid therapy
Concurrent cytotoxic therapy known to cause hyperglycemia

HYPOGYCEMIA IN PEOPLE ON SACT

Although anti-cancer therapies and glucocorticoid use lead predominantly to hyperglycemia, there are risks of hypoglycemia that require consideration. People at risk of hypoglycemia should be counselled on the signs and symptoms to be aware of, and of the requirement to inform the driver and vehicle licensing agency should they experience any episodes of hypoglycemia requiring third party assistance.

Poor oral intake and nausea/vomiting from the underlying cancer or treatments put individuals at increased risk of hypoglycemia. Poor glycemic control can cause weight loss and precipitate nutrition impact symptoms (NIS) such as nausea, poor appetite, and altered bowel movements, further increasing the risks of hypoglycemia, particularly when dietary intake has been poor for some time. People with diabetes on an insulin secretagogue (sulfonylureas or meglitinides), or those on insulin, are also at higher risk of hypoglycemia.

In patients with end-stage metastatic disease, and shortened life expectancy, tight glucose control is not indicated, potentially placing individuals at unnecessary risk for hypoglycemia, particularly in those with a poor performance status >2. Individual risk for hypoglycemia and prognosis should be considered and recommended glycemic measurement targets are between 6.0 mmol/L – 15 mmol/L (108 – 225 mg/dl) (117).

People with new onset ICPi-induced insulin deficiency often have labile glucose control (99). More relaxed glucose targets may be required to avoid hypoglycemia wherever possible. Immune checkpoint inhibitors can also induce hypopituitarism leading to secondary adrenal insufficiency. This may lead to hypoglycemia (together with any of the following - hyponatremia, hyperkalemia and hypotension). Adrenalitis leading to primary adrenal insufficiency is very rare. Presentation of adrenal insufficiency ranges from asymptomatic laboratory alterations to the

acutely unwell, with management depending on the severity (118). Other causes of adrenal or pituitary deficiency leading to hypoglycemia include metastases at these sites, surgery, irradiation, azole class of anti-fungal medication, and inappropriate abrupt cessation of glucocorticoid medication.

In oncology patients being weaned from long-term steroids, glucose monitoring will need to be continued after glucocorticoid cessation, with doses of anti-diabetic treatments adjusted accordingly, and individuals advised on risks of hypoglycemia. Caution is also required whilst using certain hematological anti-cancer therapies, including lenalidomide (119) and bortezomib (120), which can precipitate hypoglycemia, particularly in people with an underlying diagnosis of diabetes.

All cancer patients at risk from hypoglycemia should receive advice regarding appropriate treatment with 15–20 g of fast-acting carbohydrate, taken immediately (121). Comprehensive guidelines from the Joint British Diabetes Societies for Inpatient Care on the management of hypoglycemia can be found at this reference (122).

MANAGEMENT RECOMMENDATIONS

Despite the effects of hyper- and hypoglycemia in people with diabetes (PWD) and those without known diabetes in cancer, there is a sparsity of guidance on the specific management considerations of these individuals. To address this, collaborative guidelines have recently been produced by the UK Chemotherapy Board (UKCB) and Joint British Diabetes Society for Inpatient Care (JBDS) (123, 124). The scope of these guidelines are to provide advice for the oncology/hemato-oncology and diabetes multidisciplinary teams to manage people with diabetes, commencing anti-cancer/ steroid therapy, as well as identifying individuals without a known diagnosis of diabetes who are at risk of developing hyperglycemia and new onset diabetes. These guidelines are intended for the outpatient management of people with cancer, particularly in the setting of the oncology/hemato-oncology clinic, and provision of advice for individuals at home, but where necessary, may be applied to inpatients as well. Whilst covering these guidelines in detail is beyond the scope of this chapter, key management considerations are summarized in tables 4-9.

Table 4. At Baseline

- HbA_{1c} and venous plasma glucose should be checked in all people with cancer at baseline clinic visit
- Provide high risk individuals with capillary blood glucose (CBG) meter and glucose testing strips, or if baseline plasma glucose is ≥12 mmol/L (216 mg/dl)
- Individuals with raised baseline HbA_{1c} (>47 mmol/mol [6.5%]) should be referred to primary care for management of hyperglycemia prior to next follow up visit
- When initiating SACT/glucocorticoids individuals must be informed of the risk of developing hyperglycemia/diabetes and potential symptoms to expect
- The recommended glucose target level is 6.0-10.0 mmol/L (108 – 180 mg/dl), allowing a range of 6.0-12.0 mmol/L (108 – 216 mg/dl)
- There are differences in opinion at where the threshold for intervention should be drawn - 12.0 mmol/L (216 mg/dl) is a pragmatic threshold

Table 5. Commencing Glucocorticoids (GC) /Systemic Anti-Cancer Therapy
• Check baseline HbA_{1c} and random venous plasma glucose before starting therapy • Monitor random plasma glucose at each treatment visit • Educate patients in symptoms of hyperglycemia • Consider commencing gliclazide 40mg if raised blood glucose ≥12mmol/L (216 mg/dl) on two occasions • Gliclazide may require frequent and significant increases in dose to reduce glucose levels, particularly on high dose steroids • Inform diabetes care provider if persistently raised blood glucose • If blood glucose is ≥20mmol/L (360 mg/dl), rule out DKA/HHS

Table 6. Commencing Immune Checkpoint Inhibitors (ICP)
• Educate patients to be aware of symptoms of hyperglycemia • Rule out DKA or HHS which often occurs precipitously • Withhold ICP if evidence of ICP-induced diabetes emergency. Once patient has been regulated with insulin substitution, consider restarting ICP • Almost all patients require insulin therapy – refer urgently to diabetes team

Table 7. Managing Nausea and Vomiting
• People with diabetes should be made aware of likely exacerbation of hyperglycemia whilst on anti-emetic therapy • People with diabetes receiving emetogenic chemotherapy should be offered an NK1 antagonist (e.g., aprepitant) with a long acting 5HT3 inhibitor (e.g., ondansetron) • Consider the use of a GC in the first cycle and reduce doses or withdraw completely based on the PWD's emetic control and on blood glucose management

Table 8. For Non-Insulin-Treated Individuals with Type 2 Diabetes
• Check baseline HbA_{1c} and random venous plasma glucose before starting therapy • Monitor random plasma glucose at each treatment visit • Educate patients in symptoms of hyperglycemia • If plasma glucose is ≥12 mmol/L (216 mg/dl) on two occasions, screen for symptoms of hyperglycemia and ketonuria/ketonemia • In individuals already on a sulphonyurea such as gliclazide or meglitinides, up-titrate morning dose of gliclazide to a maximum doses of 240 mg. Evening dose of gliclazide may be initiated to achieve a maximum daily dose of 320 mg • Insulin therapy may be required • In individuals on a diet-controlled regimen, or on other non-sulfonylurea treatments (e.g., metformin, DPP4 inhibitors, pioglitazone, SGLT2 inhibitors) commence gliclazide 40 mg, and up-titrate

Table 9. For Insulin-Treated Individuals with Type 2 Diabetes
• Check baseline HbA_{1c} and random venous plasma glucose before starting therapy • Monitor random plasma glucose at each treatment visit • If plasma glucose is ≥12 mmol/L (216 mg/dl) on two occasions, screen for symptoms of hyperglycemia and ketonuria/ketonemia • Contact usual diabetes team for support in titrating insulin • Consider titrating insulin by 10-20% of the original dose daily • Individuals should be made aware of 'sick day rules' with insulin administration

Full management guidelines can be found at the UK Chemotherapy Board (UKCB) and Joint British Diabetes Society for Inpatient Care (JBDS) websites.

ADDITIONAL MANAGEMENT CONSIDERATIONS: CHOICE OF DIABETES THERAPEUTIC AGENT

Special consideration should also be given to the non-glycemic effects of hypoglycemic agents, including specific side effects and the impact on weight. Although weight reduction is associated with improvement in glycemic and metabolic profile in people with type 2 diabetes and is a key consideration in the choice of therapy, significant weight loss would usually be an unwanted effect in the oncology population. Indeed, weight gain is often used as a metric of improving nutritional state, especially in cancer related cachexia. This also has implications when counselling people with cancer about dietary choices when there is an additional cancer diagnosis. It is imperative that personalized advice is offered by healthcare professionals considering the global impact on the individual of any dietary or even lifestyle advice. SGLT2 inhibitors and GLP-1 agonists, for their potential weight reduction effects, are therefore less attractive options in the oncology setting. Insulin and sulfonylureas, on the other hand, offer an anabolic effect and therefore may be more desirable. Gastrointestinal side effects are common among hypoglycemic agents including metformin, DPP4 inhibitors, and GLP-1 agonists, and have the potential to complicate issues with nausea, vomiting, and oral intake from the underlying cancer and its treatment. Similarly, poor oral intake and nephrotoxic effects of certain SACT, added to a potential osmotic diuretic effect of SGLT2 inhibitors, could also increase the risk of acute kidney injury. The associated risk of genital tract infections with SGLT2 inhibitors would also be an additional consideration especially within an immunocompromised population (125). The impact and significance of these non-glycemic effects in the oncology population clearly differ to that of the general population, therefore highlighting the importance of a personalized approach with regular review of patients' diabetes treatment through their oncology journey.

CONCLUSIONS

It is common practice in oncology to initiate systemic anti-cancer therapy (including chemotherapy, targeted treatment, immunotherapy and steroids) in people with pre-existing diabetes. Diabetes, or risk of developing diabetes are by no means a contraindication to treatment but treating clinicians should be aware of the risks to patients, and counsel them appropriately. As more sophisticated anti-cancer treatments become licensed for use, the metabolic effects of these treatments will become better understood, and oncology teams should utilize and collaborate with endocrinology and primary care services to minimize the risks to individuals from poor glycemic control and diabetes. The recent publication of specific guidelines should act as a reference aid for clinicians and wider healthcare professionals to aid in risk recognition, diagnostic and screening for treatment induced diabetes, and provide the tools to appropriately

manage these individuals and reduce the risks of complications.

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