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Joint British Diabetes Societies for inpatient care

UKONS Oncology Nursing Society

The Royal College of Pathologists
Pathology: the science behind the cure

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UK CHEMOTHERAPY BOARD

The Management of Glycaemic Control in People with Cancer

Guidance for the oncology and diabetes multidisciplinary team

Report of a working party on behalf of the UK Chemotherapy Board and Joint British Diabetes Societies for Inpatient Care

September 2021

ABCD
Association of British Clinical Diabetologists

DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

DISN
UK GROUP

UKCPA
CLINICAL PHARMACY ASSOCIATION

About the UK Chemotherapy Board (UKCB)

The UK Chemotherapy Board is the national overarching body which provides guidance, oversight and support for the continuing development of chemotherapy (SACT – systemic anticancer therapy) services in the UK. Its core membership comprises representatives of the Association of Cancer Physicians (ACP), the Royal College of Radiologists (RCR), the Royal College of Physicians (RCP), the Royal College of Pathologists (RCPath), the British Oncology Pharmacy Association (BOPA) and the UK Oncology Nursing Society (UKONS). The Royal College of Paediatrics and Child Health (RCPCH) is also a member, although has not provided input on these guidelines directed at adult cancer patients. The Board also has representation from the four UK nations and from other organisations closely involved in chemotherapy services.

About the Joint British Diabetes Society (JBDS)

The Joint British Diabetes Societies (JBDS) for Inpatient Care group was created in 2008 to 'deliver a set of diabetes inpatient guidelines and proposed standards of care within secondary care organisations', with the overall aim of improving inpatient diabetes care through the development and use of high quality evidence based guidelines, and through better inpatient care pathways. The JBDS–IP group was created and supported by Diabetes UK, Association of British Clinical Diabetologists (ABCD) and the Diabetes Inpatient Specialist Nurse (DISN) UK group, and works with NHS England, Trend Diabetes and with other professional organisations.

About this guidance

This guidance has been produced by a multidisciplinary working party on behalf of the UK Chemotherapy Board (see Writing Committee) and JBDS which includes specialist representation from medical, diabetes and dietetic teams across the UK.

Scope of guidance

It is common practice in oncology to start anti-cancer therapy (including chemotherapy, targeted treatment, immunotherapy and steroids) in people with pre-existing diabetes for a range of cancers. This guidance aims to provide advice for the oncology / haemato-oncology multidisciplinary team 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 hyperglycaemia and new onset diabetes. These guidelines are intended for the outpatient management of people with cancer, particularly in the setting of the oncology/haemato-oncology clinic, and provision of advice for individuals at home, but where necessary, may be applied to inpatients as well.

How to Use These Guidelines

These guidelines are a joint venture of the UKCB and JBDS, summarising the issues around glycaemic control in nonsurgical oncology patients, aiming to facilitate clinical practice and propose the principles of management based on consensus expert opinion. Each individual hospital and service is recommended to adopt these guidelines and template information sheets for local use. It is recommended that local oncology services develop strategic and operational links with their local diabetes specialist teams including nurses and dietetics, both within the hospital and community settings. Whilst recommendations on care are given within the document it is recognised that local services may operate under varying models of care but the core principles of monitoring blood glucose control and subsequent management remain.

This document is coded JBDS 17 in the series of JBDS documents:

Other JBDS documents:

The hospital management of hypoglycaemia in adults with diabetes mellitus	*JBDS 01*
The management of diabetic ketoacidosis in adults	*JBDS 02*
Management of adults with diabetes undergoing surgery and elective procedures: improving standards	*JBDS 03*
Self-management of diabetes in hospital	*JBDS 04*
Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes	*JBDS 05*
The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes	*JBDS 06*
Admissions avoidance and diabetes: guidance for clinical commissioning groups and clinical teams	*JBDS 07*
Management of hyperglycaemia and steroid (glucocorticoid) therapy	*JBDS 08*
The use of variable rate intravenous insulin infusion (VRIII) in medical inpatients	*JBDS 09*
Discharge planning for adult inpatients with diabetes	*JBDS 10*
Management of adults with diabetes on the haemodialysis unit	*JBDS 11*
Management of glycaemic control in pregnant women with diabetes on obstetric wards and delivery units	*JBDS 12*
The management of diabetes in adults and children with psychiatric disorders in inpatient settings	*JBDS 13*
A good inpatient diabetes service	*JBDS 14*
Inpatient care of the frail older adult with diabetes	*JBDS 15*
Diabetes at the front door	*JBDS 16*
The Management of Glycaemic Control in Patients with Cancer	*JBDS 17*

These documents are available to download from the ABCD website at https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group , the Diabetes UK website at www.diabetes.org.uk/joint-british-diabetes-society and the chemotherapy board website at www.ukchemotherapyboard.org

These guidelines can also be accessed via the Diabetologists (ABCD) app (need ABCD membership to access the app)

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Copyright statement

These guidelines are free for anyone to distribute, amend and use. However, we would encourage those who use them to acknowledge the source of the document and cite the Joint British Diabetes Societies for Inpatient Care and the UK Chemotherapy Board.

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Disclaimer

The information contained in this guidance is a consensus of the development and consultation groups' views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician. The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way.

To enable the guideline to stay relevant, it is envisaged that all of the JBDS guidelines will be updated or reviewed each year. As such these are 'living' documents – designed to be updated based on recently published evidence or experience. Thus, feedback on any of the guidelines is welcomed. Please email christine.jones@nnuh.nhs.uk with any comments, suggestions or queries.

Conflict of interest statement
The authors declare no conflicts of interest

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British Oncology Pharmacy Association (BOPA)
Diabetes Inpatient Specialist Nurses UK Group (DISN)
Diabetes UK (DUK)
Royal College of Pathologists (RCPath)
Royal College of Physicians (RCP)
Royal College of Radiologists (RCR)
UK Clinical Pharmacy Association (UKCPA)
UK Oncology Nursing Society (UKONS)

2. List of Abbrevations

ADT	Androgen Deprivation Therapy
ALK	Anaplastic Lymphoma Kinase
CBG	Capillary Blood Glucose
CI	Confidence Interval
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
DCP	Diabetes Care Provider
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DSN	Diabetes Specialist Nurse
EGFR	Epidermal Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase-3
GADA	Glutamic Acid Decarboxylase Antibody
GC	Glucocorticoid
GP	General Practitioner
HbA1c	Haemoglobin A1c (Glycated Haemoglobin)
HHS	Hyperglycaemic Hyperosmolar State
HR	Hazard Ratio
ICP	Immune Checkpoint Inhibitors
IR	Immediate Release
MR	Modified Release
mTOR	Mammalian Target of Rapamycin
NICE	National Institute for Health and Care Excellence
NIS	Nutrition Impact Symptoms
OS	Overall Survival
PD-1	Programmed Cell Death-1
PI3K	Phosphoinositide-3 Kinase
PWD	People with Diabetes
SACT	Systemic Anti-Cancer Therapy
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
T3cDM	Type 3c Diabetes Mellitus
TKI	Tyrosine Kinase Inhibitor

Executive Summary

Individuals with cancer are at increased risk of developing new onset diabetes mellitus and hyperglycaemia, and an estimated 20% of people with cancer already have an underlying diagnosis of diabetes mellitus.

People with both cancer and diabetes may have an increased risk of toxicities, hospital admissions and morbidity, with hyperglycaemia potentially attenuating the efficacy of chemotherapy often secondary to dose reductions and early cessation. Numerous studies have demonstrated that hyperglycaemia is prognostic of worse overall survival (OS) and risk of cancer recurrence.

These guidelines aim to provide the oncology/haemato-oncology multidisciplinary team with the advice to manage people with diabetes (PWD) commencing anti-cancer/glucocorticoid (GC) therapy, as well as identifying individuals without a known diagnosis of diabetes who are at risk of developing hyperglycaemia and new onset diabetes.

IDENTIFYING DIABETIC EMERGENCIES

Hyperglycaemic hyperosmolar state (HHS)

- Hypovolaemia
- Marked hyperglycaemia (30 mmol/L or more) without significant hyperketonaemia
    (<3 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L)
- Osmolality usually 320 mosmol/kg or more (calculated 2[Na+] + Glucose + Urea)

Diabetic ketoacidosis (DKA)

- Ketonaemia ≥3.0 mmol/L or significant ketonuria
  (more than 2+ on standard urine sticks)
- Blood glucose >11.0 mmol/L or known diabetes mellitus
- Bicarbonate (HCO3-) ≤15 mmol/L and/or venous pH<7.3

Symptoms of hyperglycaemia

- Polyuria
- Nocturia
- Fatigue
- Thirst
- Dry mouth
- Abdominal pain
- Nausea
- Blurred vision
- Headaches
- Confusion
- Unintentional weight loss

Symptoms of hypoglycaemia

- Perspiration
- Fatigue
- Dizziness
- Hunger
- Perioral paraesthesia
- Tremor/ Shaking
- Palpitations
- Mood change
- Pallor
- Confusion

Individuals Commencing Anti-Cancer Therapy Without A Previous Diagnosis Of Diabetes

Commencing Glucocorticoids (GC) / Systemic Anti-Cancer Therapy

Section 5A/B Appendix 1A

- Check baseline HbA1c and random venous plasma glucose before starting GC therapy
- Monitor random plasma glucose at each treatment visit
- Educate patients in symptoms of hyperglycaemia (section 4d)
- Consider commencing gliclazide 40mg if raised blood glucose ≥12 mmol/L 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 ≥20 mmol/L, rule out DKA/HHS (section 4d)

Commencing Immune Checkpoint Inhibitors

Section 5C Appendix 1B

- Educate patients to be aware of symptoms of hyperglycaemia (Section 4d)
- Rule out DKA or HHS which often occurs precipitously (Section 4d)
- 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

Hypoglycaemia

Section 5D

- Patients receiving end of life care may not require tight blood glucose control
- Patients with ICP induced insulin deficiency may have labile glucose control and are at risk of hypoglycaemia
- Adrenal deficiency, liver disease and renal impairment can lead to hypoglycaemia

Commencing Anti-Cancer Therapy In A Person With Pre-Existing Diabetes

Managing Nausea and Vomiting

Section 6A

- PWD should be made aware of likely exacerbation of hyperglycaemia whilst on antiemetic therapy
- PWD 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

Managing a person with diabetes

Section 6B Appendix 1C/D

- Ensure PWD has been supplied with a blood glucose meter
- Individuals with known diabetes should undertake regular CBG monitoring upon commencing SACT
- Monitor HbA1c 3 monthly whilst receiving SACT
- Rapid antidiabetic therapy changes may be required when commencing high dose GCs /SACT to maintain CBG between 6-12 mmol/L
- Modifications to antidiabetic therapy may be necessary if CBG is found to be ≥12mmol/L. See appendix 1C/D for advice on titrating glucose lowering agents

3. Pathways

These pathways have been devised to facilitate the management of patients in the following settings:

Without Known Diabetes:

a) Commencing chemotherapy/ targeted agents/ glucocorticoid (GC) therapy in cancer patients without a previous diagnosis of diabetes (Appendix 1A – page 39)

All oncology patients should have a baseline HbA1c and random plasma glucose checked prior to commencing anti-cancer therapy or steroids. Notify primary care of individuals at high risk of hyperglycaemia, and ensure they have been provided with a blood glucose meter. Consider commencing gliclazide 40 mg daily if plasma glucose ≥12 mmol/L on 2 occasions. Rule out DKA or HHS.

b) Commencing immune checkpoint inhibitors (ICP) in cancer patients without a previous diagnosis of diabetes (Appendix 1B – page 40)

All oncology patients should have a baseline HbA1c and random plasma glucose checked prior to commencing immune checkpoint inhibitors. Continue to check random plasma glucose at each treatment visit. Individuals are at risk of ICP-induced precipitous hyperglycaemia that behaves like new-onset type 1 diabetes, and frequently presents as diabetic ketoacidosis. Almost all individuals require commencement of insulin therapy - early/prompt referral to the diabetes team is required. Immune checkpoint inhibitors can also induce hypoadrenalism, which can potentially cause hypoglycaemia.

With a History of Diabetes:

c) Commencing SACT/ glucocorticoid (GC) therapy in cancer patients with type II diabetes on oral glucose lowering agents (Appendix 1C – page 41)

All people with cancer with a history of diabetes should be counselled on the risks of worsening glycaemic control with anti-cancer or GC therapy. Check baseline HbA1c and random plasma glucose prior to commencing treatment. Ensure all individuals have a blood glucose meter, with glucose testing strips, and know how to use it. Monitor random plasma glucose at treatment visits/each cycle. If individuals have diet controlled diabetes or are not on sulfonylureas or meglitinides (the insulin secretagogues) and blood glucose is ≥12 mmol/L on 2 occasions, add in gliclazide 40 mg and contact diabetes team. In those already on gliclazide, uptitrate dose at each treatment visit, and contact diabetes team if at maximum dose. Be aware that rapid dose escalation may be required and close liaison with the primary diabetes care giver to enable this to happen safely is essential.

d) Commencing SACT/ glucocorticoid therapy in cancer patients with diabetes treated with insulin (Appendix 1D – page 42)

All people with cancer with a history of diabetes should be counselled on the risks of worsening glycaemic control with anti-cancer or glucocorticoid therapy, and potential increasing insulin requirements. Check baseline HbA1c and random plasma glucose prior to commencing treatment. Ensure all individuals have a blood glucose meter, with glucose testing strips, and know how to use it. Monitor random plasma glucose at treatment visits/ each cycle. Seek advice from local diabetes team/ DSN if insulin requires up-titration.

4. Introduction

4a. Background

Types of Diabetes Mellitus (DM)

Diabetes is typically divided into two major subtypes, type 1 and type 2 diabetes. **Type 1 diabetes (T1DM)** results from autoimmune destruction of insulin-producing islet cells of the pancreas. The resulting loss of insulin secretion leads to increased blood glucose levels and increases the risk for severe high (hyperglycemia) or low (hypoglycemia) blood glucose as well as long-term complications of diabetes.

Type 2 diabetes (T2DM) is the most common form of diabetes. It is due to both reduced insulin secretion and increased insulin resistance. It is often associated with other metabolic problems, including weight gain, high cholesterol, high blood pressure and increased risk for cardiovascular disease, such as heart attack or stroke.
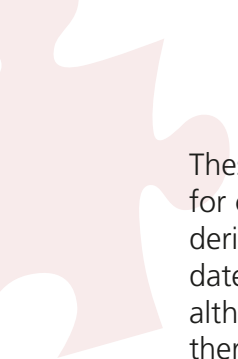
Type 3c diabetes (T3cDM) is a much less common cause of diabetes, and is caused by surgical removal of all or part of the pancreas or by damage to pancreatic function (for example by pancreatitis or pancreatic cancer) (1). T3cDM is also known as Pancreatogenic Diabetes or Secondary Diabetes. T3cDM results in endocrine and exocrine pancreatic dysfunction. Loss of islet cells results in the potential loss of all pancreatic hormones (insulin, glucagon, somatostatin and pancreatic polypeptide). This can lead to challenges in achieving glycaemic control due to fluctuations from hypoglycaemia to hyperglycaemia. Management of type 3c diabetes mellitus typically uses the same pharmacological agents as for T2DM, however the progression to insulin therapy is often faster.

Hyperglycaemia and Cancer Outcomes

Individuals with a diagnosis of DM are at a higher risk for developing several cancers, possibly due to shared risk factors between the two diseases (2). It is estimated that 20% of people with cancer have concurrent diabetes, with cancer the leading cause of death in people with DM (3, 4). People with cancer are also at an increased risk of developing new onset DM or hyperglycaemia, independent of an underlying diagnosis, as well as worsening control of pre-existing DM (5).

A number of observational studies have demonstrated an increased risk of cancer amongst individuals with diabetes. An umbrella review of meta-analyses of observational studies reported an increased risk of developing cancer for participants with versus without diabetes (6). The evidence was demonstrated to be most robust for breast cancer, intrahepatic cholangiocarcinoma, colorectal cancer, and endometrial cancer, although most included studies demonstrated substantial heterogeneity. Data is also emerging to suggest that hyperglycaemia may be associated with worse overall survival (OS) and increased risk of cancer recurrence in a number of cancer subtypes, including both solid and haematological malignancies (5, 7-16). One of the largest of these reviewed 12 retrospective studies comprising 9872 people with cancer and without diabetes. Individuals with hyperglycaemia were found to have a significantly worse disease-free survival (hazard ratio (HR) 1.98, 95% confidence interval (CI) 1.20-3.27) compared to those with normo-glycaemia, as well as worse overall survival (HR 2.05, 95% CI 1.67-2.551)(17).

Furthermore a number of preclinical and observational studies have suggested that hyperglycaemia may specifically attenuate the efficacy of chemotherapy in people with cancer with or without diabetes (18) (19), perhaps accounting in part for these worse outcomes. High blood glucose levels, regardless of a diagnosis of diabetes, were shown to significantly enhance oxaliplatin chemo-resistance in patients with stage III colorectal cancer receiving fluorouracil and oxaliplatin (FOLFOX) chemotherapy (20).

These studies highlight the importance of adequate glycaemic control during treatment for cancer to potentially improve outcomes. However, the majority of the evidence base is derived from observational data, and there have been no randomised controlled trials to date to support the contention that better glucose control improves outcomes in cancer, although several trials are currently underway evaluating the role of glucose lowering therapies as cancer therapeutic agents.

Hyperglycaemia and Risk of Toxicity

Individuals with cancer and diabetes are shown to be at higher risk of developing infections, and hospitalisation compared to those without diabetes, but also at risk of chemotherapy dose reductions and early treatment cessation (21-24). A meta-analysis of 10 observational studies involving 8688 cases found the odds of having chemotherapy-induced neutropenia were higher amongst people with cancer and diabetes or hyperglycaemia than those without (odds ratio (OR) 1.32, 95% CI 1.06-1.64) (25). Chemotherapy-induced neutropenia poses a significant risk for infection and hospitalisation, with subsequent morbidity and possibly mortality, and increased rates of hospital mortality and sepsis have been found in individuals with raised blood glucose levels (26). Both severe haematological and non-haematological toxicity have also been associated with hyperglycaemia during chemotherapy in people with prostate cancer (27). One single centre retrospective analysis found that individuals with cancer and diabetes with good glycaemic control are at equal risk for treatment-related complications when compared with individuals without diabetes (28). Review of all admissions at a specialist cancer hospital in London demonstrated that 11% of inpatients had either diabetes or hyperglycaemia (29), and individuals with hyperglycaemia have been shown to have higher rates of emergency hospital admissions during cancer therapy than those without (30). In these individuals particularly, early intervention to manage glycaemic control is likely to be benefit and may improve tolerability of anti-cancer therapy (28).

Risks of New Diagnosis of Diabetes during Anti-Cancer Therapy

A recent study, carried out in a district general hospital, measured the HbA1c in 134 people undergoing routine chemotherapy, using the diagnostic criteria as per NICE guidelines. 15/134 (11%) of the cohort met the criteria for a new diagnosis of diabetes (without a previous known diagnosis), in whom the majority (73%) had been receiving short course glucocorticoid with chemotherapy, and 40% were being treated in the curative setting (31). A similar prospective cohort study screening n=90 individuals taking glucocorticoids as part of therapy protocols for primary brain tumour or metastases, lymphoma or for bone marrow transplant, found hyperglycaemia in 58% and diabetes mellitus range hyperglycaemia in 18.9% (14, 32). The risk of developing new onset diabetes and hyperglycaemia needs better understanding and clinical attention by the oncology multidisciplinary team to optimise patient care and avoid long-term consequences.

Effect of Hyperglycaemia on Quality of Life

Adherence to glucose lowering drugs often decreases in individuals following a cancer diagnosis (33). However, symptoms of hyperglycaemia, in addition to cancer-specific and chemotherapy side effects, can be debilitating. Cancer treatment and cancer-related symptoms can have major negative impacts on diabetes self-care, including appetite, stamina, access to diabetic care, but may also have financial and social impacts. Cancer and its treatments have been shown to have a negative impact on diabetes self-management behaviours in adults with diabetes who are undergoing chemotherapy (34). This can lead to a potential increased risk for poor glycaemic control during this critical period (34), and therefore hospitalisation and risk of morbidity. As a result individuals are likely to have a lower quality of life, with a higher burden of symptoms, including pain severity and fatigue (21). A systematic review of 10 studies evaluating patient reported outcomes (PRO) found that having both cancer and diabetes resulted in worse PROs compared to having either one of the diseases (35).

4b. Anti-Cancer Drugs with Associated Risk of Diabetes/Hyperglycaemia

Observational studies have shown that a number of systemic anti-cancer therapies (SACT) used in the treatment of solid tumour and haematological malignancies may be associated with worsening glycaemic control in people with cancer without diabetes, including, but not limited to the following (36, 37):

Type of SACT	Drug Examples	Risk of Diabetes Hyperglycaemia (Range of any grade)	Type of Diabetes Most Likely to Develop
Targeted therapy			
mTOR inhibitors	Everolimus (32, 33)	12-50%	T2DM
	Temsirolimus (33)	26%	
PI3K inhibitors	Alpelisib (34)	37%	T2DM
	Idelialisib (31)	28/30%	
EGFR inhibitor	Osimertinib (35)	2%	T2DM
	Panitumumab (36, 37)	1-10%	
Multikinase inhibitor	Sunitinib (38-40)	0-8% Risk of hypoglycaemia	Reverses T1DM & T2DM, but also leads to hyperglycaemia
	Pazopanib (40)		
Tyrosine Kinase inhibitor (TKI)	Nilotinib (41)	6%	T2DM
	Ponatinib (42)	3%	
ALK Inhibitor	Ceritinib (43)	49%	T2DM
FLT3 inhibitor	Midostaurin (44, 45)	7-20%	T2DM
	Gilteritinib (46)	13%	
Monoclonal antibody	Gemtuzumab (anti-CD33) *inpatient use (47)	10%	T2DM
Somatostatin Analogues	Octreotide, Lanreotide(48)	Up to 30%	T2DM Risk of hypoglycaemia
Chemotherapy			
Anti-metabolite	5-fluorouracil (49, 50)	Up to 10%	T2DM
	Pemetrexed (51, 52)	4%	
	Decitadine/Azacitidine (53)	6-33%	
Alkylating agents	Busulfan (54)	66-67%	
Platinum based	Oxaliplatin (55, 56)	4%	
Anthracyclines	Doxorubicin (50, 57)	Up to 10%	
Other	Arsenic trioxide (ATO) (58)	45%	
Immune Checkpoint Inhibitors			
PD-1	Nivolumab (59)	<1%	T1DM
	Pembrolizumab (60)	1-2.2%	
CTLA-4	Ipilumumab (59)	0.02%	
	Combination ICP (61)	4%	
Hormone Therapy			
Hormone Treatment	ADT (31, 62)	Risk ratio 1.39 (95% CI 1.27 1.53) n=65,595 cases	T2DM
	Tamoxifen (63)	Diabetes risk adj. odds ratio 1.24 (95% CI 1.08-1.42)	

There have been a number of suggestions regarding the underlying mechanisms of worsening glycaemic control from anti-cancer therapy in people with cancer without a history of diabetes. It is predominantly thought to be due to either a loss of immune tolerance and autoimmune destruction of pancreatic ß-cells or dysregulation of the insulin signalling pathway resulting in insulin resistance (37, 70), depending on the type of anti-cancer therapy used.

Glucocorticoid (GC) Therapy and Hyperglycaemia

Glucocorticoid therapy is often used in people with cancer, including those with:

- Metastatic spinal cord compression
- Multiple Myeloma/ Lymphoma
- Immunotherapy toxicity
- Superior Vena Cava Obstruction (SVCO)
- Graft Versus Host Disease (GVHD)
- Symptomatic brain metastases
- Supportive treatment during chemotherapy (chemotherapy induced nausea and vomiting, prevention of allergic reactions etc.)

Glucocorticoid (steroid) dose equivalents (71)

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

These guidelines are intended for the management of individuals on supra-physiological doses of glucocorticoids, approximating to a dose of prednisolone greater than 5 mg per day – or an equivalent dose of the alternative synthetic (as shown in the table above). An example of a high dose is prednisolone ≥20 mg per day, with risk highest at this dose or greater.

The incidence of glucocorticoid- (steroid) induced hyperglycaemia has been shown to occur in up to 30% (72), but could be as high as 50%. The consequences of missing it can lead to significant harm, including the development of Hyperosmolar Hyperglycaemic State (HHS), hospitalisation, and in extreme circumstances, death. In a single centre 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 (73). It is important to ensure that if glucocorticoid-induced hyperglycaemia does occur, it is picked up early. In individuals started on GCs, national guidance is available from the JBDS, containing a recommended testing regimen to allow for early detection and intervention (74).

4c. Diagnostic Criteria for Diabetes Mellitus and Abnormal Glucose Tolerance (75)

	Fasting plasma glucose (mmol/L)	2 hour plasma glucose (mmol/L)	Random plasma glucose (mmol/L)	HbA1c / Glycated haemoglobin (mmol/mol) (%)
Normal	≤6.0	<7.8	<7.8	<42 (<6.0%)
Impaired fasting glucose	6.1-6.9	And <7.8	_	_
Impaired glucose tolerance	<7.0	And 7.8-11.0	_	Pre-diabetes: 42-47 (6.0-6.4%)
Diabetes mellitus	≥7.0	Or ≥11.1	≥11.1	≥48 (6.5%)

4d. Diabetes Emergencies:

Identifying Hyperglycaemic Hyperosmolar State (HHS)/ Diabetic Ketoacidosis (DKA)

Symptoms of hyperglycaemia include the following:

- Polyuria
- Nocturia
- Fatigue
- Thirst
- Dry mouth
- Abdominal pain
- Nausea
- Blurred vision
- Headaches
- Confusion
- Unintentional weight loss

Identifying HHS

HHS is associated with a significant morbidity and higher mortality than DKA and must be diagnosed promptly and managed intensively (76). The characteristic features of the hyperglycaemic hyperosmolar state (HHS) are:

- Hypovolaemia
- Marked hyperglycaemia (30 mmol/L or more) without significant hyperketonaemia (<3 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L)
- Osmolality usually 320 mosmol/kg or more (calculated 2[Na+] + Glucose + Urea)

Further details on the inpatient management of HHS can be found on the Joint British Diabetes Society website (https://abcd.care/resource/management-hyperosmolar-hyperglycaemic-state-hhs) (77).

Identifying DKA

Diabetic ketoacidosis (DKA) has been considered to be indicative, or even diagnostic, of type 1 diabetes, but increasingly there are cases of ketone-prone type 2 diabetes being recognised. DKA consists of the following diagnostic triad (76, 78):

> - Ketonaemia ≥3.0 mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
> - Blood glucose >11.0 mmol/L or known diabetes mellitus
> - Bicarbonate (HCO3-) ≤15 mmol/L and/or venous pH<7.3

It is important to be aware that DKA can occur with relatively low glucose concentrations so-called euglycemic DKA (euDKA) (79).
Further details on the inpatient management of DKA can be found on the Joint British Diabetes Society website (https://abcd.care/resource/management-diabetic-ketoacidosis-dka-adults)(80).

Hypoglycaemia

Symptoms of hypoglycaemia include the following:

- Perspiration
- Fatigue
- Dizziness
- Perioral paraesthesia
- Tremor/ Shaking
- Palpitations
- Mood change
- Pallor
- Confusion

Please refer to the JBDS hypoglycaemia guidelines (or local hospital guidelines) for the management of hypoglycaemia (81).

4e. Conclusion

It is evident that hyperglycaemia and diabetes are common amongst people with cancer. Good glycaemic control during cancer treatment may have implications for both cancer outcomes and survivorship. Although further high level evidence is required to better understand the importance of glycaemic control in people with cancer, improved recognition and potentially more complex diabetes care is required in these individuals (29). Collaboration between the cancer multidisciplinary team and diabetes team is vital to ensure these individuals receive appropriate and timely DM treatment. There is a sparsity of guidance in the management of these individuals. We therefore developed multidisciplinary guidelines and propose the principles of management to facilitate clinical practice, based on consensus expert opinion. These guidelines aim to enable early recognition by oncologists of the potential risks of complications from poor glycaemic control and provide guidance on how to manage these issues in an outpatient setting.

5. Guidelines:
The management of hyperglycaemia in oncology patients on cancer therapy without a previous diagnosis of diabetes.

5a Commencing Glucocorticoid (Steroid) Therapy

The use of glucocorticoids (GC) in high doses is common in advanced cancer, they are the backbone of many haematological cancers SACT regimens, and frequently used for symptom control in palliative care (82). GCs are also often used as an anti-emetic when emetogenic anti-cancer therapy is prescribed (see section 6), and also in the management of immunotherapy toxicity. These agents have a direct hyperglycaemic effect which starts very early after ingestion, and they also increase appetite (71, 82). Glucocorticoids 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 if administered in the morning (71, 83). One in ten people not known to have diabetes develop GC-induced diabetes once administered supra-physiological doses of steroids (84) and this is dose dependent (85).

Objective

The aim of this section of the guidelines is to ensure that people who are initiated on systemic glucocorticoids (steroids) are monitored appropriately for risk of hyperglycaemia. JBDS have further guidelines on inpatient management (71). These guidelines are intended for the management of individuals on supra-physiological doses of GCs, approximating to a dose of prednisolone greater than 5 mg per day – or an equivalent dose of the alternative synthetic GC (see section 4b for glucocorticoid dose equivalents). With increasing doses of GC, the risk of potential hyperglycaemia increases.

Rationale

People who are not known to have diabetes are at risk of developing hyperglycaemia if they are started on high dose GCs (84). Some people may already be at higher risk due to underlying factors.

Risk factors for glucocorticoid inducted diabetes

- Pre-existing type 1 or type 2 diabetes
- Family history of diabetes
- Obesity
- Increasing age
- Ethnic minorities
- Impaired fasting glucose or impaired glucose tolerance, HbA1c 42-47 mmol/mol
- Polycystic ovarian syndrome
- Previous gestational diabetes
- Previous development of hyperglycaemia on glucocorticoid therapy
- Concurrent cytotoxic therapy known to cause hyperglycaemia (see section 5b)

This hyperglycaemia may or may not resolve once the GCs are withdrawn.

Recommendations

Prior to starting GC therapy

When initiating GCs (including repeated cycles of 2-4 days of high dose GCs as anti-emetics) individuals must be informed of the risk of developing hyperglycaemia/diabetes and potential symptoms.

Prior to commencing GCs check a baseline HbA1c and random plasma glucose in the outpatient clinic. Provide a capillary blood glucose (CBG) meter if individuals are at high risk of glucocorticoid-induced diabetes (as above), or if baseline plasma glucose is ≥12 mmol/L (contact the primary care diabetes provider).

Those individuals identified as having a raised baseline HbA1c (>47 mmol/mol/ 6.5%) should be referred to primary care for management of hyperglycaemia prior to any follow up visits, however anti-cancer therapy start dates should not be delayed, especially if clinically urgent and they are otherwise fit for SACT treatment. In asymptomatic individuals, an elevated HbA1c should be repeated. There are no data to guide the management of individuals with cancer who have an HbA1c of 42-47mmol/mol, and this issue remains outside of the remit of this document. However, in line with guidance for the general population individuals should be referred to their local diabetes prevention programme.

Glucose Target

The recommended target level is 6.0-10.0 mmol/L, allowing a range of 6.0-12.0 mmol/L. However those individuals receiving end of life care do not require such tight control (86). Glycaemic targets in patients receiving end of life care tend to be different to those traditionally given because treatment often focuses on symptomatic relief, although should be balanced with the glycaemic control required to manage symptoms. Levels should be targeted at no lower than 6.0 mmol/L and no higher than 15 mmol/L (74).

There are differences in opinion at where the threshold for intervention should be drawn, with some advocating >8.0 mmol/L, but this is likely to increase the work loads of oncology teams, primary care and specialist diabetes teams. We have chosen a threshold of 12.0 mmol/L for pragmatic reasons and local teams should be consulted to reach their own decisions.

Glucose Monitoring:

CBG monitoring should occur at least once daily - if the GC dose is taken in the morning, the CBG measurement should preferably be prior to midday or evening meal, alternatively 1–2 hrs post lunch or evening meal is acceptable (74).

Whilst CBG readings remain over 12 mmol/L individuals should be advised to increase the frequency of CBG monitoring to four times daily for 48 hours, a mix of pre-meals, 1-2 hours post meals and before bed (74), and enter the treatment algorithm (appendix 1A-D). CBG testing should continue daily whilst remaining on GCs or after a dose increase of the GC. CBG testing should continue even after GC discontinuation whilst readings remain over 12 mmol/L.

As steroid doses or SACT reduce or are discontinued, the treatment of hyperglycaemia will similarly need to be titrated down, e.g. a weekly 5mg reduction of prednisolone from 20mg may require a 20-25% reduction in insulin dose, or a 40mg reduction in gliclazide.

If CBG tests are persistently below 12 mmol/L during this time and GCs have been discontinued, then blood glucose testing can be stopped. Please see the JBDS guidelines 'Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy' for glucose monitoring advice (71).

Treatment:

In the outpatient setting e.g. outpatient clinic or chemotherapy day unit, where plasma glucose is above 12 mmol/L (on two occasions) (71):

- Commence gliclazide 40 mg in the morning and prescribe blood glucose meter and glucose testing strips (if possible), and/or prompt referral to primary care to discuss initiating treatment and education on blood glucose meter use (see Appendix 2c for template letter). Provide a copy of these guidelines for suggested treatment regimen. Counsel the individual on symptoms and management of potential risks of hypoglycaemia secondary to gliclazide (see section 4d). Advise the person to get in contact with their primary care team as soon as possible.

- Gliclazide should be avoided in those with severe hepatic and renal impairment (<30ml/minute/1.73m^2). Insulin will almost always be the treatment of choice and advice should be sought from the diabetes team regarding commencement.

- The dose of gliclazide may need incrementing by 40 mg dose levels if plasma glucose remains ≥ 12 mmol/L. This may need to be increased daily if targets are not reached. Individuals on high dose GCs may need larger incremental increases: gliclazide may be titrated to a maximum of 240 mg in the morning and an evening dose of gliclazide may also be initiated to achieve a maximum daily dose of 320 mg. (You may wish to seek advice from secondary care specialist diabetes teams on dose titration at this stage). *Please see JBDS recommendations for guidance on further dose increments of gliclazide or addition of insulin if blood glucose remain high (74).*

- The original JBDS steroid guideline was written with the use of once daily prednisolone as the main steroid being used (71). It was the effect of prednisolone on glucose that guided the use of gliclazide. However, with other, longer acting glucocorticoids used in people with cancer, e.g. dexamethasone, gliclazide may not be chosen as the sulfonylurea of choice. We acknowledge variations in local practice and differences in sulfonylurea regimens used, and local input may be sought where appropriate.

- Should plasma glucose rise above 20 mmol/L, or if the person is unwell with vomiting, abdominal pain or stupor rule out DKA/HHS (see section 4d). Where DKA/HHS has been excluded, refer individual to diabetes team for further management.

- It is anticipated that primary care will provide the majority of diabetes follow-up for the people described in this guideline. This will require regular communication between the oncology, diabetes and primary care teams (see template referral letter). These individuals should be placed on the diabetes register to ensure they receive regular appropriate care for diabetes, including foot checks and retinal photograph.

If CBG tests are ≥12mmol/L respectively on two occasions 24 hours apart whilst *at home*, individuals should be advised to:

- Consult with their usual diabetes care provider (usually primary care)

- Continue taking GC as indicated until seen by or discussed with oncology team

- If CBG test is >20 mmol/L individuals should be advised to seek medical attention

Further advice on management of hyperglycaemia and GC therapy for inpatients/outpatient is available in the JBDS national guidelines (71).

Summary:

Check baseline HbA1c and random plasma glucose when starting glucocorticoid therapy

Glycaemic target level is 6-10 mmol/L, allowing a range of 6-12 mmol/L

Inform local diabetes care provider if persistently raised blood glucose

Individuals with GC-induced hyperglycaemia should be placed on the diabetes register for ongoing follow up

Educate patients in symptoms of hyperglycaemia (section 4d)

Consider commencing gliclazide 40 mg if raised blood glucose ≥12 mmol/L (on 2 occasions) in the absence of contraindications

Gliclazide may require frequent and significant increases in dose, particularly on high dose GCs

Refer to JBDS guidelines for dose incrementing if glucose levels remain raised (65, 68)

See treatment pathway APPENDIX 1A for management of hyperglycaemia in individuals on GC therapy in outpatient setting.

5b Commencing Systemic Anti-Cancer Therapy (without Immune Checkpoint Inhibition)

Objective
The aim of this section of the guidelines is to ensure that individuals, without a known diagnosis of diabetes, who are initiated on systemic anti-cancer therapy (chemotherapy or targeted agents) are monitored appropriately for risk of hyperglycaemia.

Rationale
Several anti-cancer agents are known to increase the risk of hyperglycaemia, even without a known diagnosis of diabetes. Hyperglycaemia during chemotherapy can occur in approximately 10-30% of people with cancer (70), and although is frequently transient during treatment, can become long-term. A number of studies have shown that poor glycaemic control can increase the risk for infections and hospitalisation, particularly in individuals with metastatic advanced cancers on chemotherapy. This in turn can lead to avoidable treatment interruptions and dose reductions, as well as significant morbidity, and even mortality.

Recommendations
All people with cancer likely to commence anti-cancer therapy should have a baseline HbA1c and random plasma glucose measured prior to starting SACT or GC (>5 mg prednisolone equivalent) containing regimens.

Those individuals identified as having a raised baseline HbA1c (>47 mmol/mol) should be referred to primary care for management of hyperglycaemia prior to any follow up visits, however anti-cancer therapy start dates should not be delayed, especially if clinically urgent and patient is otherwise fit for SACT treatment. Please inform the primary care team, making them aware of the JBDS guidelines (see Appendix 2c for template letter). These individuals should be placed on the diabetes register to ensure they receive regular appropriate diabetic care, including foot checks and retinal photograph.

New consent forms for SACT available via the CRUK website are being updated to reflect the risks of hyperglycaemia.

Glucose targets are as per section 5a.

In those patients starting chemotherapy or targeted treatment

- Check HbA1c and random plasma glucose at baseline, and continue to check random venous plasma glucose at each visit.
- If plasma glucose or CBG results are consistently <12 mmol/L consider cessation of testing (until a new/ change in therapy is initiated or if on concurrent ICP)

During treatment with anti-cancer agents, continue to monitor and document random plasma glucose during outpatient visits or with each cycle of treatment.

If blood glucose levels are raised (above 12mmol/L) on two consecutive visits:

- Screen for symptoms of hyperglycaemia (polyuria, nocturia, fatigue, thirst, blurred vision, headaches, confusion, weight loss) and ketonuria/blood ketones (see section 4d).
- Commence gliclazide 40 mg in the morning and prescribe blood glucose meter and glucose testing strips (if possible), and/or prompt referral to GP to discuss initiating treatment and education on glucose meter use (see Appendix 2c for template letter), with copy of guidelines as to suggested treatment regime. Provide education on symptoms and management of potential risks of hypoglycaemia secondary to gliclazide (see section 4d). Advise the individual to get in contact with their primary care team as soon as possible.
- The dose of gliclazide may need incrementing by 40 mg dose levels at each SACT treatment visit if plasma glucose remains above 12 mmol/L.
- Individuals *may* revert to normoglycaemia on treatment completion, so please ensure they are in close contact with primary care for ongoing monitoring post treatment.
- If plasma glucose is ≥20 mmol/L or there are suggestive symptoms, rule out DKA/ HHS (Section 4d). Where DKA/HHS has been excluded, refer individual to specialist diabetes team for further management.
- It is anticipated that primary care will provide the majority of diabetes follow-up for the people described in this guideline. This will require regular communication between the oncology, diabetes and primary care teams (see template referral letter).
- Should the interval between specialist oncological follow up appointments exceed 3 months, primary care teams should ensure that glycaemic control remains appropriate during the interim.

Summary

All patients commencing anti-cancer therapy should have a baseline HbA1c and random plasma glucose

Monitor random venous plasma glucose at each treatment visit

Commence gliclazide 40 mg OD if raised blood glucose ≥12 mmol/L (on two occasions) and/or refer to primary care in the absence of contraindications

Educate patients in symptoms of hyperglycaemia (section 4d)

Inform local diabetes care provider if persistently raised blood glucose

Individuals with SACT induced hyperglycaemia should be placed on the diabetes register for ongoing follow up

If blood glucose is ≥20 mmol/L or there are suggestive symptoms, rule out DKA/HHS (Section 4d)

See treatment pathway APPENDIX 1A for management of hyperglycaemia in individuals on GC therapy in outpatient setting.

Special Considerations:

A number of anti-cancer therapies are known to cause nephrotoxicity and hepatotoxicity, and both complications may require adjustments to diabetes treatment. Please discuss these cases with the diabetes team.

Following surgery for pancreatic cancer, be aware that patients are at high risk of subsequent insulin dependent diabetes.

5c Commencing Immune Checkpoint Inhibitors (ICP)

Rationale

Immune checkpoint inhibitors (ICP), such as cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitors, may induce de novo diabetes, although this occurs at a low frequency (<1%)(65). PD-1 inhibitors (e.g. pembrolizumab/ nivolumab), PD-L1 inhibitors (e.g. durvalumab) and combination CTLA-4/PD-1 therapy have been found to precipitate diabetes more commonly than CTLA-4 inhibitors alone e.g. ipilumumab. ICP-induced insulin deficiency may present both as new-onset insulin-dependent diabetes or worsening pre-existing type 2 diabetes, however the underlying mechanism is considered similar to that of type 1 diabetes (66).

Random plasma glucose should be checked with each treatment cycle and if hyperglycaemia symptoms develop, and unlike chemotherapy induced hyperglycaemia, should be checked throughout the duration of ICP treatment, due to the risk of sporadic development of hyperglycaemia. Most immune related adverse events occur within the first 3 months after initiation of ICP, although have been documented to occur as long as 1 year after discontinuation of therapy (65). It has been demonstrated that up to 75% of people who develop ICP-induced hyperglycaemia/diabetes present with diabetic ketoacidosis (DKA) (87, 88), and tend to present acutely with a severe increase in blood glucose (89). Up to a third of individuals receiving ICP may receive high dose steroids for non-endocrine immune related adverse events (IRAEs), and they are also at risk of steroid induced hyperglycaemia. Compared to 'standard' type 1 diabetes mellitus, ICP-induced diabetes tends to have a faster onset, fulminant course and high degree of antibody negativity (89).

Prioritise this management pathway over section 5B in those patients on dual ICP and chemotherapy regimens.

Recommendations

- Prior to initiating ICP treatment patients should be educated about the rare but potentially serious risk of diabetes mellitus. The signs and symptoms of hyperglycaemia should be explained to people in detail (section 4d) and advise them to seek medical attention immediately, to avoid potential life threatening emergencies (89).

- Random plasma glucose should be checked with each treatment cycle +/- if symptoms of hyperglycaemia develop.

- If plasma glucose is ≥ 20mmol/L or there are suggestive symptoms, rule out DKA/HHS (see section 4d) (77, 80). Whilst most cases of DKA occur with hyperglycaemia, about 1 in 20 cases occur with glucose concentrations less than 13 mmol/L. If individuals have other symptoms (e.g. acetone on the breath, deep (Kussmaul) breathing) then consider DKA, irrespective of the plasma glucose.

- Pancreatic antibodies (eg. GAD65, Zn transporter 8 or anti-islet cell) should be measured (90).

- The mainstay of treatment for most ICP related toxicities is high dose GC therapy. High dose GCs, however, have not been demonstrated to reverse ICP-induced pancreatic toxicity and diabetes. There is also the potential that any high dose GCs will worsen hyperglycaemia and they should be used with caution in this setting, if at all (65, 90). It is important to emphasise to individuals, therefore, that whilst ICP-induced diabetes is a very rare side effect, it is almost certainly irreversible and will require life-long treatment.

- Commencement of insulin therapy is almost always required, and therefore early/prompt referral to the specialist diabetes team is required. Given the risk of precipitous hyperglycaemia, urgent management of hyperglycaemia is necessary. Urgent hospital admission is necessary when DKA or HHS is diagnosed.

- Withhold ICP if evidence of ICP-induced diabetic emergency. Consider restarting ICP once management for hyperglycaemia has been instigated (90).

Summary:

Educate patients in symptoms of hyperglycaemia (Section 4d)

Rule out DKA or HHS which often occurs precipitously (Section 4d)

Almost all patients require insulin therapy – refer urgently to diabetes team

Withhold ICP if evidence of ICP-induced diabetic emergency.

Once the patient has been regulated with insulin substitution, restarting ICPs may be considered

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See treatment pathway 3b: APPENDIX 1B algorithm for management of hyperglycaemia on ICP.

5d Hypoglycaemia

Glucose Targets

In patients with end-stage metastatic disease, and shortened life expectancy, tight glucose control is not indicated, potentially placing individuals at unnecessary risk for hypoglycaemia, particularly in those with a poor performance status >2. Consider prognosis and individual risk for hypoglycaemia. Glycaemic levels should be targeted at between 6.0 mmol/L – 15 mmol/L (74).

Immune Checkpoint Inhibitors

People with new onset ICP-induced insulin deficiency often have labile glucose control, and therefore they should be counselled on the risks and symptoms of hypoglycaemia (see section 4d) (89). More relaxed glucose targets may be required to avoid hypoglycaemia wherever possible.

Immune checkpoint inhibitors can also induce hypopituitarism leading to secondary adrenal insufficiency in most cases. This may lead to hypoglycaemia (together with any of the following - hyponatraemia, hyperkalaemia 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. Refer to local immunotherapy related toxicity guidelines for management. Be aware of other causes of adrenal or pituitary deficiency leading to hypoglycaemia, including metastases at these sites, surgery, irradiation, azole class of anti-fungal medication, and inappropriate abrupt cessation of glucocorticoid medication.

Somatostatin Analogues

Somatostatin analogues, such as octreotide or lanreotide, are potent inhibitors of growth hormone (GH) and glucagon secretion. They are often used in the treatment of neuroendocrine tumours and can affect glucose regulation, often causing persistent hyperglycaemia with chronic use, however can paradoxically cause severe and refractory hypoglycaemia. Patients with huge tumour mass and multiple liver metastases are at increased risk of tumour-induced hypoglycaemia, and glucose monitoring in these individuals is advised.

Haematological Treatments

Caution is required when using certain haematological SACT, including lenalidomide and bortezomib, known to be associated with hypoglycaemia, particularly in people with an underlying diagnosis of diabetes. As a result close monitoring of blood glucose levels and adjustment of the dose of diabetes medication may be required.

Recommendations

Poor oral intake and nausea/vomiting from the underlying cancer or treatments put individuals at risk for hypoglycaemia. People at risk of hypoglycaemia, as well as individuals on gliclazide, should be counselled on signs and symptoms to be aware of (see section 4d), and the requirement to inform the DVLA should they have had any episodes of hypoglycaemia requiring third party assistance.
See Dietetic Recommendations for further guidance (section 7).
Please refer to the JBDS hypoglycaemia guidelines or local hospital guidelines for the management of hypoglycaemia in adults with diabetes (91)

Summary:

Patients receiving end of life care are unlikely to require tight blood glucose control

People with ICP-induced insulin deficiency may have labile glucose control and are at risk of hypoglycaemia

Adrenal insufficiency can lead to hypoglycaemia, and awareness is required of potential causes

Individuals at risk of hypoglycaemia should be educated on signs/symptoms (section 4d)

Poor oral intake and nausea/vomiting from the underlying cancer or treatments put individuals at risk for hypoglycaemia

6. Guidelines:
Commencing Systemic Anti-Cancer Therapy (SACT) in a Person with Pre-Existing Diabetes.

It is estimated that up to 20% of all people with cancer have pre-existing diabetes (29, 92, 93). Undergoing cancer treatment can be stressful; however, it is essential that these individuals are adequately supported to appropriately manage their diabetes to optimise both treatment and quality of life.

Objective
The aim of this section is to provide health care professionals working in oncology services with guidance to appropriately support people with diabetes to manage their blood glucose during SACT/supportive care treatment. These guidelines will specifically address:

1. The management of nausea and vomiting without causing unnecessary blood glucose elevations.

2. Provide appropriate recommendations when specialist advice should be sought

6a Management of Nausea and Vomiting

The majority of antiemetic regimens given alongside SACT involve the use of a glucocorticoid (GC). GCs have demonstrated efficacy in the control of emesis in the acute nausea and vomiting stage. Over the past few decades Neurokinin 1 (NK1) antagonists (e.g. aprepitant) have improved emesis outcomes for people with cancer. Their licensing has meant that they can be used with a lower GC dose, with equivalent efficacy, due to an interaction in their mechanisms. There have been some studies involving the new generation NK1 antagonists that have demonstrated an effect without GCs.

- Individuals receiving highly emetogenic and moderately emetogenic chemotherapy should be offered an NK1 antagonist (e.g. aprepitant) with a long acting 5HT3 inhibitor (e.g. ondansetron).

- In the highly emetogenic category clinicians should consider the use of a GC in the first cycle and reduce doses or withdraw completely based on the individual's emetic control and on blood glucose management (94).

- People with diabetes should be counselled on careful self-monitoring of glucose levels and retaining liaison with the diabetes clinical team.

6b When to seek advice in managing a person with diabetes (PWD)

For the duration of SACT treatment it is important for health professionals to understand the following to ensure patients individuals are managed and referred appropriately (95):

Prior to commencing anti-cancer/glucocorticoid (GC) therapy:

- Document the type of diabetes the PWD has

- Document if the PWD has any pre-existing diabetes related complications

- Document if the PWD has hypoglycaemic awareness

- Test baseline random plasma glucose in all PWD

- Test HbA1c in all PWD if this has not been tested within 3 months.

- If plasma glucose is ≥20 mmol/L rule out DKA or HHS (see section 4d). Whilst most cases of DKA occur with hyperglycaemia, about 1 in 20 cases occur with glucose concentrations less than 13 mmol/L. If someone has other symptoms (e.g. acetone on the breath, deep (Kussmaul) breathing) then consider DKA, irrespective of the glucose.

- During pre-chemotherapy treatment counselling a health professional must ensure that the individual is in contact with their usual diabetes care provider (usually primary care), who should be made aware that systemic anticancer treatment is being commenced [see Appendix 2C for referral letter to usual diabetes care provider]. The diabetes care provider should provide urgent advice or appropriately refer to a specialist diabetes team in the event of deterioration of glycaemic control.

- People with pre-existing diabetes should be made aware of the likely exacerbation of hyperglycaemia whilst on antiemetic therapy. People with known diabetes may need to be supplied with a blood glucose meter, as they may not have tested their CBG previously. The blood glucose meter supply and education on use should be arranged by their usual diabetes care provider (usually primary care) upon liaison with the oncology/haematology specialist teams. Those who already test CBG should undertake more frequent CBG testing. These glucose readings can be reviewed by a specialist nurse, clinician or pharmacist who can determine future antiemetic management.

During treatment with anti-cancer therapy continue to monitor random plasma glucose at pre- chemotherapy clinic visits:

- Seek advice on diabetes management from specialist service when nausea and vomiting is unpredictable and poorly managed.

- Where GCs are used as part of treatment, specialist diabetes advice should be sought as it may be necessary to initiate insulin where tablets have previously been used. See JBDS steroid guidelines appendix 2 (71).

- A plasma glucose level should be taken at each hospital visit (clinic visit or treatment visit). If this visit is not scheduled within 3 weeks then the individual should be advised to have a CBG level reviewed with their usual diabetes team (primary care). If the CBG is ≥ 12 mmol/L please ensure prompt communication with the person's usual diabetes care provider (see Appendix 2c for template referral letter).

For non-insulin-treated individuals with type 2 diabetes (Appendix 1C)

Should CBG/ plasma glucose be ≥ 12mmol/L during outpatient visit:

- Screen for symptoms of hyperglycaemia (section 4d) and ketonaemia (or ketonuria) (96).

- If plasma glucose is ≥20 mmol/L or there are symptoms, rule out DKA/HHS (section 4d). Where DKA/HHS has been excluded, refer individual to specialist diabetes team for further management. Awareness should be raised that DKA can occur at normal blood glucose (79).

- For individuals already on sulfonylureas or meglitinides (the insulin secretagogues) titrate their gliclazide up to maximum dose, and contact local diabetes team for further advice. People not using insulin for their diabetes may require switching to insulin therapy, especially those people already on more than one non-insulin glucose lowering agent (including sulfonylureas).

- For individuals not on sulfonylureas or meglitinides (the insulin secretagogues), on a diet controlled regimen only, or on other non-sulfonylurea treatments (e.g. metformin, DPP 4 inhibitors, pioglitazone, SGLT2 inhibitors) add gliclazide 40 mg in the morning and notify local diabetes care provider. Consider incrementing by 40 mg at treatment visits if blood glucose levels are persistently above the target range 6 - 12 mmol/L.

- People on high dose GCs may need larger incremental increases: gliclazide may be titrated to a maximum of 240 mg in the morning and an evening dose of gliclazide may be initiated to achieve a maximum daily dose of 320 mg. Seek specialist advice if you are concerned about dose titration in those taking 160 mg with no improvement in glycaemic control.

- In individuals receiving ICP with a prior history of type 2 diabetes, a sudden change in blood glucose levels/symptoms may indicate immunotherapy-induced pancreatic dysfunction and these individuals need initiation of insulin treatment.

For insulin-treated individuals (Appendix 1D)

Appendix 1D outlines the treatment regimen for people with cancer commencing SACT or glucocorticoid therapy with a history of diabetes treated with insulin.

- As above, where plasma glucose is ≥12 mmol/L on two occasions, initially screen for symptoms of hyperglycaemia and ketonuria/blood ketones to rule out DKA.

- In all cases, contact the diabetes team for support in titrating insulin. However when unable to contact the team, and whilst in the outpatient setting, titrate insulin by 10-20% of the original dose daily, however an increase in insulin

dose by up to 40% may be required, particularly with supraphysiological doses of glucocorticoids, to maintain euglycaemia (97) (see JBDS guidelines on the management of hyperglycaemia and glucocorticoids) (74). Appendix 1D provides further detail of insulin titration according to the type of insulin received.

- If GCs are tapered down or stopped suddenly, glucose monitoring will need to be continued and assessed and doses of insulin reduced accordingly, and individuals advised on risks of hypoglycaemia.

- People with type 1 diabetes are at a particularly high risk of uncontrolled hyperglycaemia, and close liaison with the diabetes team is essential.

- Individuals should be aware of 'sick day rules' with insulin administration (including testing CBG and blood ketones every 4-6 hours, and to continue insulin regimen when unwell/reduced oral intake) and may need careful reminders at the initiation of therapy (see Trend Diabetes sick day rules leaflets for specific type 1 and 2 diabetes guidance (98)). People with type 1 diabetes should be encouraged to seek early advice and treatment when unwell with hyperglycaemia ±ketones.

- The importance of not omitting basal insulin in people with type 1 diabetes should be emphasised in individuals not eating/with cachexia to avoid DKA.

Special Considerations:

Contrast scans:
In individuals already on metformin this should only be discontinued (temporarily) if contrast media for imaging is being used, or if renal function deteriorates significantly (estimated GFR <30 ml/min).

Glycaemic control in PET scanning
Glycaemic excursions affect scan quality and can be a reason for cancelling the scan on the day.

- Aim for a stable glucose within the range of 4-11 mmol/L

- Avoid antidiabetic agents in the 4-6 hours prior to scanning

- Consider adding a corrective dose of rapid acting insulin analogue for those with a blood glucose above 12 mmol/L prior to scan

See treatment pathway 3c and 3d/ APPENDIX 1C and 1D for managing hyperglycaemia in people with known diabetes who are commencing anti-cancer/glucocorticoid therapy in oncology clinic.

Summary

Individuals with known diabetes should undertake regular CBG monitoring upon commencing SACT

Standard antiemetic schedules should be amended to avoid agents that cause hyperglycaemia

Antidiabetic therapy changes may be required when commencing high dose glucocorticoids/SACT to maintain CBG between 6-12 mmol/L

Modifications to antidiabetic therapy may be necessary if CBG is found to be ≥12 mmol/L

7. Dietetic Recommendations

Objective

The aim of this section is to provide health care professionals working in oncology services with guidance to provide appropriate first line nutritional advice and when to refer to dietetic services to support people with diabetes (established, newly diagnosed or glucocorticoid-induced) undergoing SACT. The provision of dietetic services will vary across the country. Referral may be to an oncology dietitian or a diabetes dietitian.

7a General Nutrition Advice

Background / Rationale

TThe general advice regarding eating well for cancer prevention and people living with cancer is very similar to those with diabetes - a healthy balanced diet and lifestyle interventions (99, 100).

The combination of weight maintenance, a balanced diet and physical activity optimisation (aerobic and resistance) collectively demonstrate a benefit for both glycaemic control and systemic anti-cancer therapy tolerance (99, 101).

Meta-analyses and randomised controlled trials demonstrate that physical activity in people with cancer is associated with maintenance or significant improvements in aerobic capacity, muscle strength, health-related quality of life, self-esteem, and with reduction in fatigue and anxiety (102).

Recommendations

1. Most individuals with a concurrent diagnosis of cancer and diabetes will not require dietary changes during cancer treatment.

2. Healthy eating is recommended in order to maintain weight during treatment.

3. Physical activity in people with cancer should be encouraged for all and advice should be individualised.

4. Due to the increased infection risk during SACT, standard food safety and food hygiene advice should be encouraged.

5. Due to the risk of delayed wound healing during SACT, advice should be provided on optimising blood glucose control and how to increase protein dietary intake.

6. Referral for dietetic assessment and dietetic counselling may be offered to people with a new diabetes diagnosis, those starting insulin for the first time, and for individuals requiring carbohydrate awareness education to encourage self-management of diabetes.

7b Nutrition Support

Background / Rationale

The prevalence of malnutrition in people with cancer is highly variable. Recent studies suggest that the prevalence is around 51% to 71% (103, 104). Malnutrition in cancer patients is associated with increased morbidity and mortality, decreased treatment tolerance and quality of life and increased hospital admissions (105, 106). Multivariate analysis has shown weight loss and body mass index to be independent predictors of median survival (107).

30-40% of people with cancer experience malnutrition, which is characterised by unintentional weight loss (108). Cancer-related malnutrition can occur due to the presence of the cancer itself, the effect of cancer treatment on the consumption or absorption of nutrients, or patients undertaking restrictive cancer diets. The risk of malnutrition is largely dependent on the type and stage of cancer in addition to the level of symptom burden (108). Poor glycaemic control can cause unintentional weight loss through urinary glucose losses. Rapid unintentional weight loss leads to loss of muscle and strength, which may compromise performance status and the ability to tolerate or continue with treatment.

Cancer Cachexia and Sarcopenia

Cancer cachexia is a complex and progressive syndrome of systemic inflammation and catabolic alterations. It is characterised by the loss of skeletal muscle mass, with or without loss of fat mass, in those with cancer. Skeletal muscle mass loss and decline in functional status is known as sarcopenia. Sarcopenia is common in older adults (>55 years) with diabetes (109). Prolonged hyperglycaemia can impact on muscle mass and contribute to sarcopenia. Cancer cachexia and sarcopenia can lead to decreased physical activity, adverse psychological side effects, poor performance status and higher mortality rates (110, 111).

Nutrition Impact Symptoms (NIS)

Poor glycaemic control can cause weight loss and precipitate nutrition impact symptoms (NIS) such as nausea, poor appetite and altered bowel movements. Loss of appetite and poor oral intake in those on insulin, sulfonylureas or meglitinides can increase the risk of hypoglycaemia. Symptoms of hyperglycaemia (polyuria, nocturia, fatigue, thirst, blurred vision, headaches, confusion, weight loss) can induce weight and muscle mass loss.

Individuals with unintentional weight loss and diabetes have the added challenge of needing to optimise their oral intake to help preserve their nutritional status whilst simultaneously maintaining adequate glycaemic control. Successful management of both aspects of care are crucial.

Nutrition Support

Nutrition support should be considered in people who are malnourished as defined by the following criteria:

- BMI of less than 18.5 kg/m2
- Unintentional weight loss greater than 10% within the last 3–6 months

- A BMI of less than 20 kg/m2 and unintentional weight loss greater than 5% within the last 3–6 months
- Individuals who have eaten little or nothing for more than 5 days and/or are likely to eat little or nothing for the next 5 days or longer
- Individuals with a poor absorptive capacity, and/or have high nutrient losses and/or have increased nutritional needs from causes such as catabolism (112)

Nutrition support is recommended to increase energy and protein intake via an appropriate route (oral, EN and/or PN) (102). Various methods of nutritional support can be implemented to optimise nutritional intake. Choice of method depends on clinical circumstances, which include treatment, prognosis, anatomy and symptom profile and require advice from a dietitian.

Oral nutritional support

Healthcare professionals should consider oral nutrition support to improve nutritional intake for people who can swallow safely and are malnourished or at risk of malnutrition (112).

Individuals with unintentional weight loss or who are underweight (<18.5 kg/m2) are advised to follow nutritional support interventions to help meet nutritional requirements. Symptom control of NIS is an essential supportive measure alongside nutritional support which can be provided through nutritional counselling and medical management (102). Strategies to optimise nutritional intake may include modifications to the diet such as food fortification and small, frequent meals with a particular focus in high calorie and protein foods and snacks. Reassurance should be provided to individuals that relaxation of a healthy balanced diet is appropriate if they are losing weight during treatment and dietary intake is poor. Additionally, oral nutritional supplements may be recommended if nutritional intake cannot be maximised with a food first approach and weight loss is ongoing through SACT.

Enteral Nutritional Support

Healthcare professionals should consider enteral tube feeding (EN) in individuals who are malnourished or at risk of malnutrition and have:

- Inadequate oral intake
- Unsafe swallow (i.e. in head and neck cancers)
- AND a functional, accessible gastrointestinal tract (112)

EN is a method of artificial nutritional support using the gastrointestinal tract. EN may be used as the only method of delivering nutrition or it might be used supplementary to oral intake and / or parenteral nutrition. Methods of delivering EN may be continuous using a feeding pump over a number of hours or bolus feeding which involves delivering larger volumes of feed using a syringe administered through the tube. The UK currently has no enteral feeds that are designed specifically for diabetes. Refer individuals requiring EN for diabetes specialist support, as they will likely need a tailored approach to matching medication with carbohydrate content in the feeds (113).

Parenteral Nutrition

Healthcare professionals should consider parenteral nutrition (PN) in people who are malnourished or at risk of malnutrition and meet either of the following criteria:

- Inadequate oral and/or enteral nutritional intake
- A non-functional, inaccessible or perforated (leaking) gastrointestinal tract (112)

PN is typically initiated in hospital when there has been gut failure. In the context of cancer, specific clinical scenarios include bowel obstruction, radiation enteritis, ileus, short gut syndrome and high output stoma. PN involves the administration of amino acids, lipids and glucose through a central line. EN may run concurrently in selected cases as may some oral nutrition.

Where dietary intake has been poor for some time individuals are at risk of hypoglycaemia, or even normalisation of glycaemic control. The introduction of oral, EN or PN may reverse this to precipitate hyperglycaemia, therefore follow local re-feeding guidelines and blood glucose monitoring as described in section 5 (QDS blood glucose monitoring at commencement of feeding). Home parenteral nutrition (HPN) may be considered in certain clinical situations (114) and may run concurrently with SACT.

Recommendations

NIS management:

1. Medication optimisation is crucial to control symptoms to enable appropriate nutrition support advice.
2. Referral for dietetic counselling may be needed to manage NIS (102).
3. Individuals should be made aware and follow relevant 'sick day rules' depending on their current diabetes medications

    Guidance for people with diabetes: https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf and https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/illness

4. Encourage individuals to communicate with their oncology and diabetes teams regarding managing their diabetes as certain medications (such as metformin or SGLT2 inhibitors) may need to be stopped during severe episodes of vomiting or diarrhoea due to an increased risk of dehydration.

Nutrition support:

1. Should nutrition support be indicated, optimisation of medications to resolve symptoms that are affecting food and fluid intake is required as dietary restrictions are rarely indicated.
2. It is important not to reduce nutritional intake or encourage a healthy balance to achieve glycaemic control. Changes to diabetes medication are a priority and may be required.
3. If blood glucose levels are raised with any method of nutritional support, the dietitian, the individual (if able) and medical team should discuss this to decide on the optimum management plan.

4. It is vital to ensure blood glucose levels are closely reviewed and appropriate medical management is provided. This may need to be as frequent as four times daily blood glucose monitoring, particularly on initiation of nutritional support.

5. Individuals must be given appropriate recommendations for when to monitor their blood glucose if required.

Oral Nutrition support

1. Provide first line oral nutrition support advice and refer to the dietitian if weight or muscle mass loss is ongoing.

2. Juice style supplements should be avoided first-line due to their high sugar content. Supplements that are considered to be suitable may still raise blood glucose levels but are safe to be prescribed if nutritional requirements cannot be met with food fortification alone. Where this occurs, medications used for diabetes management should be reviewed or an alternative supplement with a lower carbohydrate or sugar content may need to be considered. It is important not to cease ONS due to hyperglycaemia as they may be a valuable source of nutrition for individuals.

Enteral and/or Parenteral Nutrition support

1. Collaborative working between the dietetic and medical team is important in designing and monitoring a feed regimen that aligns with medical interventions for glycaemic control.

2. There is some evidence for increasing energy by substituting carbohydrates to fat in people with insulin resistance who are losing weight whilst having EN and/or PN (102).

7c Glucocorticoids (GCs)

Background / Rationale

Short term GCs may be used in selected individuals with significant anorexia to stimulate appetite (102). They are also routinely prescribed to patients within their treatment antiemetic protocol.

GCs can impair glucose metabolism and close monitoring of blood glucose levels are required for those who have diabetes.

Recommendations

1. If blood glucose levels rise, medical management is required (i.e. starting or increasing medications) rather than dietary restrictions (see section 5a of guidelines).

2. If there is an increase in appetite with steroids, offer advice on a healthy balanced diet, including information on non-carbohydrate snacks. Nutrition support and food fortification advice is not indicated if intake is good.

7d Alternative Diets

Background / Rationale

It is important to establish if individuals are on restrictive diets including ketogenic and fasting style diets that can affect dietary adequacy and glycaemic control. Myths around sugar 'feeding' the cancer to stimulate tumour growth are not supported by current research. Restrictive diets of any nature are not recommended and have the potential to cause harm in people with cancer with or at risk of malnutrition (102, 115, 116).

Recommendations

If restrictive alternative diets are causing poor glycaemic control or impacting nutritional status refer to a dietitian for dietetic counselling.

7e Type 3c Diabetes

Background / Rationale

See section 4a for background of Type 3c Diabetes

Use of exocrine pancreatic enzyme therapy, e.g. Creon, Nutrizym or Pancrease is commonplace in T3cDM and can influence glycaemic control. Enzyme use is vital to help control symptoms of steatorrhea, but can also prevent malnutrition, metabolic complications and vitamin and mineral deficiencies. Pancreatic enzyme therapy promotes the digestion of ingested food which can lead to increased absorption of glucose, amino acids and lipids into the bloodstream. The introduction of pancreatic enzyme therapy can potentially mask underlying diabetes or lead to hyperglycaemia in people with known diabetes.

Since the dosing of pancreatic enzyme therapy can directly affect blood glucose control, regular blood glucose monitoring during dose changes is imperative.

Recommendations

1. Offer collaborative working across the oncology and endocrinology multidisciplinary teams for individuals with T3cDM to deliver best possible care.

2. Refer individuals with T3cDM and/or pancreatic exocrine insufficiency to the dietitian for dietetic counselling.

7f Hypoglycaemia

Background / Rationale

Individuals on an insulin secretagogue e.g. sulfonylureas or meglitinides, or those on insulin and/or poor oral intake and/or T3cDM are at an increased risk of hypoglycaemia See section 5d of the guidelines for further information about individuals at risk of hypoglycaemia.

Recommendations

All individuals who are at risk of hypoglycaemia should receive advice regarding appropriate treatment with 15–20 g of fast-acting carbohydrate, taken immediately. For example 4–7 glucose tablets, 150–200 ml of pure fruit juice or 5 jelly babies (81). Then follow up with a meal or snack containing slower-acting carbohydrate. Full JBDS guidelines on the management of hypoglycaemia can be found in this reference (91). See section 4d of the guidelines for further information about symptoms of hypoglycaemia.

8. Communication aids

The following communication aids have been developed to be downloaded and for hospitals to add local information as required.

a) Patient information sheet: 'Developing high blood glucose on anti-cancer therapy in a person not known to have diabetes
(Appendix 2A – page 43-44)

This information sheet should be provided to people who develop high blood glucose following commencement of anti-cancer therapy or glucocorticoids without a prior known diagnosis of diabetes.

b) Patient information sheet: 'Starting systemic anti-cancer therapy/ glucocorticoids in a person with diabetes'
(Appendix 2B – page 45-46)

This information sheet should be provided to individuals at risk of worsening glycaemic control, i.e. those commencing anti-cancer therapy or glucocorticoids (as above) with a known diagnosis of diabetes.

c) Letter to diabetes care provider (primary care/ diabetes team)
(Appendix 2C – page 47-48)

This letter should be sent to the primary care diabetes care provider (or secondary care diabetes team as appropriate) as a referral to provide further management in a person with diabetes who develops worsening glycaemic control on anti-cancer therapy (a), or in a person not known to have diabetes who develops high blood glucose (b).

d) Template blood glucose diary
(Appendix 2D – page 49)

This diary can be provided to individuals for daily self-check of blood glucose at home.

e) Blood glucose monitoring form: Oncology Clinic/ Chemotherapy Day Unit
(Appendix 2E - page 50)

This blood glucose monitoring table can be used by day care team on the chemotherapy unit, or by clinical nurse specialists/clinic nurse in the oncology clinic to monitor blood glucose with each cycle of treatment.

9. Appendix 1: Pathways

Appendix 1a Commencing anti-cancer agents/ glucocorticoid therapy in cancer patients without a prior diagnosis of diabetes

Check **HbA1c** at baseline for all cancer patients

If >47 mmol/mol at baseline visit, refer to GP

Do not delay initiating anti-cancer therapy

Check **random plasma glucose** prior to commencing anti-cancer therapy / steroids

Commence anti-cancer/GC therapy

Check plasma glucose at each treatment visit

<12 mmol/L

≥12 mmol/L <20 mmol/L

≥20.1 mmol/L

Recheck plasma glucose at each treatment visit
- If consistently <12 mmol/L consider cessation of testing

Provide relevant information leaflet (steroids)

Provide glucose meter if 'high risk' or commencing steroids, to monitor daily pre-meal

Ensure patient has a glucose meter & testing strips

Check: - Hyperglycaemia symptoms
for   - Ketonuria/ ketonaemia

if DKA/HHS excluded

Commence gliclazide 40 mg with breakfast if ≥ 12 mmol/L and/or prompt referral to primary care to initiate treatment

Ensure blood glucose meter provided
Advise to test CBG 4x daily

Recheck plasma glucose at each treatment visit

IR max dose 320 mg/day
MR max dose 120 mg/day

Max morning dose 240 mg & evening dose 80 mg

Increase gliclazide by 40 mg increments if remains ≥12 mmol/L
May need higher increments, potentially daily, if on high dose GCs – needs close liaison with diabetes care provider (usually primary care)
Consider giving gliclazide pm if on BD steroids ¥

If: Hyperglycaemia symptoms
Ketonuria (>2+) or Ketonaemia >3 mmol/L
Venous Bicarb <15 mmol/L +/- pH <7.3*

DKA/HHS diagnosed φ

DKA/HHS excluded

Refer to local AE/ MAU department urgently

Urgent referral to diabetes team to start treatment

Ensure blood glucose meter provided

Advise to check 4x daily

If treatment reduced/discontinued:
- Continue plasma glucose/CBG testing if ≥12 mmol/L
- Any changes made should be reviewed and consideration given to reverting to previous therapy or doses
- Discuss with diabetes team if unsure at any stage

* Patients not meeting this criteria may still require referral to MAU/AE – exercise clinical judgement
¥ See JBDS steroid guidelines appendix 2 for further details [71,74]
φ See JBDS DKA/HHS guidelines [77, 80]

Appendix 1b
Commencing immune checkpoint inhibitors (ICP) in cancer patients without a prior diagnosis of diabetes

Check **HbA1c** at baseline for all cancer patients

If >47 mmol/mol at baseline visit, refer to GP — Do not delay initiating anti-cancer therapy

Check **random plasma glucose** prior to commencing ICP

Counsel patients to seek immediate medical attention if there are symptoms of hyperglycaemia as DKA can occur rapidly in these patients

Commence ICP

Check plasma glucose at each treatment visit

<12 mmol/L

Recheck with each ICP treatment visit

≥12 mmol/L <20 mmol/L

Check: - Hyperglycaemia symptoms
for - Ketonuria/ Ketonaemia

if DKA/HHS excluded

Refer to diabetes team early

Recheck at each treatment visit

Advise patient re: symptoms of hyperglycaemia

Ensure patient has CBG meter/ test strips
Advise to test CBG 4x daily
To seek medical advice if ≥ 20 mmol/L at home

≥20.1 mmol/L

Check: Hyperglycaemia symptoms
Ketonuria (>2+) or Ketonaemia >3 mmol/L
Venous Bicarb <15 mmol/L +/- pH <7.3*

if yes | if no

DKA/HHS diagnosed ¥

Refer to local AE/ MAU department urgently

DKA/HHS excluded

Check anti-GAD +/- anti islet cell antibodies

Urgent referral to diabetes team/ consider admission

Patient requires treatment with insulin therapy φ

¥ See JBDS DKA/HHS guidelines [77, 80]
* Patients not meeting this criteria may still require referral to MAU/AE – exercise clinical judgement
φ ICP should be withheld with grade 3 hyperglycaemia. Consider restarting once regulated with insulin

Appendix 1c
Commencing SACT/ glucocorticoid therapy in cancer patients with type 2 diabetes on oral glucose lowering therapies

Check **HbA1c** at baseline for all cancer patients

→ If >60 mmol/mol at baseline visit refer to usual diabetes care provider (DCP)

Check **random plasma glucose** prior to commencing anti-cancer therapy / steroids

Ensure patient has a blood glucose meter & testing strips

Check plasma glucose at each treatment visit

<12 mmol/L

Continue usual diabetes regimen

≥12 mmol/L On 2 separate readings

≥20.1 mmol/L

Rule out DKA/HHS*

Urgently refer and contact diabetes team

PWD – diet controlled or on other NON SULFONYLUREA treatments eg:
- Metformin
- Gliptins eg Sitagliptin, Linagliptin
- Flozins eg. Dapagliflozin, Canaglifozin
- Pioglitazone
- Non-insulin injectables (eg. Victoza, Byetta)

If no hypo symptoms, commence gliclazide 40 mg morning

Refer to usual diabetes care provider

PWD already on SULFONYLUREA eg
- Gliclazide

(IR max dose 320 mg/day)
(MR max dose 120 mg/day)

Max morning dose 240 mg & evening dose 80 mg

Patients has no symptoms of hypoglycaemia, day or night. Is patient on max dose?

No

Aim CBG 6-15 mmol/L pre-evening meal

Yes

Titrate morning dose up to max dose

Contact usual diabetes care provider

If CBG remains ≥12 contact usual DCP ¥

PWD = Person with diabetes
IR = Immediate Release
MR = Modified Release
¥ See JBDS steroid guidelines appendix 2 [71,74]
*See JBDS DKA/HHS guidelines [77, 80]

If treatment reduced/discontinued any changes made should be reviewed and consideration given to reverting to previous therapy or doses (discuss with diabetes team if unsure at any stage)

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Appendix 1d
Commencing SACT/ glucocorticoid therapy in cancer patients with diabetes treated with insulin (89)

Check **HbA1c** at baseline for all cancer patients

→ If >60 mmol/mol at baseline visit, refer to usual diabetes care provider (DCP)

Advise patients to monitor/record CBGs QDS

Check **random plasma glucose** prior to commencing anti-cancer therapy / steroids

On 2 separate readings → **≥12 mmol/L** → Check for urinary ketones

Review patient recorded blood glucose at each visit

If on once daily insulin* e.g. Insulatard, Humulin I, Lantus or Degludec

Contact diabetes team

If unable to contact DM team: Titrate by 10-20% according to pre evening meal CBG ¥

If on twice daily insulin

Contact diabetes team

If unable to contact DM team: Morning dose will need to increase 10-20% according to pre-evening meal CBG ¥

If on basal bolus insulin

Contact diabetes team

If unable to contact DM team: Increase short/fast acting insulin by 10-20% until glycaemic target reached ¥

If treatment reduced/discontinued any changes made should be reviewed and consideration given to reverting to previous therapy or doses (discuss with diabetes team if unsure at any stage)

*If long acting insulin is taken once nightly, move this pre-bed injection to the morning and increase dose according to pm CBG

¥ See JBDS steroid guidelines appendix 2 for further management on titration [71, 74]

Appendix 2: Communication Aids

Appendix 2a

Patient information sheet: 'Developing high blood glucose (blood sugar) on anti-cancer therapy in a person not known to have diabetes'

You have been given this information sheet by the Oncology clinic because you have been found to have high blood glucose before or during cancer treatment.

What is diabetes (high blood glucose)?

Diabetes is the name given to a group of conditions where the levels of glucose (sugar) in your blood becomes too high.

What causes high blood glucose /diabetes during cancer treatment?

High blood glucose during cancer treatment are usually a side effect of the cancer treatment or, most commonly, of other medications given to control the side effects of cancer treatment. The most common medications that cause high blood glucose during cancer treatments are steroids, but there are many others that can also cause high blood glucose.

Your cancer doctor or specialist nurse will be able to give you more information about what the most likely cause was for you.

Why is it important to get blood glucose/diabetes under control during cancer treatment?

High blood glucose matters because it can affect how you feel in yourself (your general wellbeing). Some of the symptoms of high blood glucose include:

Feeling very thirsty, and drinking lots of water

Passing urine more often, or a new need to pass urine at night

Feeling very tired

Blurred vision, headaches, confusion and weight loss

There is some evidence from studies to suggest that having high blood glucose during cancer treatment may make the side effects of the treatment worse.

There is also evidence that keeping blood glucose under control may improve your overall wellbeing.

Does having high blood glucose mean I will always have diabetes?

Often the high blood glucose (diabetes) is the result of medicines that are given for cancer. Usually the diabetes goes away once the treatment ends. There are a few special situations in which the diabetes doesn't go away after the end of treatment:

Sometimes people are found to have diabetes when they start cancer treatment, and they probably already had diabetes but didn't know it.

A few specific cancer treatments can cause a special type of diabetes that doesn't go away- but this is rare.

Surgery for cancer involving the pancreas (the organ that makes insulin) may cause a type of diabetes that doesn't go away.

Your doctor or specialist nurse will be able to give you more information that is specific to your situation.

How will my high blood glucose be treated during cancer treatment?

- You will usually be asked to check your blood glucose (with a finger prick blood sugar monitor), if you don't already do this. *If you haven't already been shown how to do this then ask in the clinic.*
- You may be asked to make changes to the food you eat (e.g. avoiding sugary food and drinks),
- If your blood glucose is high you may need to start tablets or sometimes insulin injections to bring them down.
- Your cancer doctor may make changes to your cancer treatment or supportive treatment to help bring your blood glucose down.

Important: Don't make changes to your cancer treatment or stop taking your steroids without talking to your cancer doctor first.

If you need to start treatment for your blood glucose you will be guided through it, and there will be lots of support available. Your cancer team and your other healthcare teams will be on hand to help work with you to improve your blood glucose. If you are finding things difficult tell your cancer doctor, cancer specialist nurse or diabetes team. We are here to help you.

If you have any questions about the contents of this information sheet, or about your treatment in general please ask your doctor or nurse.

Appendix 2b

Patient information sheet - 'Starting anti-cancer treatment/steroids in a person with diabetes'

About 1 in 10 people receiving cancer treatment also have diabetes, or high blood glucose (blood sugar). You have been given this information sheet by the Oncology clinic **because you have diabetes and you will be starting cancer treatment.**
Some cancer treatments, and other supportive treatments (including steroids), can raise blood glucose. **This may lead to a worsening of your blood glucose control.**

Keeping your blood glucose under good control during cancer treatment may:

- Reduce the risk of infections and other side effects from cancer treatment

- Improve overall wellbeing

This sheet is aimed at helping us work with you, and with those involved in your diabetes care, to keep your blood glucose under control during treatment.

Today's date:
Patient name: **Date of birth:**   **MRN:**
Type of diabetes you have: **Type 1:** ☐   **Type 2:** ☐   **Other:** _____
Diabetes care under: **GP/Practice nurse** ☐   **Hospital diabetes doctor/specialist nurses** ☐   **Name/contact details:**
Current diabetes treatment: **Diet control only** ☐   **Tablets** ☐   **Insulin injections** ☐   **Insulin pump** ☐
Please list current diabetes medicines here:
Latest HbA$_{1c}$ result: **Date:**
Name(s) of the cancer treatment medication you will be taking that can raise blood glucose:

Before you start treatment:

-You will be having blood tests (glucose and HbA1c) to check how well your diabetes is controlled at the moment.

-If your tests show that your blood glucose could be improved, we may refer you to a diabetes specialist for help with this.

During treatment:

-You will have your blood glucose checked when you come to the cancer clinic.

-You will be given a blood glucose monitor (if you don't already have one) and shown how you can use it at home to check your own blood glucose.

Let your doctor or nurse know

if you develop any **symptoms of high blood glucose**, these include:

- Feeling very thirsty, and drinking lots of water

- Passing urine more often, or a new need to pass urine at night

- Severe tiredness

- Blurred vision, headaches, confusion and weight loss

Your individual action plan:

Blood glucose checking plan:
Check here if blood glucose monitor given
__ times a day/week (*delete as*
Urine testing plan:
Test your urine for ketones ☐
Test your urine for glucose ☐
Blood glucose management plan:
If your blood glucose is more than _____ on 2 readings within the same
day Contact: _____
If your blood glucose is more than 20.1: seek urgent medical advice
Sick day rules:

If you have any questions about the contents of this information sheet, or about your treatment in general please ask your doctor or nurse.

For more information about managing diabetes and cancer treatment see the Macmillan leaflet "Diabetes and cancer treatment".

Appendix 2c

Template referral letter for diabetes management of patient who has developed high blood glucose whilst on systemic anti-cancer therapy/ steroids

Patient details	Hospital details
Surname:	Referring hospital:
Forename:	Name of referrer:
Date of birth:	Role:
NHS number:	Contact number/bleep:
Address:	Consultant:
Telephone:	
Date of referral:	Cancer diagnosis:

Dear colleague

The above patient has been seen in the oncology clinic and has developed hyperglycaemia whilst receiving systemic treatment for cancer.

Hyperglycaemia and cancer treatment outcomes:

Individuals with cancer are at increased risk of developing new onset diabetes mellitus and hyperglycaemia, and an estimated 20% of people with cancer already have an underlying diagnosis of diabetes mellitus, with cancer now the leading cause of death in people with diabetes[1].

Several anti-cancer agents are known to increase the risk of hyperglycaemia, even in individuals without a known diagnosis of diabetes. Hyperglycaemia during chemotherapy can occur in approximately 10-30% of people with cancer, and although is frequently transient during treatment, can become long-term. People with both cancer and diabetes may have an increased risk of toxicities, hospital admissions and morbidity, with hyperglycaemia potentially attenuating the efficacy of chemotherapy often secondary to dose reductions and early cessation.

A meta-analysis comprising 9872 cancer patients without diabetes showed that patients with hyperglycaemia had significantly worse disease-free survival (hazard ratio (HR) 1.98, 95% confidence interval (CI) 1.20-3.27) compared to normo-glycaemic patients[2].

Further high level evidence is lacking regarding the importance of glycaemic control in people with cancer, however improved recognition and potentially more complex diabetes care is required in these individuals[3]. The UK Chemotherapy Board and Joint British Diabetes Society have produced guidance recommending good glycaemic control during cancer treatment[4]. The guideline recommends treating diabetes in cancer patients as a special circumstance. Please find further details on recommended treatment regimen at this reference.

Details of the above patient's current oncology treatment is as detailed below:

Current oncology Treatment (including steroids)	Include frequency and planned duration:
Diabetes history and blood glucose results	
Past diabetes history: YES/NO (delete as appropriate)	If yes, please provide details:
Relevant results:	e.g.: HbA$_{1c}$, example blood glucose results.
Reason for referral additional information:	
If treatment for hyperglycaemia initiated in clinic, provide details:	

Thank you for your assistance in improving this patient's glycaemic control.

If you have any further questions, please do not hesitate to get in touch.

Best wishes

[Name]

[Role]

References:

1. Pearson-Stuttard J et al. *The Lancet Diabetes & Endocrinology*. 2021;9(3):165-173
2. Barua R, et al. Clin Oncol (R Coll Radiol). 2018;30(4):215-24
3. Morganstein DL, et al. *The British Journal of Diabetes & Vascular Disease*. 2012;12(4):178-180
4. UK Management of Glycaemic Control in Patients with Cancer: Guidance for the oncology multidisciplinary team https://www.ukchemotherapyboard.org/information

Appendix 2d

Template blood glucose diary (self-check)

🩸 Daily blood glucose record chart

Blood glucose targets

Before meals: After meals:

Date		Waking	1-2h after breakfast	Before lunch	1-2h after lunch	Before evening meal	1-2h after evening meal	Comments
Monday	Time							
	Reading							
Tuesday	Time							
	Reading							
Wednesday	Time							
	Reading							
Thursday	Time							
	Reading							
Friday	Time							
	Reading							
Saturday	Time							
	Reading							
Sunday	Time							
	Reading							

Appendix 2e

Blood glucose monitoring form: Oncology Clinic/ Chemotherapy Day Unit

Affix patient label here

Treatment regimen: _____

Pre-treatment bloods (to be documented prior to cycle 1, day 1):

Random blood glucose _____ mmol/L   Date: _____

HbA_{1c}: _____ mmol/mol   Date: _____

Please notify the Oncology team if glucose is ≥12mmol/L on two separate occasions **or** >20mmol on one occasion

Date	Cycle/Day	Random venous glucose		Notes
		Time		
		Reading		
		Time		
		Reading		
		Time		
		Reading		
		Time		
		Reading		
		Time		
		Reading		
		Time		
		Reading		
		Time		
		Reading		
		Time		
		Reading		

APPENDIX 3: Membership of JBDS-IP Group

Dr Ahmed Al-Sharefi, South Tyneside and Sunderland Hospital NHS Foundation Trust

Dr Parizad Avarai, Imperial College Healthcare NHS Trust

Elizabeth Camfield, Guy's and St Thomas' NHS Foundation Trust

Erwin Castro, (East Sussex) Chair, DISN UK Group

Dr Jason Cheung, Norfolk and Norwich University Hospitals NHS Foundation Trust

Dr Umesh Dashora, East Sussex Healthcare NHS Trust

Dr Parijat De, Sandwell and West Birmingham Hospitals NHS Trust

Professor Ketan Dhatariya, (Norwich), Chair, Joint British Diabetes Societies (JBDS) for Inpatient Care

Dr Daniel Flanagan, Plymouth Hospitals NHS Trust

Dr Stella George, East and North Hertfordshire NHS Trust

Dr Chris Harrold, University Hospitals Coventry and Warwickshire NHS Trust

Dr Masud Haq, Maidstone and Tunbridge Wells NHS Trust

Dr Kath Higgins, University Hospitals of Leicester NHS Trust

Klea Isufi, Diabetes UK

June James, University Hospitals of Leicester NHS Trust

Andrea Lake, Cambridge University Hospitals NHS Foundation Trust

Dr Anthony Lewis, Belfast Health and Social Care Trust, Northern Ireland

Dr Sue Manley, University Hospitals Birmingham NHS Foundation Trust

Dr Omar Mustafa, King's College Hospital NHS Foundation Trust, London

Philip Newland-Jones, University Hospital Southampton NHS Foundation Trust

Dr Dipesh Patel, Royal Free London, NHS Foundation Trust

Professor Gerry Rayman, The Ipswich Hospitals NHS Trust

Dr Stuart Ritchie, NHS Lothian

Dr Aled Roberts, Cardiff and Vale University Health Board

Professor Mike Sampson, Norfolk and Norwich University Hospitals NHS Foundation Trust

Professor Alan Sinclair, Director Diabetes Frail Ltd

Esther Walden, Diabetes UK

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