Oncology and palliative care

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Disclosures

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Oncology and palliative care

- Diabetes and cancer risk
- Managing diabetes with chemotherapy
- Deprescribing and managing diabetes in end-of-life care

Diabetes and cancer risk

People with diabetes are at a higher risk for developing several cancers, possibly due to shared risk factors between the two diseases[1]

It is estimated that 20% of people with cancer have concurrent diabetes, with cancer the leading cause of death in people with diabetes[2,3]

Breast cancer, intrahepatic cholangiocarcinoma, colorectal cancer, and endometrial cancer show the greatest increased risk.[4]

1. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21
2. UK. D. Diabetes and Cancer. https://www.diabetes.org.uk/diabetes-the-basics/relatedconditions/diabetes-and-cancer. Accessed January 2023.
3. Pearson-Stuttard J, Bennett J, Cheng YJ, Vamos EP, Cross AJ, Ezzati M, et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. The Lancet Diabetes & Endocrinology. 2021;9(3):165-73
4. Pearson-Stuttard J, Bennett J, Cheng YJ, Vamos EP, Cross AJ, Ezzati M, et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. The Lancet Diabetes & Endocrinology. 2021;9(3):165-73.

The incidence of diabetes and cancer has increased significantly in recent years

There are many common risk factors for both diabetes and cancer, such as:

- obesity
- sedentary lifestyle
- smoking
- ageing

Although the underlying biological mechanisms have not been totally understood, studies have validated that:

- insulin resistance, hyperinsulinaemia, hyperglycaemia and inflammatory cytokines provide good circumstances for cancer cell proliferation and metastasis.
- hyperglycaemia provides energy for cancer cell growth

Wang M, Yang Y, Liao Z. Diabetes and cancer: Epidemiological and biological links. World J Diabetes. 2020 Jun 15;11(6):227-238. doi: 10.4239/wjd.v11.i6.227. PMID: 32547697; PMCID: PMC7284016

Pancreatic cancer and diabetes

Pancreatic cancer is one of the deadliest malignant diseases, with a 5-year survival rate less than 10%

Greater incidence of pancreatic cancer in those with diabetes

New onset diabetes is also an indicator of pancreatic cancer

Some evidence to suggest the link between diabetes and pancreatic cancer is bidirectional

Wang M, Yang Y, Liao Z. Diabetes and cancer: Epidemiological and biological links. World J Diabetes. 2020 Jun 15;11(6):227-238. doi: 10.4239/wjd.v11.i6.227. PMID: 32547697; PMCID: PMC7284016

diabetes can increase the risk of pancreatic cancer

Type 3c diabetes (also known as **pancreatogenic diabetes**) is diabetes that comes secondary to pancreatic diseases, involving the exocrine and digestive functions of the pancreas.

Gudipaty, Lalitha. Rickels, Michael R. (2015). Pancreatogenic (Type 3c) Diabetes. *Pancreapedia: Exocrine Pancreas Knowledge Base*, DOI: 10.3998/panc.2015.35

What are the causes of pancreatic diabetes?

- pancreatitis (acute and chronic)
- trauma or pancreatectomy
- neoplasia
- cystic fibrosis
- hemochromatosis
- fibrocalculous pancreatopathy
- rare genetic disorders
- idiopathic forms

…..as such, pancreatic diabetes is the preferred umbrella terminology

However, pancreatitis is the commonest cause

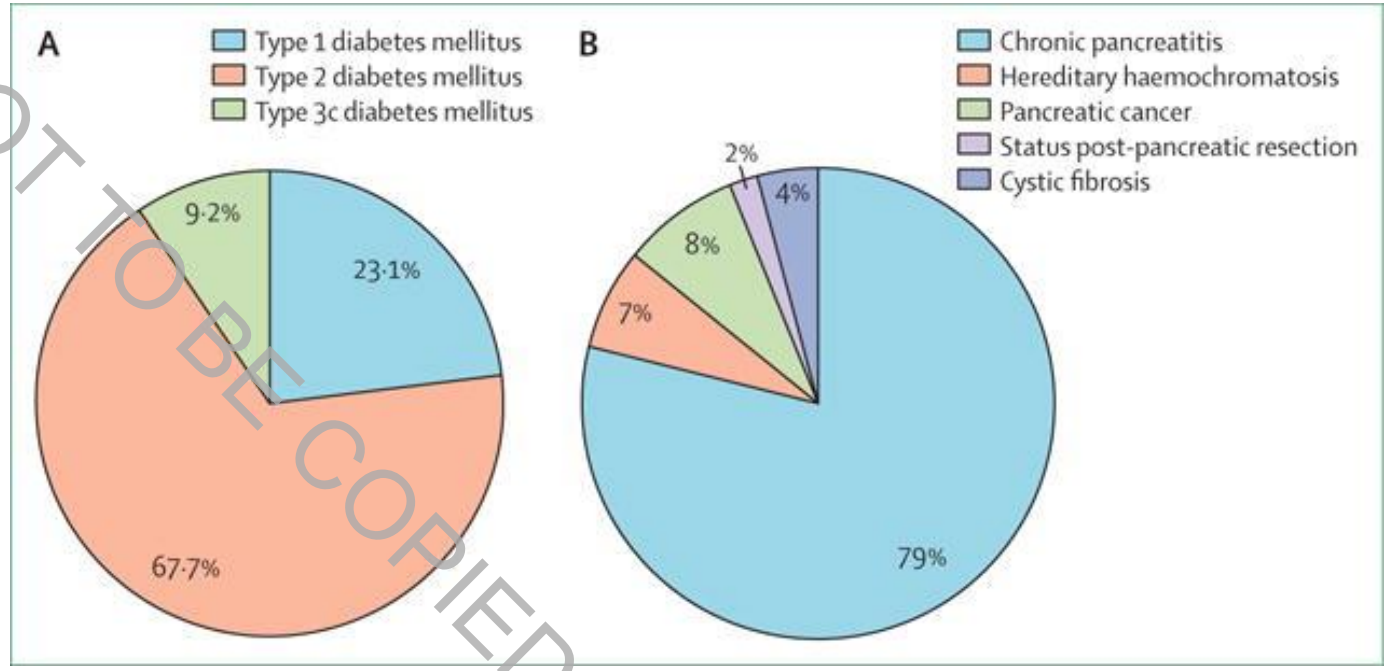
Pancreatitis, even a single bout, can lead to postpancreatitis diabetes mellitus (PPDM)

Both acute and chronic pancreatitis can lead to PPDM

the risk is highest with recurrent bouts

causes of type 3c diabetes mellitus

Prevalence of type 3c diabetes in a cohort of 1868 participants with diabetes



Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c) *Diabetes Metab Res Rev.* 2012;28:338–42

How do we differentiate Pancreatic diabetes from type 1 or 2 diabetes?

NO universally accepted diagnostic criteria

So conceptually the three following criteria need to be met:

- diagnosis of diabetes
- present disease of the exocrine pancreas
- diabetes is reasonably certain to be secondary to their exocrine pancreatic disease

Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC, Pandol SJ, Yadav D, Chari ST; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer(CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016 Nov;1(3):226-237. doi: 10.1016/S2468-1253(16)30106-6. Epub 2016 Oct 12. PMID: 28404095; PMCID: PMC5495015

So how do we do this?

A distinguishing feature is concurrent pancreatic exocrine insufficiency (defined by monoclonal fecal elastase 1 test or direct function tests)

Pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography)

An absence of type 1 diabetes–associated autoimmunity

Ewald N and Hardt PD (2013). Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World Journal of Gastroenterology 19 (42); 7276–7281

Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study

Chris Woodmansey,[1] Andrew P. McGovern,[1] Katherine A. McCullough,[1,2] Martin B. White,[1,2] Neil M. Munro,[1] Ana C. Correa,[1] Piers A.C. Gatenby,[1,3] Simon A. Jones,[1,4] and Simon de Lusignan[1,5]

Diabetes Care 2017;40:1486–1493 | https://doi.org/10.2337/dc17-0542

Insulin use within 5 years was:

4.1% (3.8–4.4) with type 2 diabetes,

20.9% (14.6–28.9) with diabetes following acute pancreatitis

45.8% (34.2–57.9) with diabetes following chronic pancreatic disease.

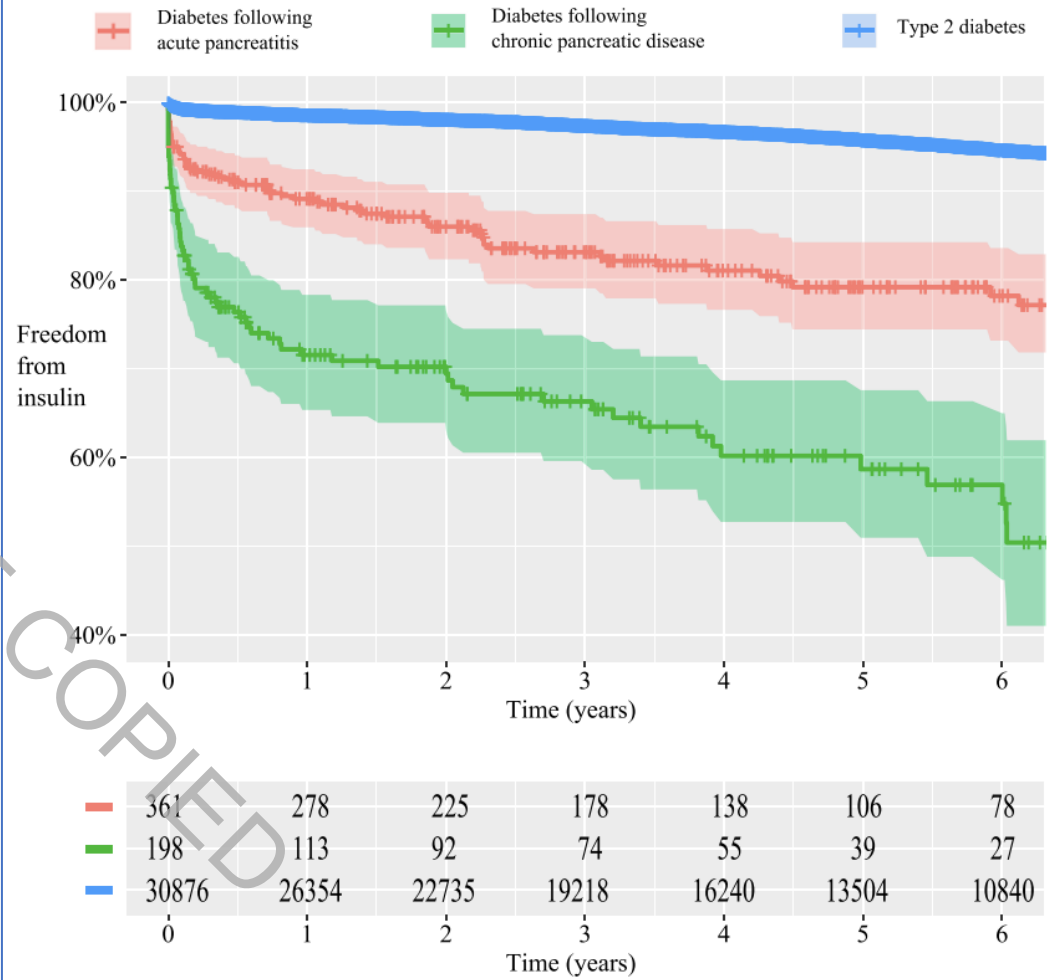
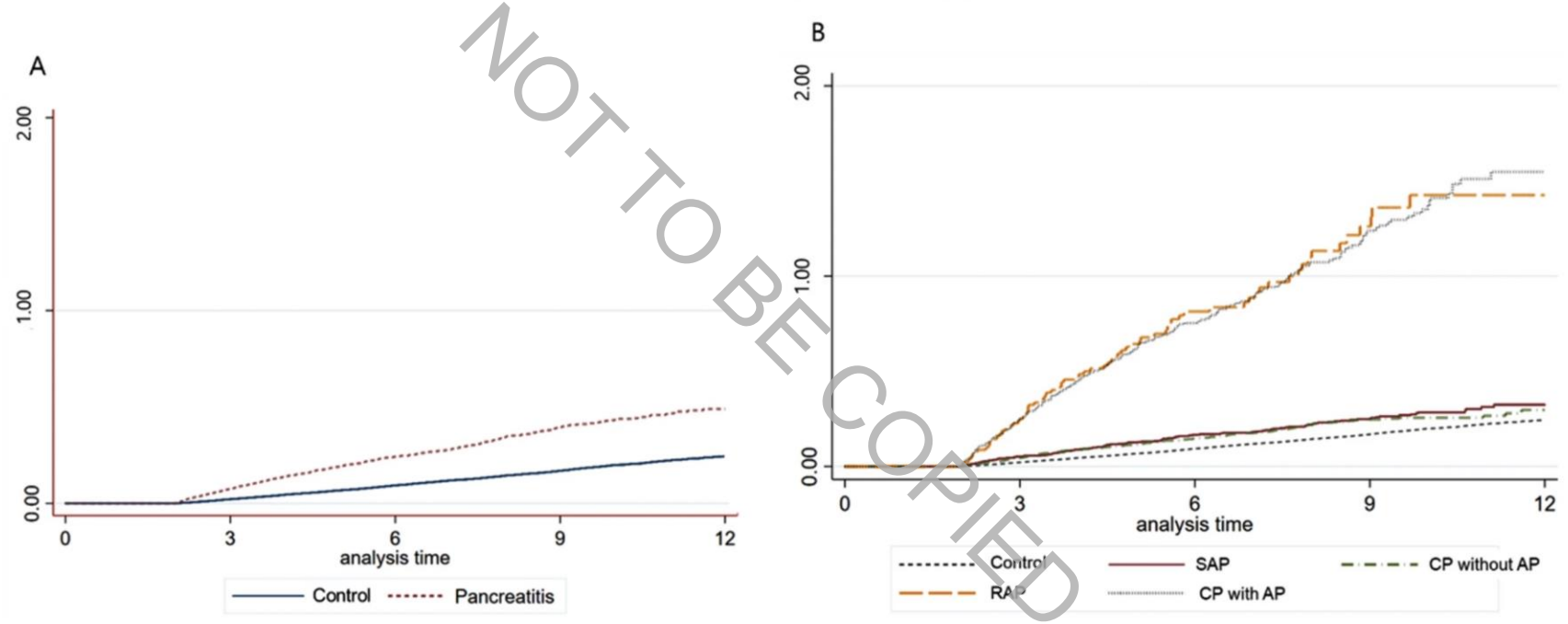


Figure 2—Kaplan-Meier curves of freedom from insulin use over time for type 2 diabetes, diabetes following acute pancreatitis, and diabetes following chronic pancreatic disease. The shaded areas represent the 95% CIs. Log-rank *P* for difference: $P < 0.001$. The table is the number of patients at risk over time.

Pancreatic cancer is a known complication of chronic pancreatitis and sometimes manifests with new onset diabetes.

From: Incidence and risk of pancreatic cancer in patients with acute or chronic pancreatitis: a population-based cohort study



Cumulative incidences of pancreatic cancer among patients with pancreatitis followed for more than 2 years and controls. (**A**) Comparison between pancreatitis and control groups. (**B**) Comparison among SAP, RAP, CP with AP, CP without AP and control groups. SAP, single episode of acute pancreatitis; RAP, recurrent acute pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis.

Park, S.M., Kim, K.B., Han, JH. *et al.* Incidence and risk of pancreatic cancer in patients with acute or chronic pancreatitis: a population-based cohort study. *Sci Rep* **13**, 18930 (2023). https://doi.org/10.1038/s41598-023-45382-y

Gastrointestinal tract (upper) cancers - recognition and referral

Last revised in February 2021

Print this page

- Pancreatic cancer — nearly 9000 new pancreatic cancers are diagnosed each year in the UK. A full time GP is likely to diagnose approximately one person with pancreatic cancer every 3–5 years. The 5 year survival is less than 5%. Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for pancreatic cancer if they are aged 40 years and over and have jaundice.
- Consider an urgent direct access CT scan (to be performed within 2 weeks), or an urgent ultrasound scan if CT is not available, to assess for pancreatic cancer in people aged 60 years and over with weight loss and any of the following: diarrhoea, back pain, abdominal pain, nausea, vomiting, constipation, or new-onset diabetes

Managing diabetes with chemotherapy

Why we need to manage hyperglycaemia

Hyperglycaemia may specifically reduce the efficacy of chemotherapy[1].

PWD are at greater risk of infections and hospitalization[2,3].

Chemotherapy induced neutropenia is greater in people with hyperglycaemia[4].

Increased rates of hospital mortality and sepsis have been seen in people with hyperglycaemia[5].

Equal treatment related complications has been demonstrated in people with good glycaemic control compared to people without diabetes[6]

1. Hershey DS. Importance of Glycemic Control in Cancer Patients with Diabetes: Treatment through End of Life. Asia Pac J Oncol Nurs. 2017;4(4):313-8.
2. Liu X, Ji J, Sundquist K, Sundquist J, Hemminki K. The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. Cancer. 2012;118(5):1353-61.
3. Park JH, Kim H-Y, Lee H, Yun EK. A retrospective analysis to identify the factors affecting infection in patients undergoing chemotherapy. European Journal of Oncology Nursing. 2015;19(6):597-603.
4. Chao C, Page JH, Yang SJ, Rodriguez R, Huynh J, Chia VM. History of chronic comorbidity and risk of chemotherapy-induced febrile neutropenia in cancer patients not receiving G-CSF prophylaxis. Annals of Oncology. 2014;25(9):1821-9.
5. Harris D, Barts A, Connors J, Dahl M, Elliott T, Kong J, et al. Glucocorticoid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: an observational cohort study. Curr Oncol. 2013;20(6):e532-e8.
6. Attili V, Bapsy P, Dadhich HK, Batra U, Lokanatha D, Babu KG. Impact of diabetes on cancer chemotherapy outcome: A retrospective analysis. International Journal of Diabetes in Developing Countries. 2007;27(4).

Effect of Hyperglycaemia on Quality of Life

Following a diagnosis of cancer, PWD often have a reduced adherence to their diabetes medications.

Symptoms of hyperglycaemia, in addition to cancer-specific and chemotherapy side effects, can be debilitating.

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.

This can lead to a potential increased risk for poor glycaemic control during this critical period 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.

1. Pettit S, Cresta E, Winkley K, Purssell E, Armes J. Glycaemic control in people with type 2 diabetes mellitus during and after cancer treatment: A systematic review and meta-analysis. PloS one. 2017;12(5):e0176941-e.
2. Hershey DS, Tipton J, Given B, Davis E. Perceived impact of cancer treatment on diabetes self management. Diabetes Educ. 2012;38(6):779-90.

Commencing Anti-Cancer Therapy in a person with pre-existing diabetes

1

Managing nausea and vomiting

- likely exacerbation of hyperglycaemia whilst on antiemetic therapy
- PWD receiving emetogenic chemotherapy should be offered NK1 antagonist (aprepitant) with a long acting 5HT3 (ondansetron)
- Consider use of GCs in the first cycle and reduce doses or withdraw based on emetic control and blood glucose management

2

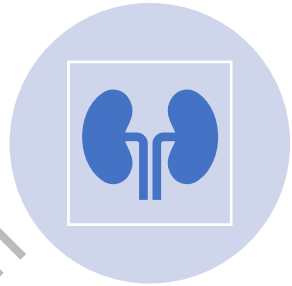
Managing a person with diabetes

- offer blood glucose monitoring or CGM
- undertake regular monitoring when commenced on SACT
- Monitor HbA1c 3 monthly whilst on SACT
- Rapid diabetes medication changes may be required when commencing high dose SACT or GCs

SACT - Systemic Anti Cancer Therapy GCs - Glucocorticoids

Use of glucocorticoids and effect of glucose levels

Steroids reduce the action of insulin by increasing insulin resistance and decreasing production and secretion of insulin



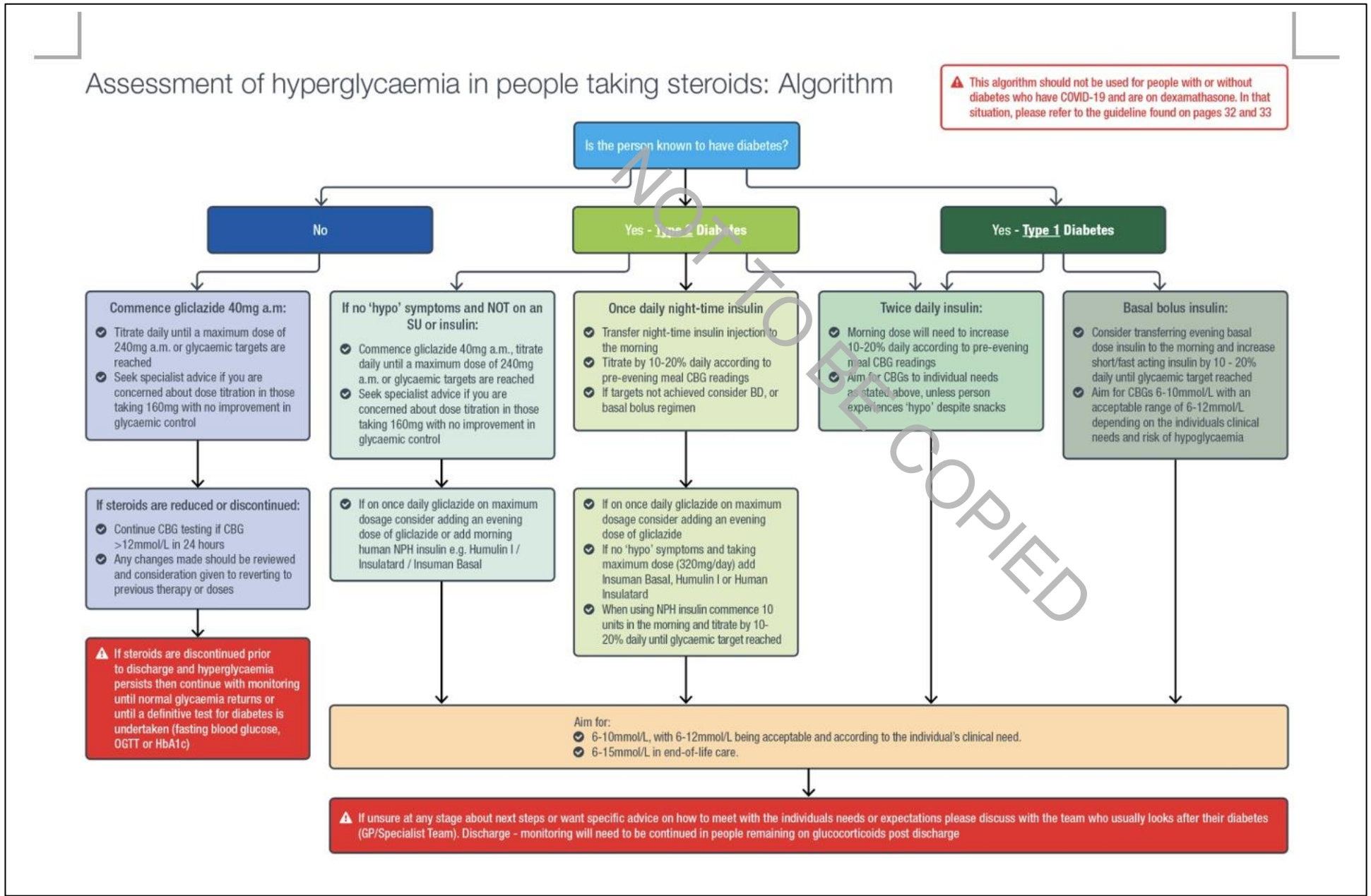
The effects of corticosteroid use on glucose concentration may vary depending on the type of corticosteroid

hyperglycaemia may develop a few hours after prednisolone is taken and may then wear off

more prolonged hyperglycaemia may occur with the use of dexamethasone, which has a longer half-life

https://doi.org/10.1016/j.clinthera.2023.11.013

JBDS 08 Management of Hyperglycaemia and Steroid (Glucocorticoid) Therapy



JBDS-IP Joint British Diabetes Societies for Inpatient care

Deprescribing and managing diabetes in end-of-life care

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.
- Sarcopenia and cancer cachexia lead to decreased physical activity, adverse psychological effects, poor performance status and higher mortality rates.
- consideration of nutritional support depending on clinical circumstances, prognosis and symptom profile
- Consideration of de-escalation of diabetes medications

Possible benefits of nutrition support for people expected to live longer than a month include the following:

- Improved quality of life.
- Less risk of death due to malnutrition.
- Fewer physical, mental, and psychologial problems

People with cancer and their families decide how much nutrition and fluids will be given at the end of life.

- Decreasing food and fluid intake is a natural part of the dying process.
- Most dying people do not experience hunger or thirst.
- Providing food or fluids by artificial means may, in fact, increase symptoms such as shortness of breath, mucous/fluid build-up in the throat or lungs, restlessness, nausea and vomiting

plan of care frequently needs to be reviewed as situation changes

- sometimes the person (or their loved ones) want to keep tight control of diabetes, its something they can control when the situation around them is falling apart….
- But this can change at any time and we need to be responsive to that change

end of life care

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.

Consider prognosis and individual risk for hypoglycaemia. Glycaemic levels should be targeted at between 6.0 mmol/L – 15 mmol/L

Tailoring medication at different stages of illness

Life expectancy > 3 months

- consider whether cardio-protective drugs, such as SGLT-2 inhibitors, ACE inhibitors, angiotensin-receptor blockers, aspirin and statins could be stopped.

Life expectancy < 2 months

- for those on combinations of diabetes medications, consider converting to insulin alone, OD or BD regime. If the patient is already on BD insulin, consider changing to OD Isophane insulin at 75% of the total previous BD dose.

Life expectancy weeks only

- relax blood glucose control targets but continue to assess for symptoms of hypo- and hyperglycaemia.

If the prognosis is days…

FOR TYPE 2 DIABETES

stop all oral hypoglycaemic agents and consider whether insulin should be continued

FOR TYPE 1 DIABETES

aim to continue long acting insulin. When continuing insulin, change to OD (morning) long acting insulin, giving dose 25% less than previous total daily insulin dose.

Check blood glucose at teatime, and if < 8 mmol/l, reduce insulin by 10-20%, but if >20mmol/l, increase insulin by 10-20% to reduce risk of ketosis.

For both Type 1 and Type 2 diabetes, once a patient is unconscious (not induced by hyper or hypoglycaemia), and prognosis <48hours, consider discontinuing insulin entirely

General rules for oral diabetes medications

Metformin

- usually inappropriate in patients with an advanced malignancy due to its effect on appetite, weight and gastrointestinal side effects. It should be discontinued if creatinine is >150mmol/l or eGFR <30

Sulphonylureas (e.g. gliclazide)

- should be reviewed in patients experiencing weight loss, anorexia or dysphagia. Sulphonylureas can also cause hypoglycaemia in patients with reduced liver function. Maybe useful if steroid treatment is required

General rules for oral diabetes medications

Pioglitazone

- rarely appropriate in terminally ill patients and should not be used in patients with bladder tumours or heart failure.

Gliptins, e.g. sitagliptin

- review in deteriorating renal function as doses may need to be reduced. Consider impact on appetite and discontinue as weight reduces.

GLP-1 analogues

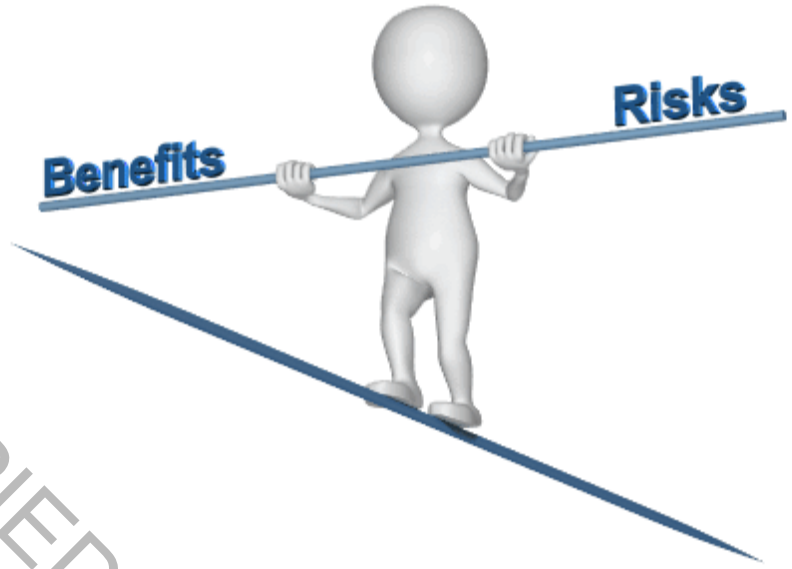
- rarely appropriate in terminally ill patients and not recommended for patients with significant weight loss and should be withdrawn if the patient develops abdominal pain, pancreatitis or any other GI related symptoms.

SGLT2 inhibitors

- Current advice is to withhold SGLT2 inhibitors before surgery, prolonged fasting, or critical medical illness as such they are rarely appropriate in the terminally ill.

Glucose monitoring

- generally looking to reduce as much as possible
- Consider use of CGM to reduce the invasive nature of CBGM
- aim for symptom relief as condition deteriorates, preventing hypoglycaemia and looking for symptoms of hyperglycaemia



Communication communication communication!

- planning and being aware of a persons wishes at the end of their life is massively important
- Achieving a good, comfortable death is important not only for the person but for their loved ones

Gold standard framework

everyone deserves gold standard care at the end life

summary

Diabetes can increase the risk of some cancers

The management of diabetes needs to change at each stage of prognosis

De-escalating diabetes management and end of life is cruicial to achieving a comfortable death