Belfast Health and Social Care Trust

Pancreatic CANCER UK

Diabetes and pancreatic cancer: medical management

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Agenda

01 Introduction: Pancreatic cancer and diabetes

02 Glycaemic management with illustrative clinical cases

03 Hypoglycemia management

04 Illness management

05 Management of pancreatic diabetes

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What percentage of adults with new onset diabetes will develop pancreatic cancer within 3 years ?

1. 1%
2. 3%
3. 5%
4. 7%
5. 10%

What is the optimal initial treatment for patients with pancreatic cancer and associated hyperglycaemia ?

1. Metformin

2. SGLT-2-dapagliflozin

3. Sulphonylurea-gliclazide

4. GLP-1-semaglutide

5. DPP-4 linagliptin

6. Insulin- basal bolus or biphasic regimen

Which clinical features could help distinguish between pancreatic cancer associated diabetes (type 3c) from other forms of diabetes (t1/t2dm) ?

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1. Age > 65

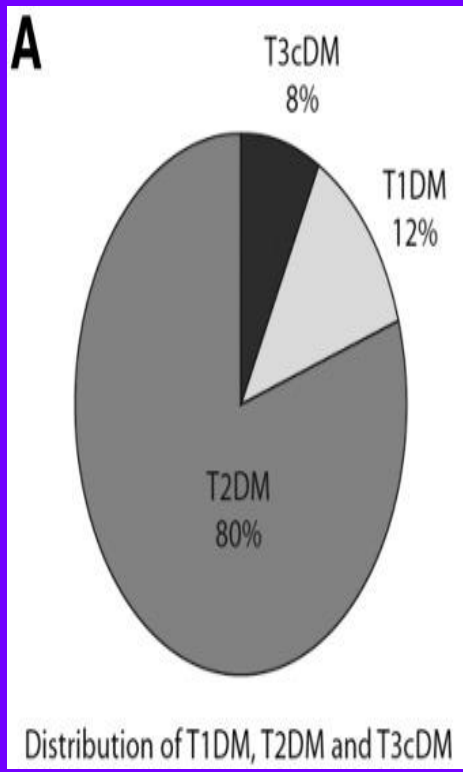
2. Weight loss > 2kg

3. BMI < 25

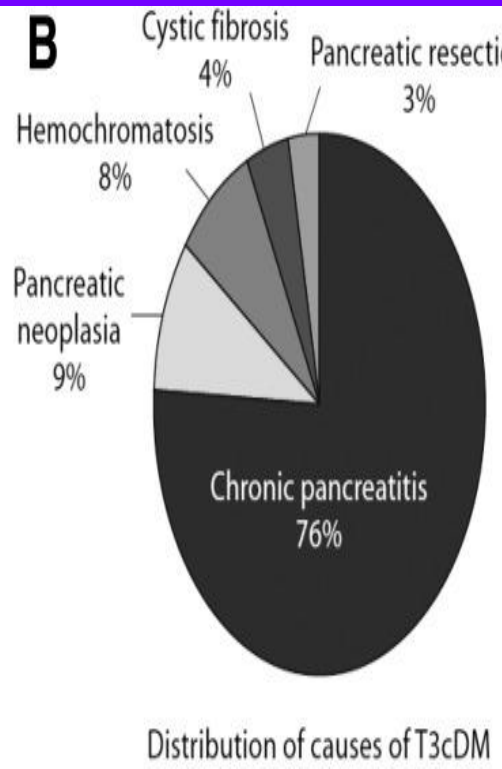
4. Alcohol/smoking history

5. All of the above

Type 3c diabetes mellitus



Distribution of T1DM, T2DM and T3cDM



Distribution of causes of T3cDM

TABLE 1: Proposed diagnostic criteria for type 3c diabetes mellitus.

Major criteria
(i) Presence of exocrine pancreatic insufficiency (faecal elastase)
(ii) Pathological pancreatic imaging (endoscopic ultrasound (EUS), MRI, and CT)
(iii) No type 1 diabetes mellitus-associated autoimmune markers
Minor criteria
(i) The absence of pancreatic polypeptide (PP) secretion
(ii) Impaired incretin secretion
(iii) No excessive insulin resistance (HOMA-IR)
(iv) Impaired beta cell function (HOMA-B, C-peptide/glucose-ratio)
(v) Low serum levels of lipid soluble vitamins (A, D, E, and K)

Ewald N, et al. Diabetes Metab Res Rev. 2012 28(4)338-342

Type 3c diabetes-considerations

- Neglected disease
- Often misdiagnosed as T1/T2DM-opportunities for tailored approach therefore missed
- Paucity of research
- Lack of management guidelines
- Small numbers
- Limited data on clinical outcomes
- Requires multi-disciplinary team

Duggan S, Johnston PC. Type 3c Diabetes and Nutritional Management. Clinical Nutrition. 2024:24;10-13

Diabetes and pancreatic cancer

- Long standing diabetes is a modest risk factor for pancreatic cancer-risk x 1.5-2 fold
- Other risk factors for pancreatic cancer include smoking, alcohol, family history, obesity and chronic pancreatitis
- Diabetes is a symptom of pancreatic cancer
- Diabetes and pancreatic cancer could both benefit from earlier detection
- 5 in 10 patients with pancreatic cancer have diabetes
- Pancreatic cancer and diabetes-chicken and egg

Diabetes and pancreatic cancer

- Around 80% of pancreatic cancer patients have glucose intolerance or overt diabetes

- Hypothesis: pancreatic cancer causes diabetes and that diabetes is a risk factor for the development of pancreatic cancer

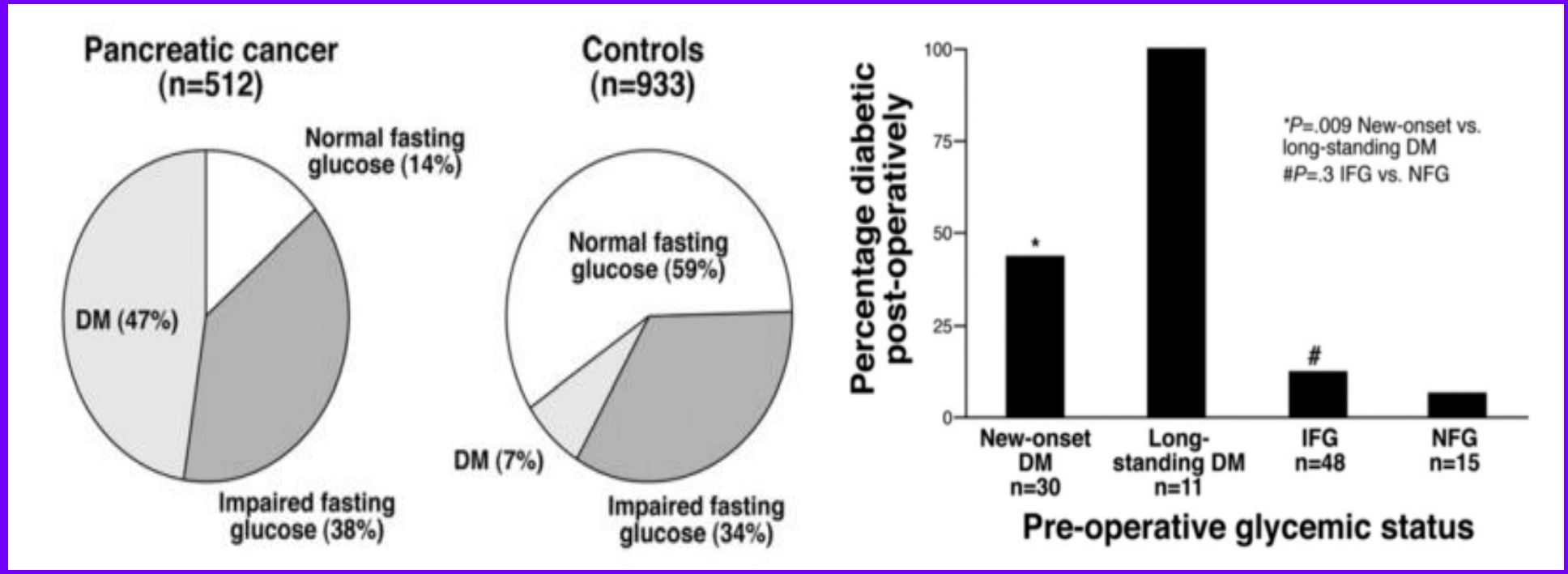
- In distinguishing pancreatic cancer-associated diabetes (type 3cDM) and T2DM, a lack of family history, age 65 years or older, recent weight loss of >2 kg, and a BMI < 25 kg/m2 suggest that type 3c is more likely

- Diabetes is associated with a 2.86-fold increase in the risk of pancreatic cancer, the risk increasing to 6.49-fold for those treated with insulin, compared to 2.12-fold for those treated with oral hypoglycaemic agents

- Metformin associated with reduced risk of pancreatic cancer

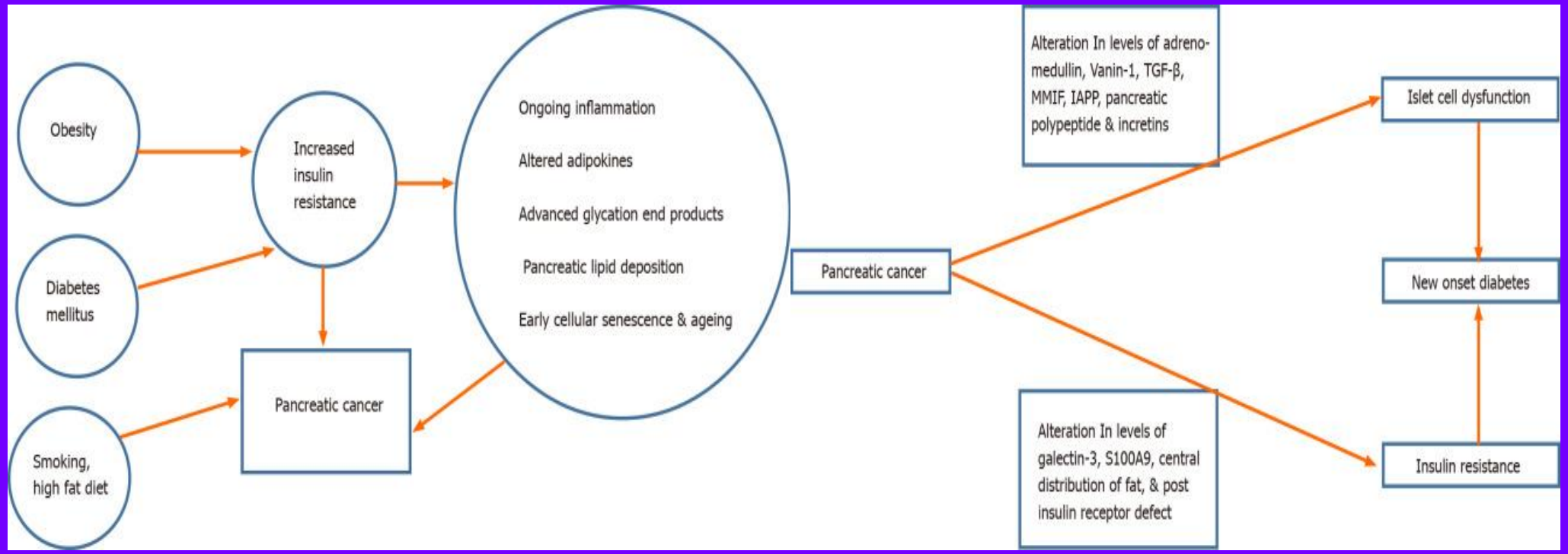
Bonelli L, et al.. Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: a case-control study in northern Italy. Pancreas. 2003;27(2):143-9

Prevalence of diabetes in PCAD



DK. Andersen, et al. Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer. *Diabetes* 2017; 66 (5): 1103–1110

Relationship between diabetes and pancreatic cancer



Roy A, et al. Diabetes and pancreatic cancer: Exploring the two-way traffic. World J Gastroenterol. 2021 Aug 14;27(30):4939-4962

Case 1

- EN
- Age 86, female
- Presented July 2015 with malaise, nausea and vomiting and weight loss
- New hyperglycaemia CBG 25 mmol/l, Hba1c 95
- LFT’s normal, ca-19-9 103
- Abdominal imaging:5 cm mass at head of pancreas, biopsy-pancreatic adenocarcinoma –treated palliative care
- Started metformin and creon
- RIP 3/12 later

Can we distinguish PCAD from T2DM ?

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Factors that can help in differentiating pancreatic cancer associated new onset diabetes from type 2 diabetes mellitus

Clinical indicators	Biochemical markers
Age > 65 yr	Carbohydrate antigen 19-9
Heavy smoker	Galectin 3
Low body mass index	S100A9
History of chronic pancreatitis or gall stone disease	Insulin like growth factor-1
Recent worsening of hyperglycemia in an elderly patient	Osteoprotegerin
Weight loss associated with diabetes onset	Pancreatic polypeptide
Loss of subcutaneous fat and muscle mass in imaging studies like dual energy X-ray absorptiometry or magnetic resonance imaging	Thrombospondins- 1
	Vanin 1
	Matrix metalloproteinase-9
	MicroRNAs

Hart PA, et al. Distinguishing diabetes secondary to pancreatic diseases from type 2 diabetes mellitus. Curr Opin Gastroenterol. 2021;1;37(5):520-525

UK-EDI-early detection initiative for pancreatic cancer

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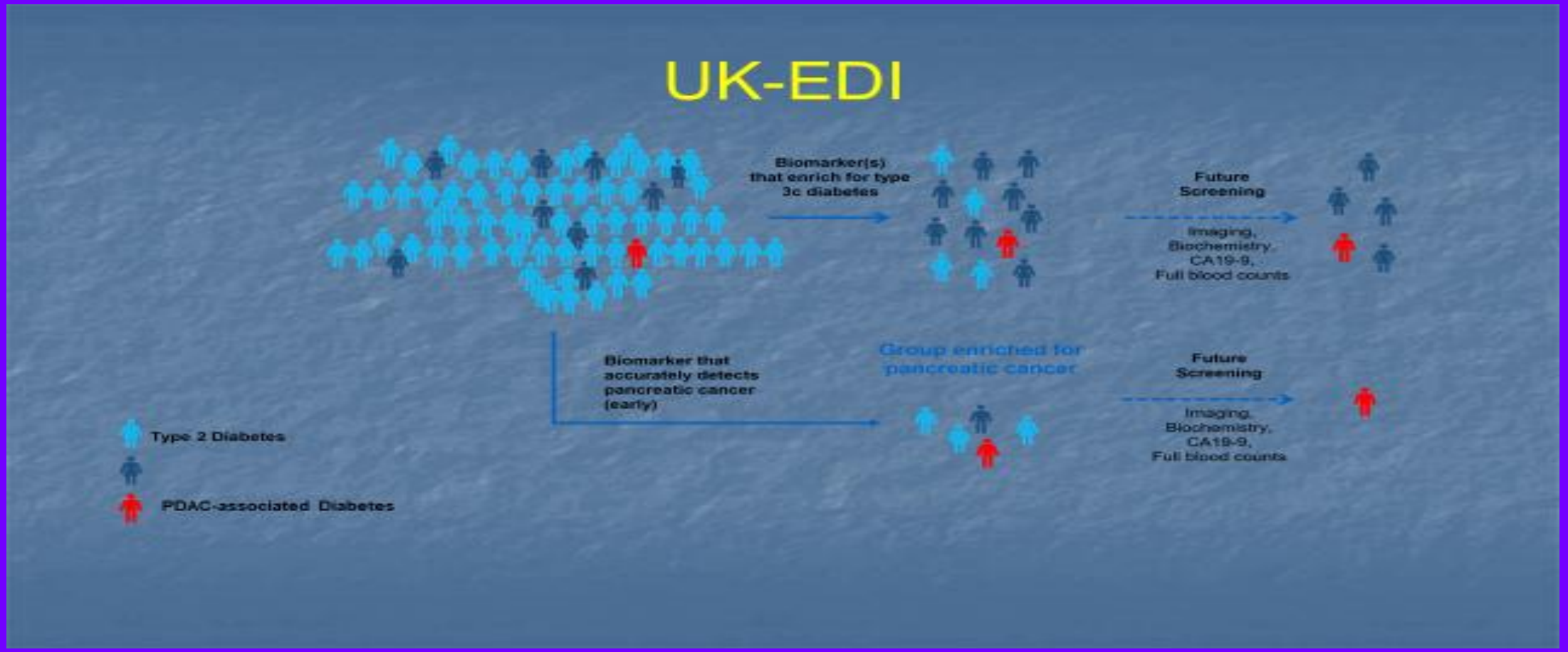

Case 2

- SK
- Age 62, female
- Presented with painless jaundice, 3 cm mass in pancreatic head-pancreatic carcinoma
- Attempted Whipples–unresectable as locally advanced
- Chemotherapy-4 months
- Hba1c 63 –pre-operatively, no history of diabetes
- Hba1c 63, 81 (+ 4 months), 94 (+ 8 months)-no steroids
- Continues to lose weight 8kg over 8 months, BMI 22.4
- GP commenced Gliclazide 40 mg bd
- Gliclazide to be uptitrated, Libre 2, next step insulin

Glucose lowering therapy in pancreatic cancer

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- Metformin
- Sulphonylureas-gliclazide
- Insulin-BB insulin or biphasic
- SGLT-2-dapagliflozin
- GLP-1-semaglutide
- DPP-V-linagliptin
- TZD’s

Anti-hyperglycaemic medication in pancreatic cancer patients

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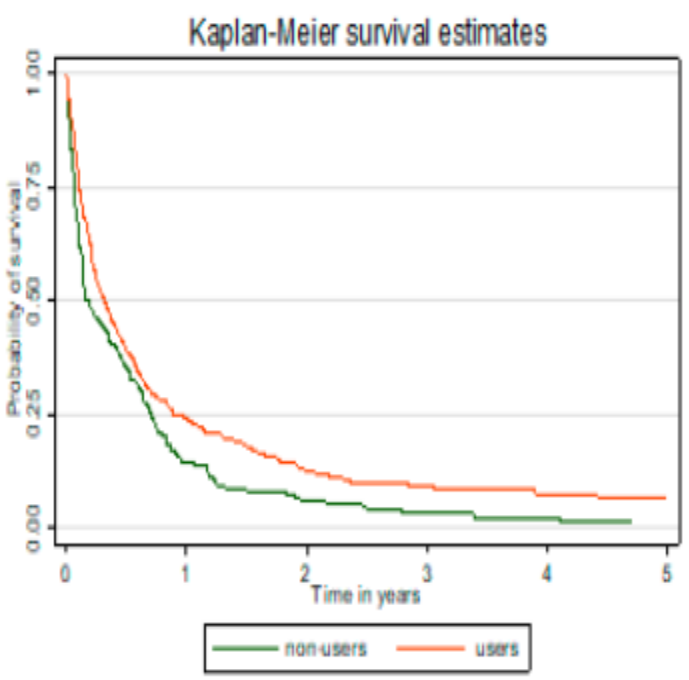

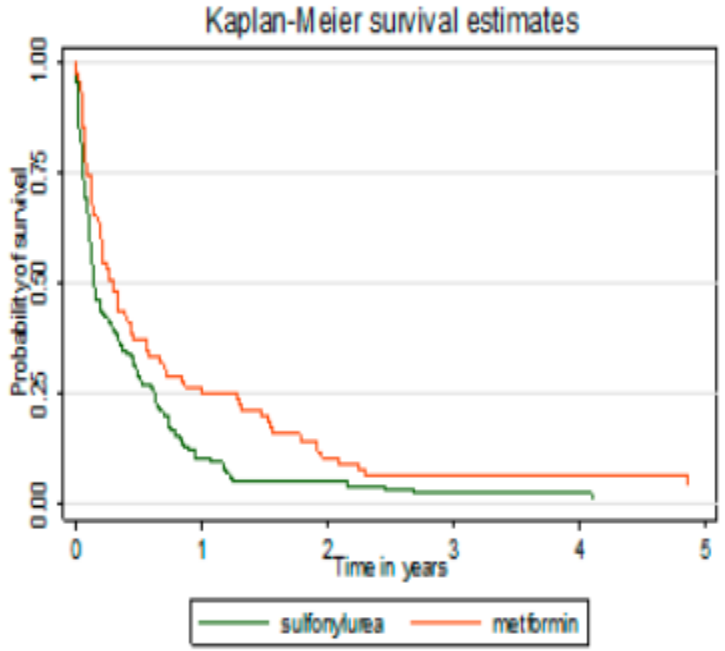

Antihyperglycemic medications		
Sulfonylurea	1.00	ref.
Metformin	0.80 (0.59–1.09)	0.15
Sulfonylurea and metformin	0.79 (0.61–1.02)	0.08
Metformin and other medications	0.94(0.68–2.29)	0.69
Insulin	1.31 (0.83–2.04)	0.24
Other medications	0.61 (0.36–1.03)	0.07

Dulskas A, et al. Cohort Study of Antihyperglycemic Medication and Pancreatic Cancer Patients Survival. Int J Environ Res Public Health. 2020 19;17(17):6016

Anti-diabetic medication and prognosis in pancreatic cancer

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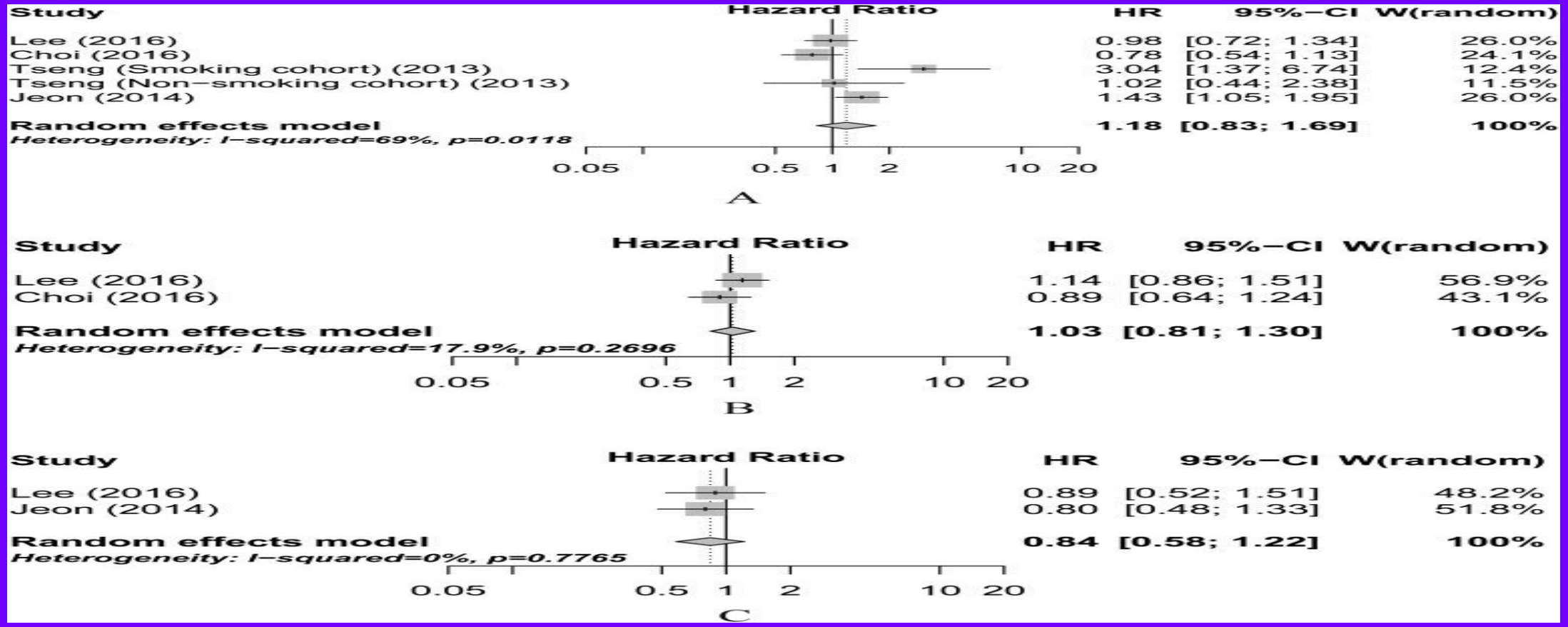


Zhou DC, et al. Prognostic significance of anti-diabetic medications in pancreatic cancer: A meta-analysis. Oncotarget. 2017 May 9;8(37):62349-62357

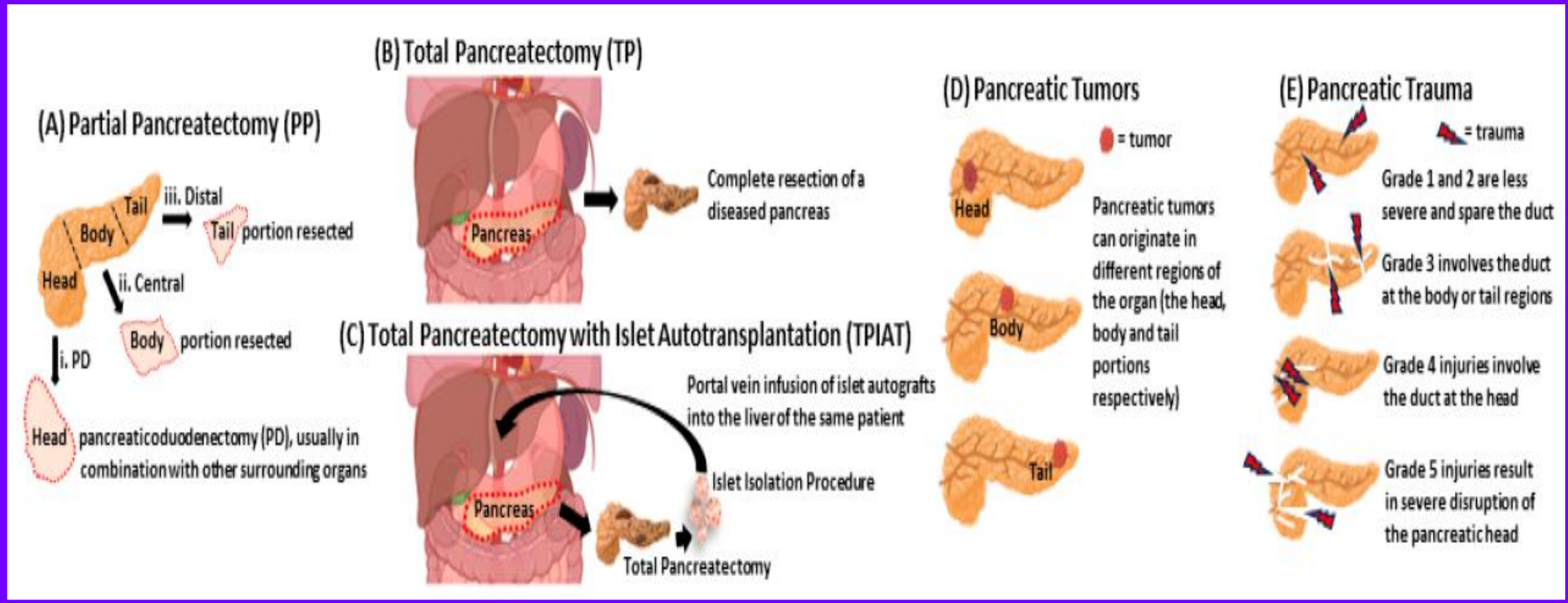
Case 3

- VM
- Age 59, female
- Presented with abnormal LFT’s and weight loss-8kg
- Diagnosed T2DM 1 year prior
- Abdominal US-fatty liver, 3.5 cm mass body of pancreas-pancreatic carcinoma
- Unresectable, continuing with chemotherapy and dexamethasone
- Metformin 1g bd, novomix ‘30’ 10 units bd, Libre 2, Hba1c 47

Glycaemic control-considerations

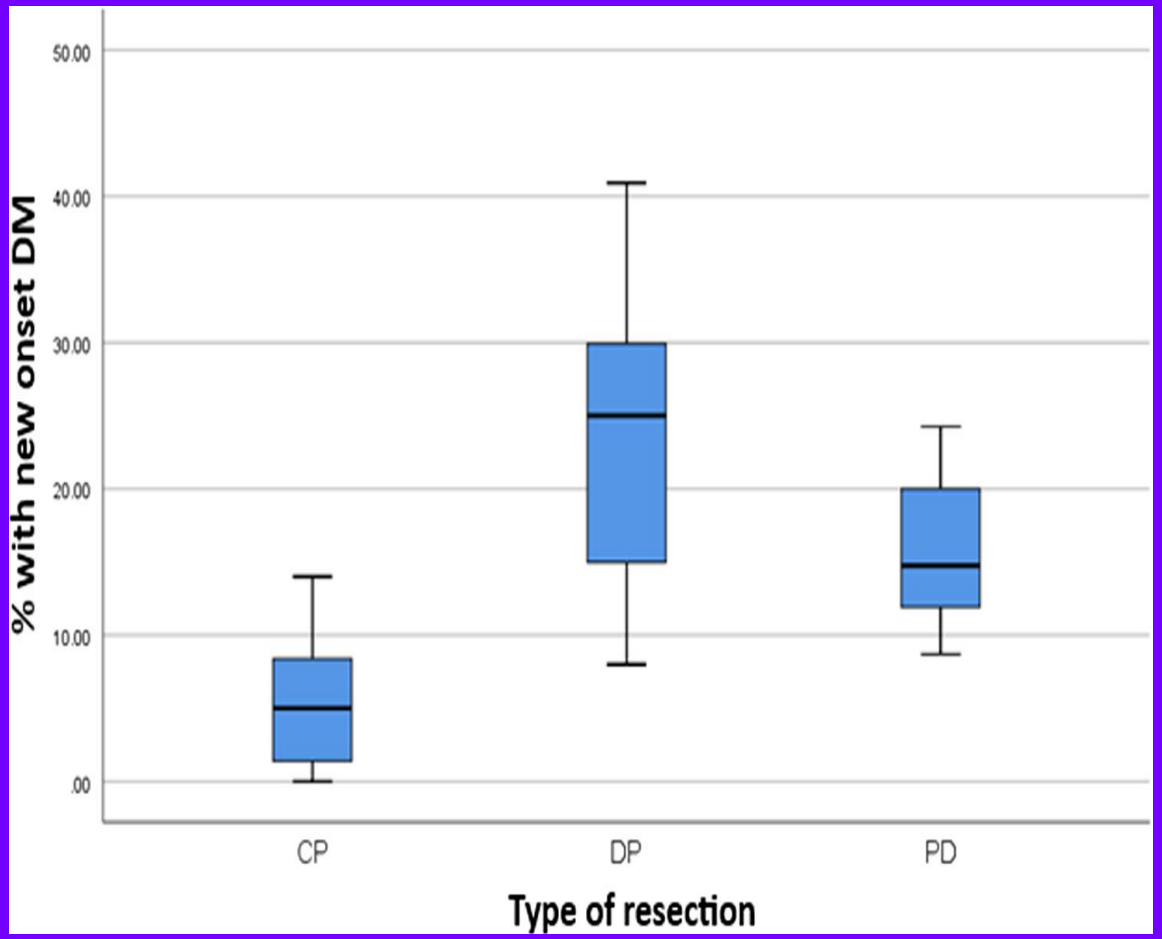
- Pancreatic resection and effect on glycaemic control
- Chemotherapy
- Nutrition-enteral/parenteral
- Variable oral intake
- Weight loss
- Pain
- What are the glycaemic targets in this population ?
- Are we trying to prevent diabetic complications-short and long term?
- Concurrent use of steroids during treatment
- Tailoring anti-diabetic medication to each individual patient
- Stage of disease process
- Use of technology

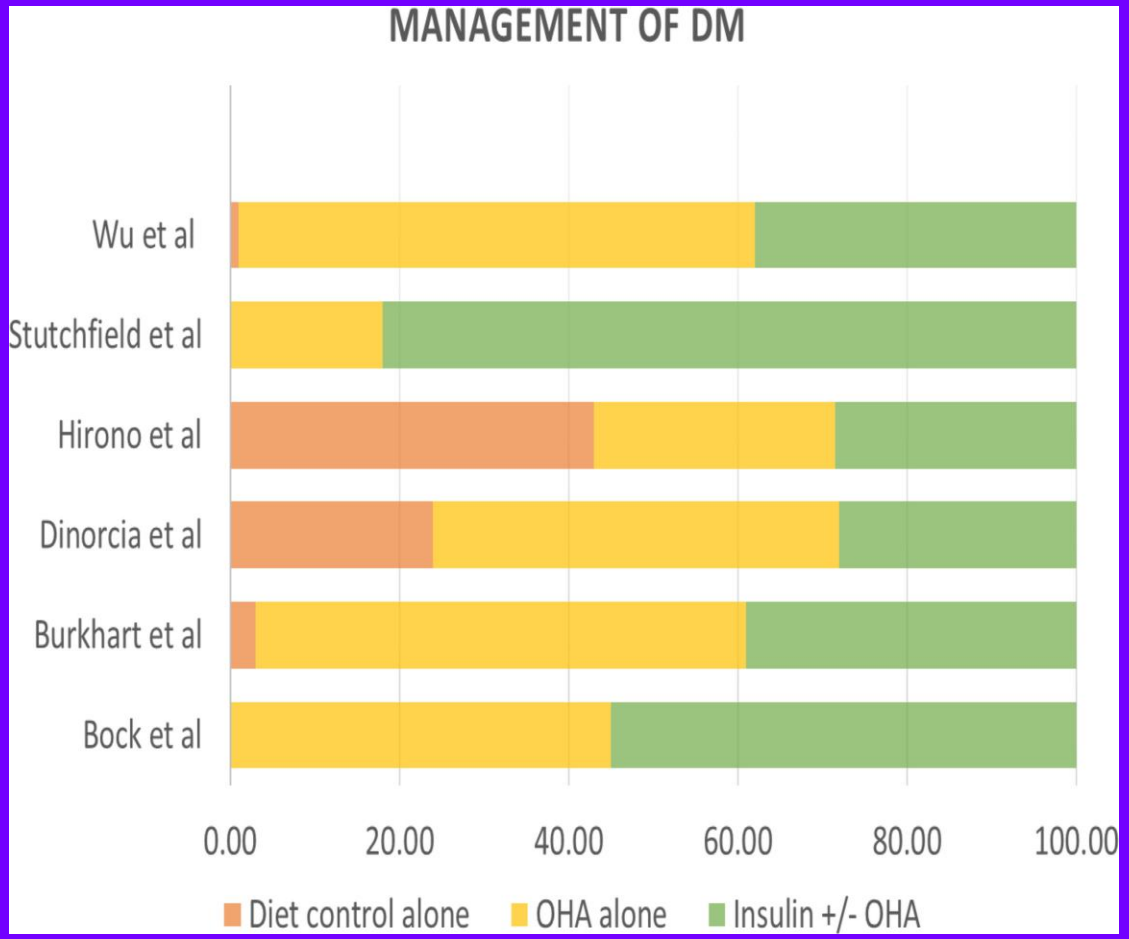
Pancreatic resection and diabetes



Wayne CD, et al. Challenges of managing Type3c Diabetes in the context of pancreatic resection, cancer and trauma. J.Clin Med. 2024:13,2993

Diabetes after pancreatic resection





Wu L, et al. Risk factors for development of diabetes mellitus (type3c) after partial pancreatectomy: A systemic review. Clinical Endocrinology. 2020;92;396-406.

Hypoglycaemia management-mild

- **Clinical context-inpatient, outpatient at home/work**
- **Degree of hypoglycaemia < 4 mmol/l, < 2 mmol/l**
- **Self treatment of hypoglycaemia < 4 mmol/l**

If you have diabetes and get symptoms of low blood sugar (a hypo) or your blood sugar is below 4mmol/L:

Eat or drink something that will raise your blood sugar quickly, such as a small glass of fruit juice or sugary fizzy drink, 5 glucose or dextrose tablets, 4 large jelly babies, or 2 tubes of glucose gel.

Check your blood sugar after 10 to 15 minutes.

If your blood sugar is still below 4mmol/L, have another sugary drink or snack, and check again after 10 minutes.

Once your symptoms have improved and your blood sugar is above 4mmol/L, eat something that will keep your blood sugar up for long

Hypoglycaemia management-severe

- If someone has very low blood sugar (a severe hypo) and becomes unconscious:
- Do not give them any food or drink as they will not be able to swallow safely
- Put them into the recovery position
- Give them a glucagon injection straight away, if one is available and you know how to use it
- If they start to recover within 10 minutes of having a glucagon injection and can swallow safely, give them some food or drink that will raise their blood sugar
- Stay with them until they're fully recovered

Hypoglycaemia management- inpatient

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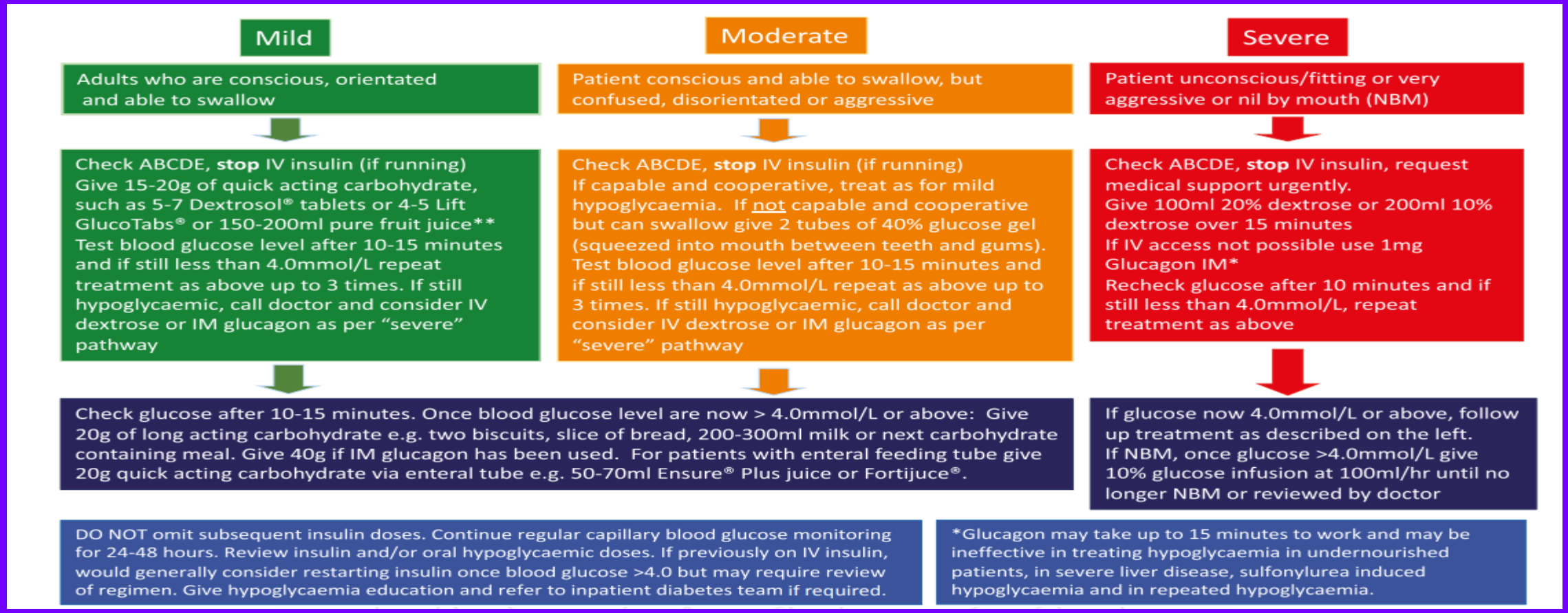

ABCD JBDS IP. The hospital management of hypoglycaemia in adults with diabetes mellitus. January 2023

Illness management

- No clear guidelines for this diabetic cohort
- Sick day rules
- Medication
- Education
- Ketometer
- Adjusting diabetic medications
- Managing insulin doses
- Frequent glucose monitoring
- Seeking medical help

Management of pancreatic diabetes

- Acute-DKA, HHS treated in same way as T1DM
- Aim CBG 6-12 mmol/l, unless EOLC
- Metformin/gliclazide/insulin
- Nutritional support
- Avoid hypoglycaemia
- PERT
- Dietician input
- Use of technology-Libre2 –CGM

ABCD JBDS 17. Management of glycaemic control in people with cancer January 2023

Management of pancreatic diabetes

Principles of Management	Management strategies
Prevent: • Hypoglycemia • Hyperglycemia • Exacerbation of malnutrition • Malabsorption • Co-morbidities associated with diabetes (e.g. retinopathy, renal disease)	• Regular meal pattern with regular, controlled amounts of starchy carbohydrates • Do not skip meals; take small, frequent meals • Measure glucose levels frequently, particularly if on insulin, after physical activity, if diet is poor, and if hypoglycaemic symptoms; CGM recommended for optimal glycaemic control • Educate re hypoglycaemia awareness • Avoid alcohol; smoking cessation • Ensure adequacy of PERT • Minimise high-sugar/ high-glycaemic index food and fluids • Consider a diary to record diet, glucose levels, PERT, exercise, at least until acceptable glucose control is maintained • An individualised medical nutrition therapy programme by a specialist RD should be implemented • Patients should engage with self-management, education, and treatment planning • Specialist MDT management including endocrinology is warranted

Summary

- Challenging, multi-disciplinary approach
- Management can be difficult due to pain, variable nutritional intake, weight loss
- Glycaemic targets are different in this population
- Glycaemic control can be very variable during the course of the disease
- Take into context, previous pancreatic surgery, current oncology treatments/regimens and stage of disease process