PCDOS 2026

masterclass

NG28 guidelines 2026

Frailty

Diabetes is associated with an accelerated ageing process that promotes frailty

- **Diabetes complications**, particularly **renal impairment** and **dementia increase risk of frailty**
- Physical frailty increases with age
  - **aged >65 years reaches up to 7%**
  - **aged >80 years up to 40%**
- Frailty is associated with a **poor survival** in a dose-response manner

Sinclair AJ and Gallagher A. Managing frailty and associated comorbidities in older adults with diabetes: Position Statement on behalf of the Association of British Clinical Diabetologists (ABCD). 2020. Available from: https://abcd.care/sites/abcd.care/files/site_uploads/Resources/Position-Papers/ABCD-Position-Paper-Frailty.pdf [Accessed Oct 2024]

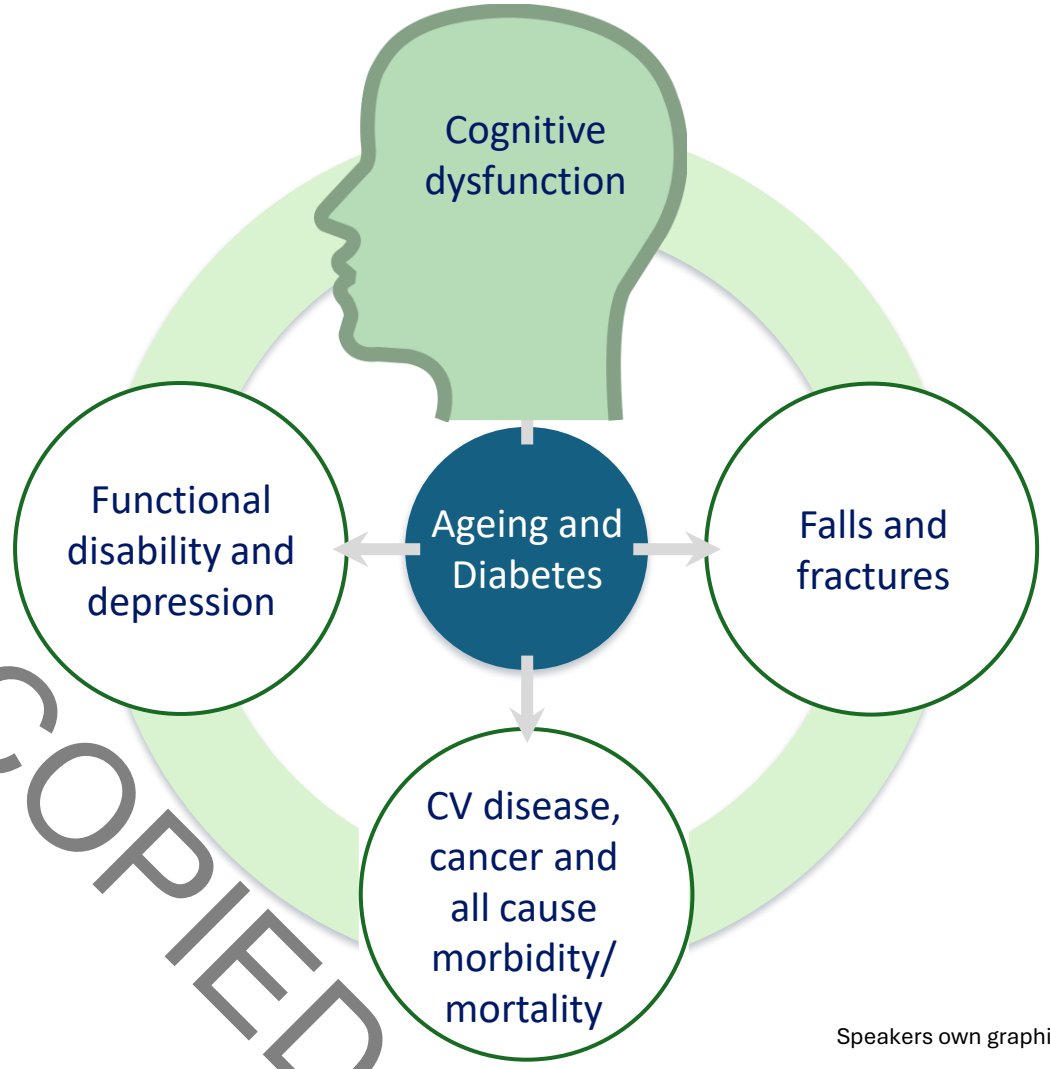
The frail elderly patient with diabetes

Older persons with diabetes are at higher risk than those without diabetes of:

- Usual complications of diabetes…[1-8]

But Also

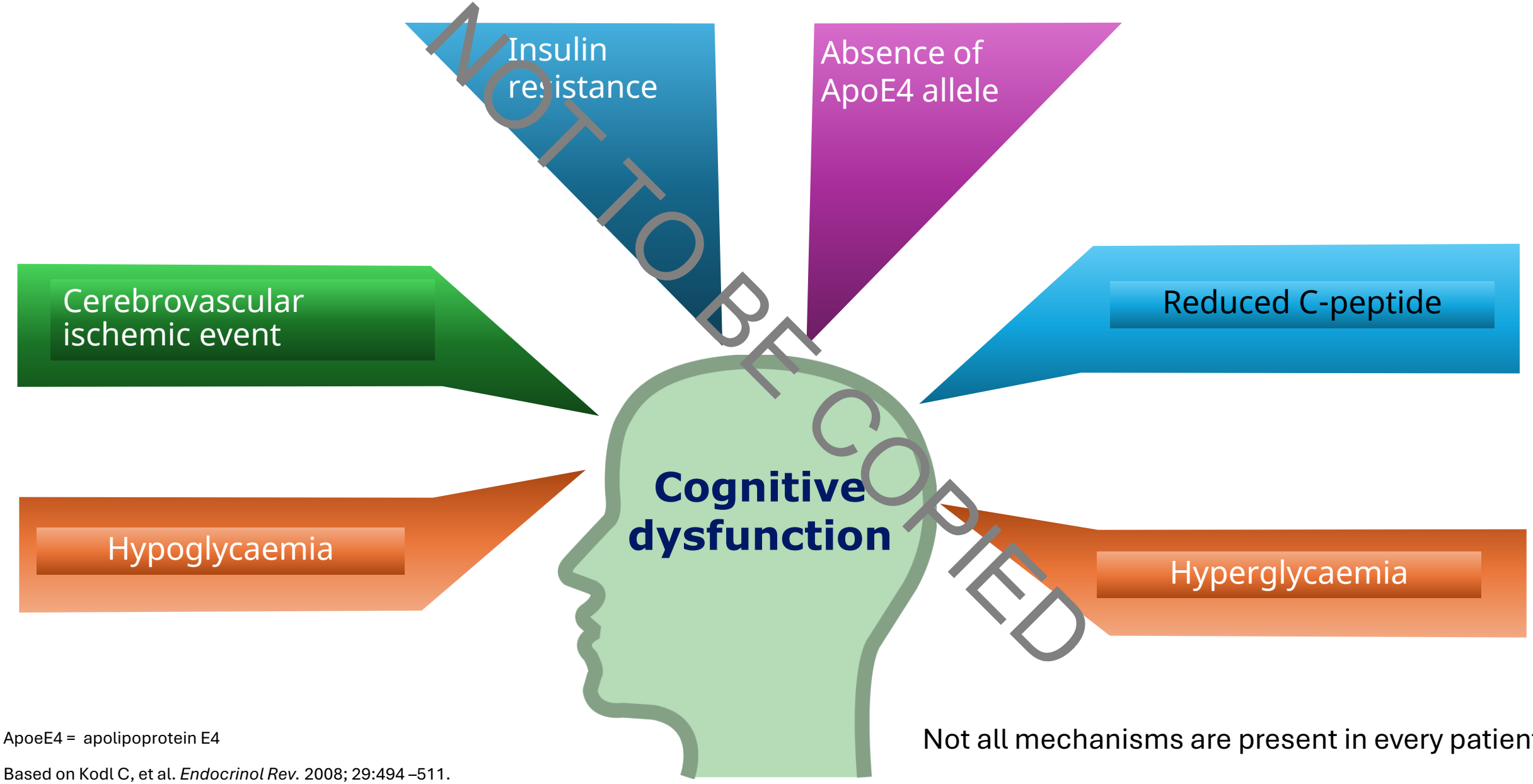
- Functional disability[7,9,10]
- Depression[2,7,8]
- Geriatric syndromes: cognitive impairment[2,6-8]



Speakers own graphic

1. Sinclair AJ et al. *The Journal of Frailty and Aging* 2018;7(1):10–20; 2. The Emerging Risk Factors Collaboration *New Eng J Med* 2011;364:829–41; 3. Bauduceau B et al. *Diabetes Care* 2018;41(1):156–62; 4. Kilvert A, Fox C. *Practical Diabetes* 2017;34(6):195–99; 5. Selvin E et al. *Diabetes Care* 2006;29:2415–9; 6. Sinclair A et al. *Lancet Diabetes Endocrinol* 2015 Apr;3(4):275–85. 7. *American Diabetes Association* Older Adults: Standards of Medical Care in Diabetes—2024. *Diabetes Care* 2024 Jan; 47(Supplement 1): S244-S257. 8. Cukierman T, et al. *Diabetologia*. 2005;48(12):2460-9; 9. Strain et al. *Diabet Med*. 2018;35:838–845. 10. Li Y et al. *Diabetes Care* 2012;35:273–7.

Pathophysiology – diabetes and dementia



ApoeE4 = apolipoprotein E4

Based on Kodl C, et al. *Endocrinol Rev.* 2008; 29:494 –511.

Not all mechanisms are present in every patient

Reliability of HbA1c in the Elderly

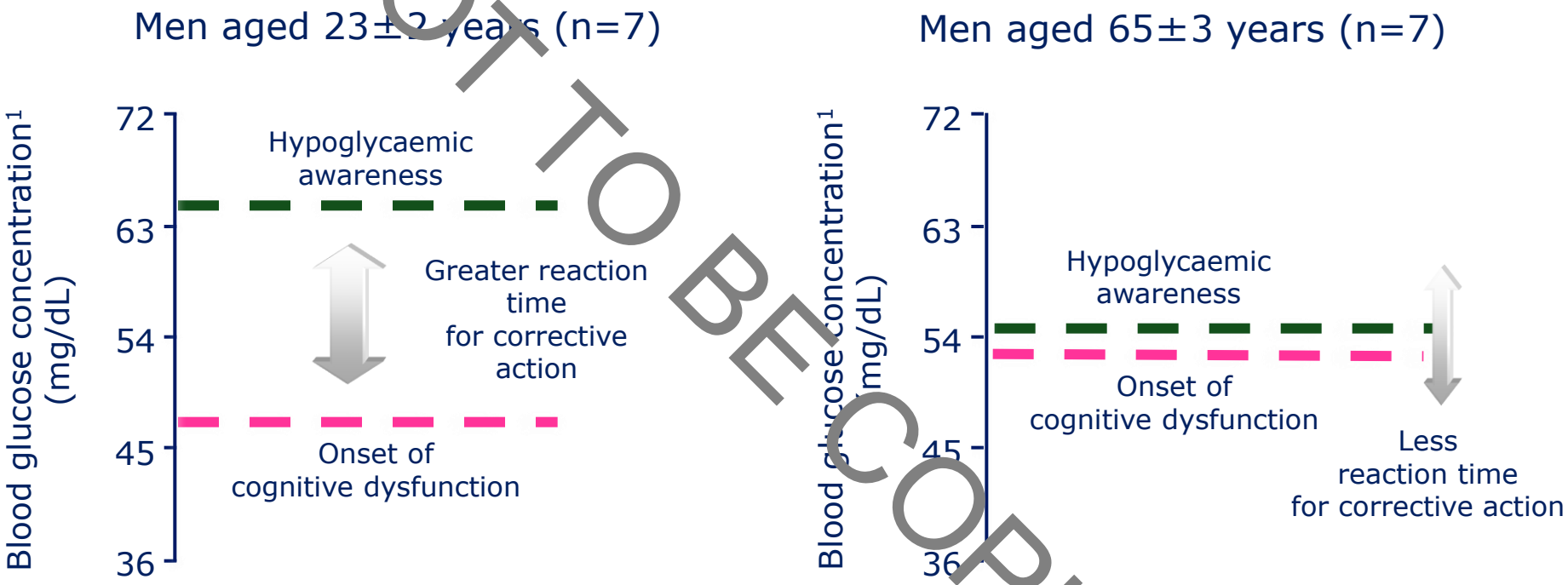
HbA1c tend to be higher in the elderly for several reasons :-

Increased Red cell survival

- Longer exposure of haemoglobin to glucose

Greater affinity of haemoglobin to glucose in the elderly

Thresholds for hypoglycaemia symptoms vary with age[1,2,*]

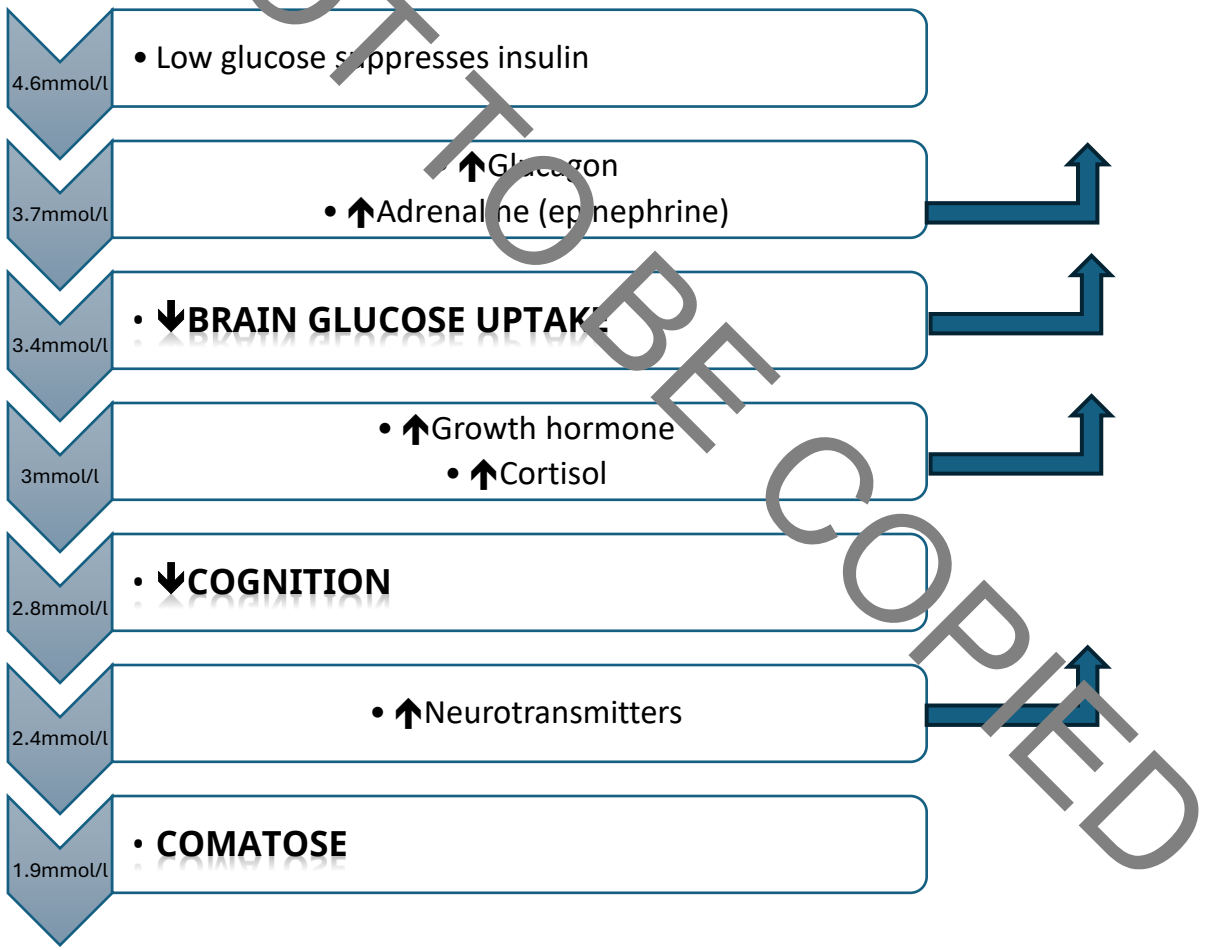


With increasing age, potential reaction time between awareness and onset of symptoms is decreased, contributing to an increased risk for asymptomatic hypoglycaemia and greater susceptibility to cognitive impairment[1,2,*]

*Based on data in patients without diabetes with no family history of diabetes.

1. Zammitt NN, Frier BM. *Diabetes Care* 2005;28:2948–61;
2. Matyka K *et al. Diabetes Care* 1997;20:135–41

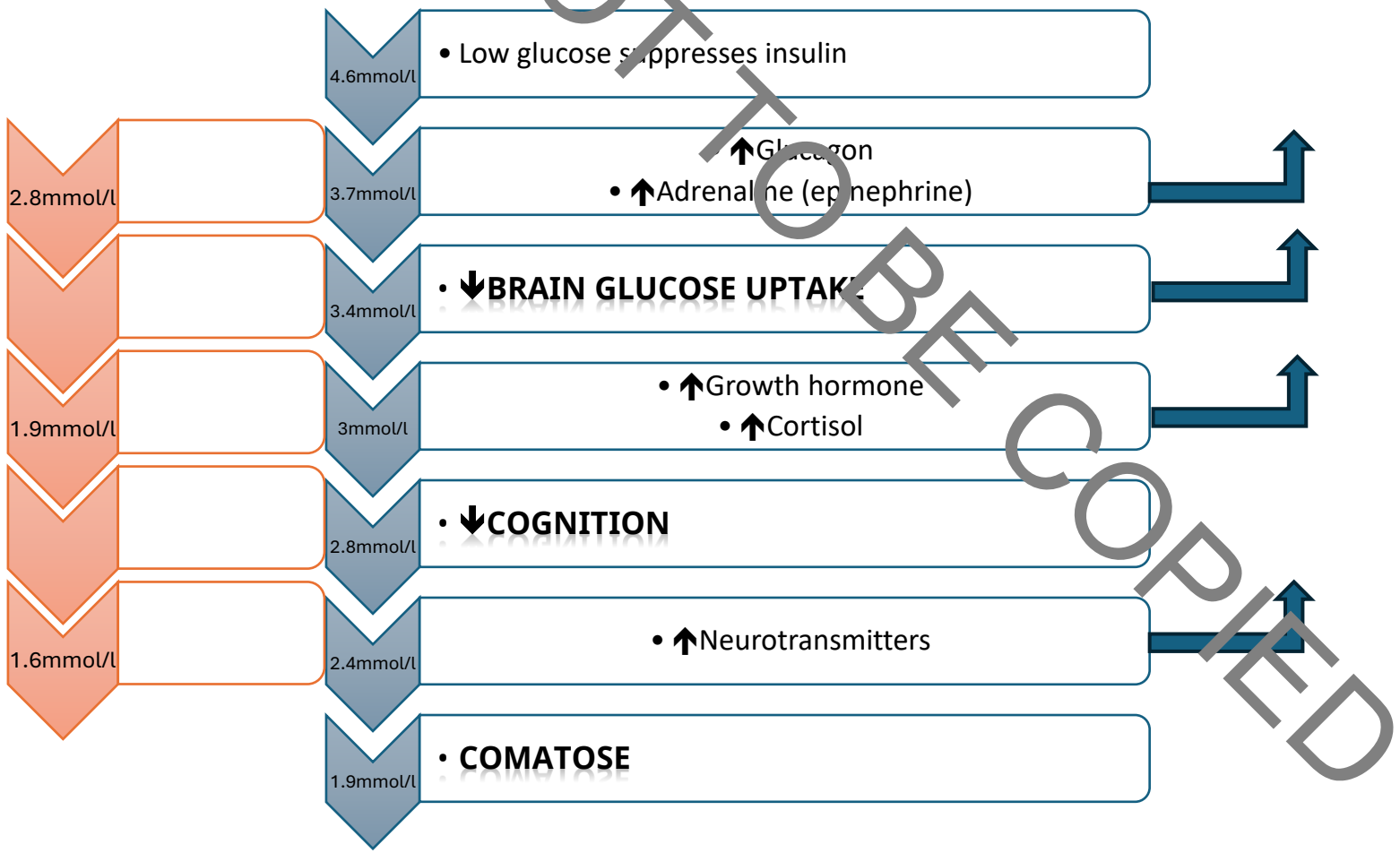
Physiology of Hypoglycaemia



- Sweating*
- Light-headedness*
- Trembling/shaking*
- Hunger*
- Anxiety*
- Fast heart rate
- Lip tingling
- Irritability
- Pallor

- Weak legs*
- Drowsiness*
- Poor concentration*
- Blurred vision*
- Headache*
- Confusion
- Poor coordination
- Slurred speech
- Glazed eyes
- Aggressive behaviour
- Seizures
- Loss of consciousness

Physiology of Hypoglycaemia



- Weak legs*
- Drowsiness*
- Poor concentration*
- Blurred vision*
- Headache*
- Confusion
- Poor coordination
- Slurred speech
- Glazed eyes
- Aggressive behaviour
- Seizures
- Loss of consciousness

Symptoms of hypoglycaemia are non-specific in older people

Autonomic:[1]

Palpitations

Sweating

Anxiety

Neuroglycopenic:[1]

Fatigue

Irritability

Confusion

Dizziness

Drowsiness

Coma

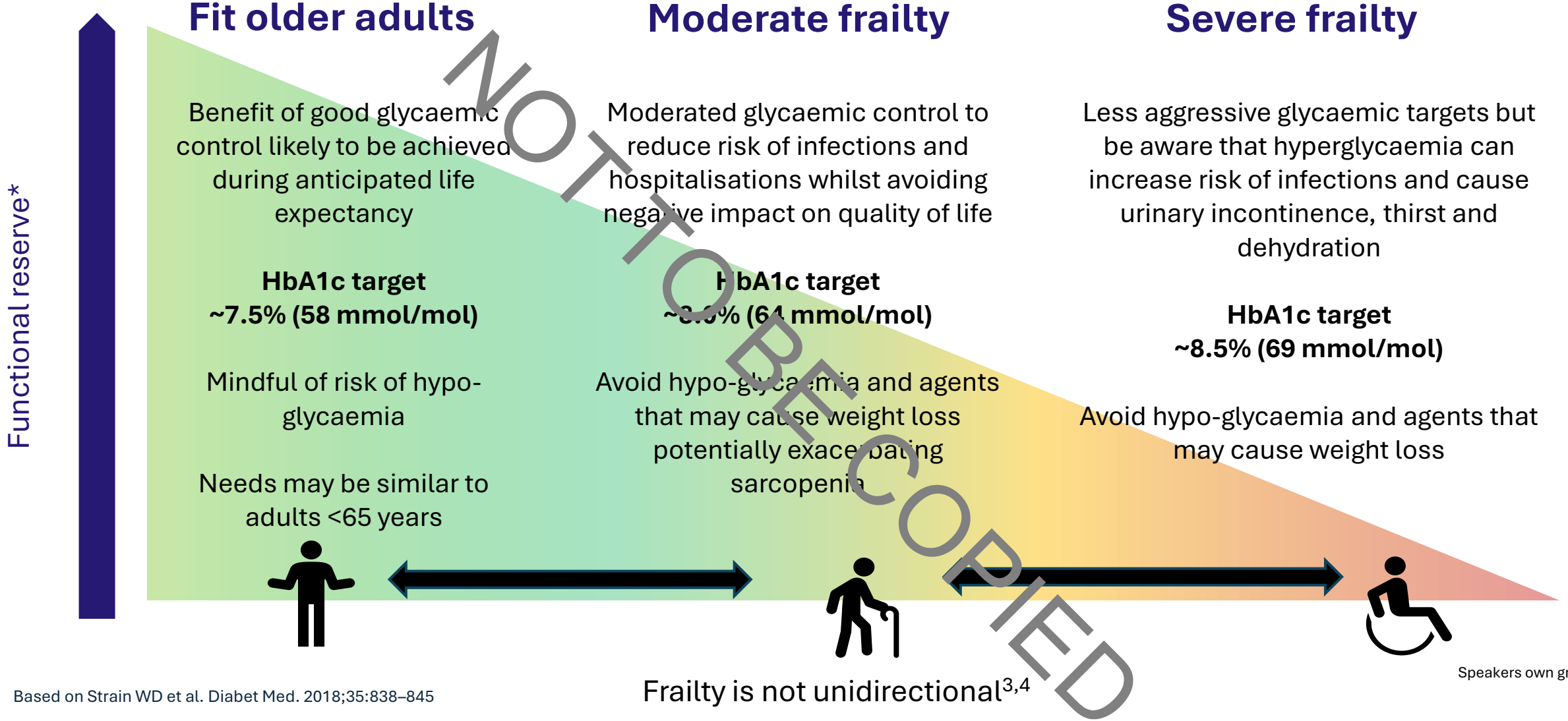
Particularly in older people (≥ 70 years):[2]

Unsteadiness

Light-headedness

All these are also common in older people without diabetes

1. Deary IJ et al. *Diabetologia*. 1993;36:771–77; 2. Jaap AJ et al. *Diabet Med*. 1998;15:398–401.



Based on Strain WD et al. Diabet Med. 2018;35:838–845

Frailty is not unidirectional[3,4]

Speakers own graphic

*Functional reserve is defined as the difference between the maximum physical or mental capacity of a construct and the minimum necessary to perform daily functioning.[5]

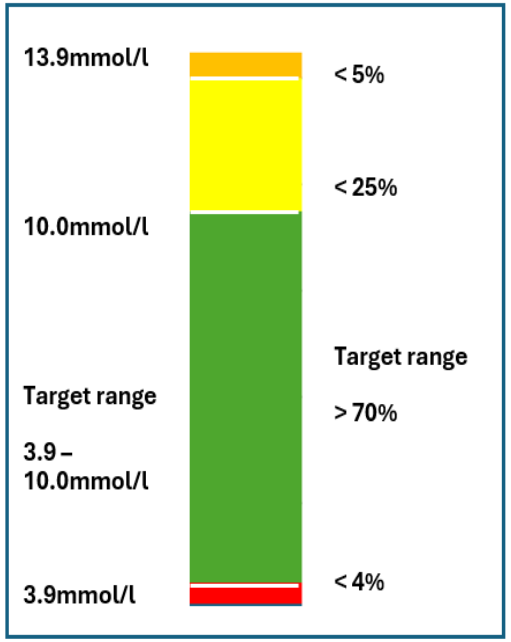
1. Strain WD et al. Diabet Med. 2018;35:838–845;
2. Strain WD et al. Diabetes Therapy 2021;12:1227–1247;
3. De Lepeleire J et al. Br J Gen Pract 2009;59:e177–82;
4. Merchant RA et al. J Nutr Health Aging 2021;25:405–409;
5. González PM et al. Rev Bras Geriatr Gerontol 2016;19:577–89

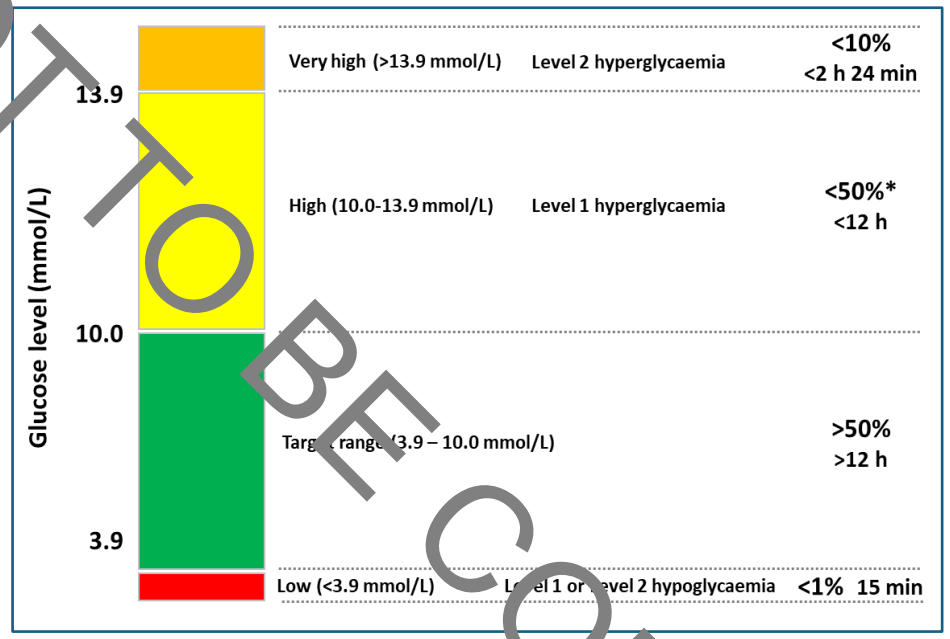
Establishing targets for older adults - 2019

Patient Type	Target HbA1c (mmol/mol)	De-escalation threshold (mmol/mol)	Suggested interventions
Fit older adult with diabetes	58	53	• Evaluate long-acting sulphonylurea and insulin therapy that may cause hypoglycaemia • Consider appropriate dosage in setting of renal function
Moderate-to-severe frailty	64	58	• Discontinue any sulphonylurea if HbA_{1c} below threshold • Avoid TZDs due to risk of heart failure • Cautious use of insulin and metformin, mindful of renal function
severe frailty	70	64	• Withdraw sulphonylureas and short-acting insulins due to hypoglycaemia risk • Review suitability of NPH insulin with regards to risk of hypoglycaemia • Therapies that promote weight loss may exacerbate sarcopenia

Based on Strain et al - Strain WD et al. Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty. A national collaborative stakeholder initiative. Diabetic Medicine 2018; 35 (7): 838–845

Targets for older people with type 1 or type 2 diabetes and those at high-risk from hypoglycaemia





* Readings >13.9 mmol/L are also included in the <50% target

THINK ABOUT INDIVIDUAL TARGETS

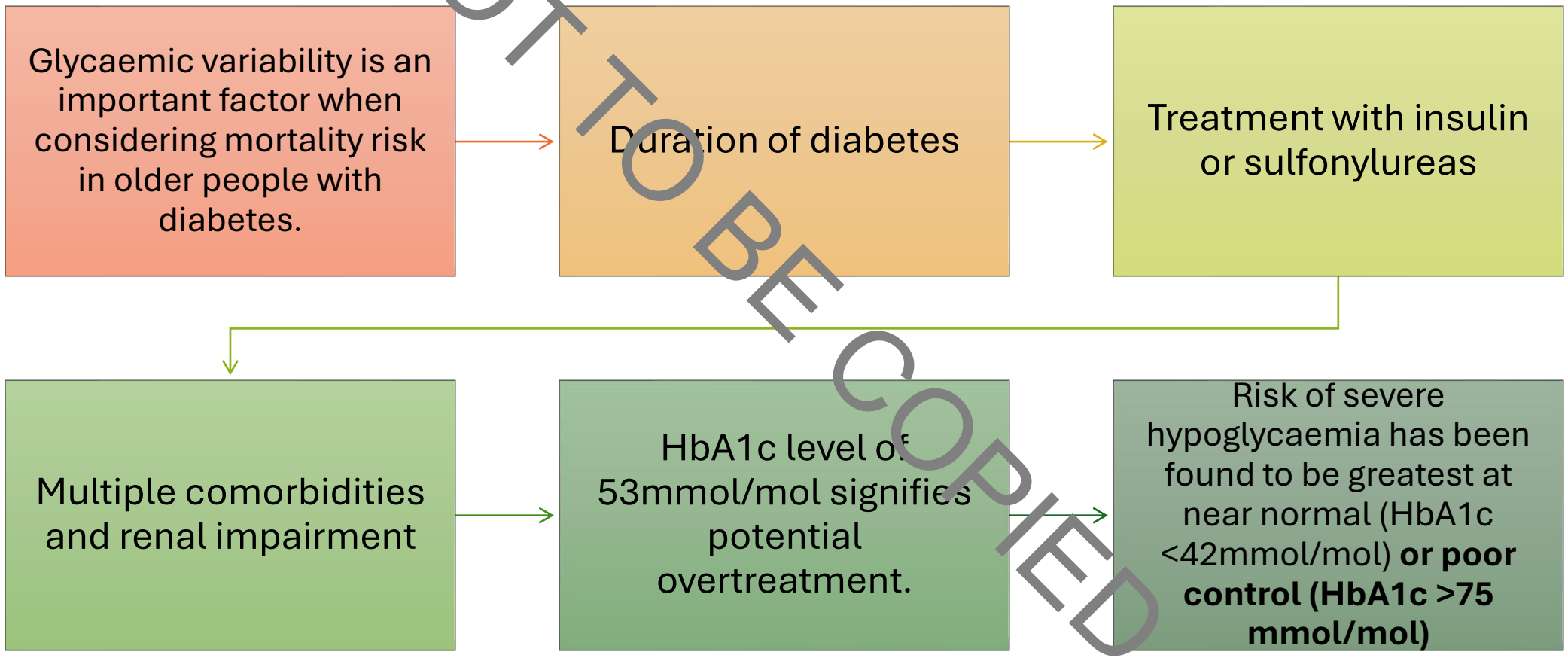
Emphasise the need to **prioritise hypoglycaemia avoidance, reducing the %TBR <3.9 mmol/L**

Recommendation is to keep %TBR <3.9mmol/L to **<1% or 15 min per day**

1. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. (2019);42(8):1593-1603.

Avoiding and Managing Hypoglycaemia

Risk factors:



Forbes A et al. Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diab Endocrinol 2018;6:476–86.

Can medications for diabetes help in the management of dementia ?

Insulin sensitizers targeting insulin resistance in the brain could potentially be beneficial in the prevention of Alzheimer's disease or dementia [1].

Metformin

- use is associated with a lower risk of dementia [2],

Sulfonylureas [3]

- hypoglycemia may increase risk [4] ,

Pioglitazone

- use in patients with type 2 diabetes mellitus is associated with a significantly lower risk of dementia
- may regulate the transcription of genes related to Alzheimer's disease and may potentially affect the risk of dementia [5].
- may alleviate insulin resistance, reduce Aβ synthesis, inhibit neuroinflammation and improve energy utilization and lipid metabolism in the brain [1].

1. De la Monte, S.M.; Tong, M.; Wands, J.R. The 20-year voyage aboard the Journal of Alzheimer's Disease: Docking at 'type 3 diabetes', environmental/exposure factors, pathogenic mechanisms, and potential treatments. *J. Alzheimers Dis.* **2018**, *62*, 1381–1390
2.Tseng, C.H. Metformin and the risk of dementia in type 2 diabetes patients. *Aging Dis.* **2017**,
3.Orkaby, A.R.; Cho, K.; Cormack, J.; Gagnon, D.R.; Driver, J.A. Metformin vs. sulfonylurea use and risk of dementia in US veterans aged ≥65 years with diabetes. *Neurology* **2017**, *89*, 1877–1885.
4.Duarte, J.M. Metabolic alterations associated to brain dysfunction in diabetes. *Aging Dis.* **2015**, *6*, 304–321.
5.Barrera, J.; Subramanian, S.; Chiba-Falek, O. Probing the role of PPARγ in the regulation of late-onset Alzheimer's disease-associated genes. *PLoS ONE* **2018**, *13*, e0196943

GLP1-RA and the brain

GLP-1 mimetic drugs have been shown to have neuroprotective, neurotrophic, and anti-inflammatory effects, that can play a role in slowing AD progression (1).

- A study demonstrated that liraglutide, a GLP-1RA, can alleviate spatial memory dysfunction and neuroinflammation that leads to cognitive impairment (2)

Adult neurogenesis is linked to memory function (3).

- In the AD brain, a decrease in neurogenesis is commonly observed and aggravates the disease pathology (4).

Studies found that GLP-1 receptor agonists increase the proliferation of neural progenitor cells and increase neurogenesis in the dentate gyrus of the hippocampus .

1. Holscher, C. Central effects of GLP-1: New opportunities for treatments of neurodegenerative diseases. J. Endocrinol. 2014, 221, T31–T41
2. McClean, P.L.; Holscher, C. Liraglutide can reverse memory impairment, synaptic loss and reduce plaque load in aged APP/PS1 mice, a model of Alzheimer's disease. Neuropharmacology 2014, 76, 57–67
3. Bruel-Jungerman, E.; Davis, S.; Rampon, C.; Laroche, S. Long-term potentiation enhances neurogenesis in the adult dentate gyrus. J. Neurosci. 2006, 26, 5888–5893
4. Hamilton,A.;Patterson,S.;Porter,D.;Gault,V.A.;Holscher,C.NovelGLP-1mimeticsdevelopedtotreattype 2 diabetes promote progenitor cell proliferation in the brain. J. Neurosci. Res. 2011, 89, 481–489

GLP-1 RA and Dementia

Positive effect with GLP-1RA have been demonstrated in neurodegenerative disease.

This is likely from a combination of factors :-

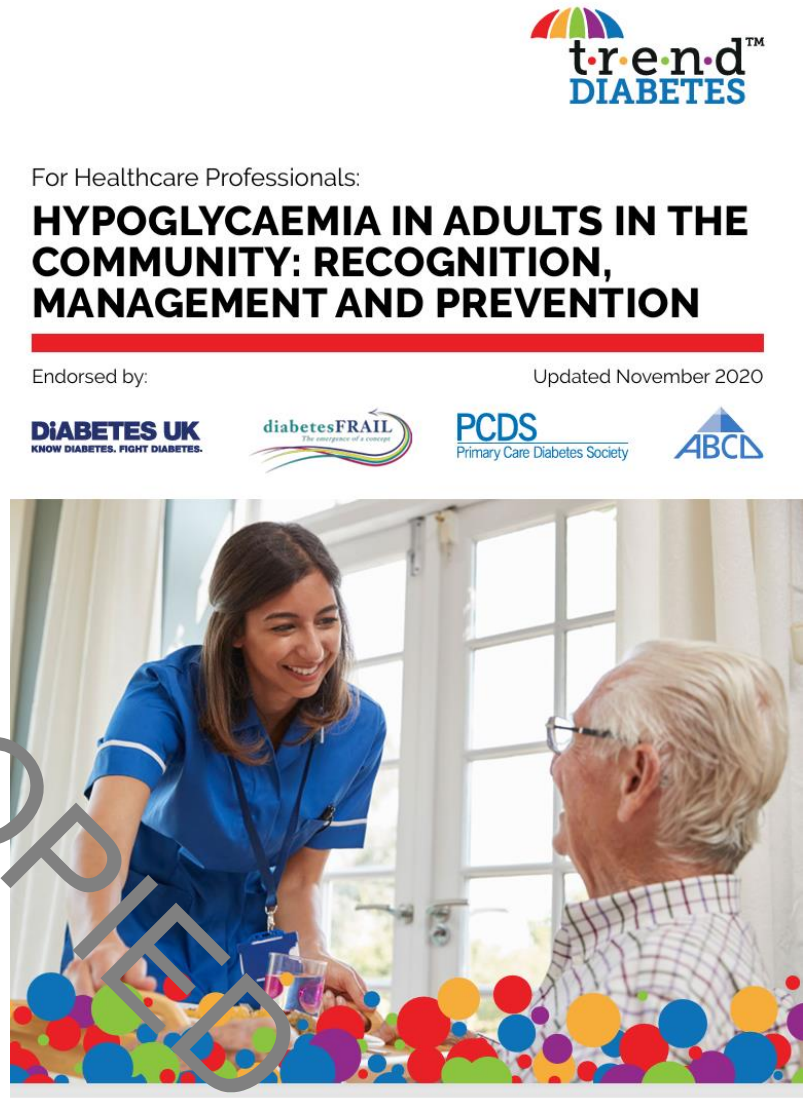
- Reduced insulin level
- Improved insulin signalling
- Increased neuroprotection
- Increased neurogenesis/proliferation and differentiation
- Decreased neuroinflammation (1)

A 6 month trail of Liraglutide demonstrated prevention in the decline in glucose metabolism by the brain but no significant cognitive improvement.

1. Feminella CD et al. Antidiabetic drugs in Alzheimer's disease mechanism of action and future perspectives J Diabetes Res. 2017: 7420796
2. Geji M et al. 6 month treatment with GLP1 analogue prevents decline of brain glucose metabolism , Aging Neuroscience. 2016 , 8:108

How to recognise and treat Hypoglycaemia

- Available at: www.trend-uk.org
- Simple useful advice and information on hypoglycaemia and its management



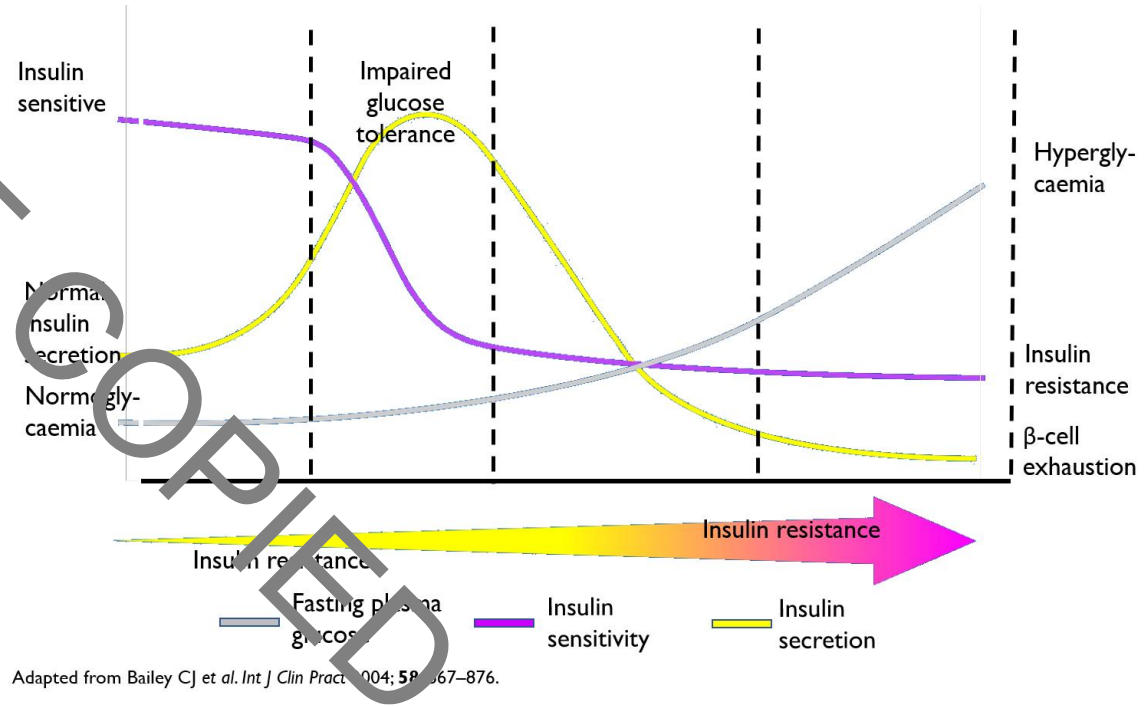
Life changes

Natural history of Type 2 diabetes: a progressive disease

Weight gain is often the cause of insulin resistance.

As weight increases , there is a fall in insulin sensitivity by the cells and a need for increased insulin production.

Type 2 diabetes develops at the time when beta cells start to become exhausted – leading to a rise in blood glucose levels.



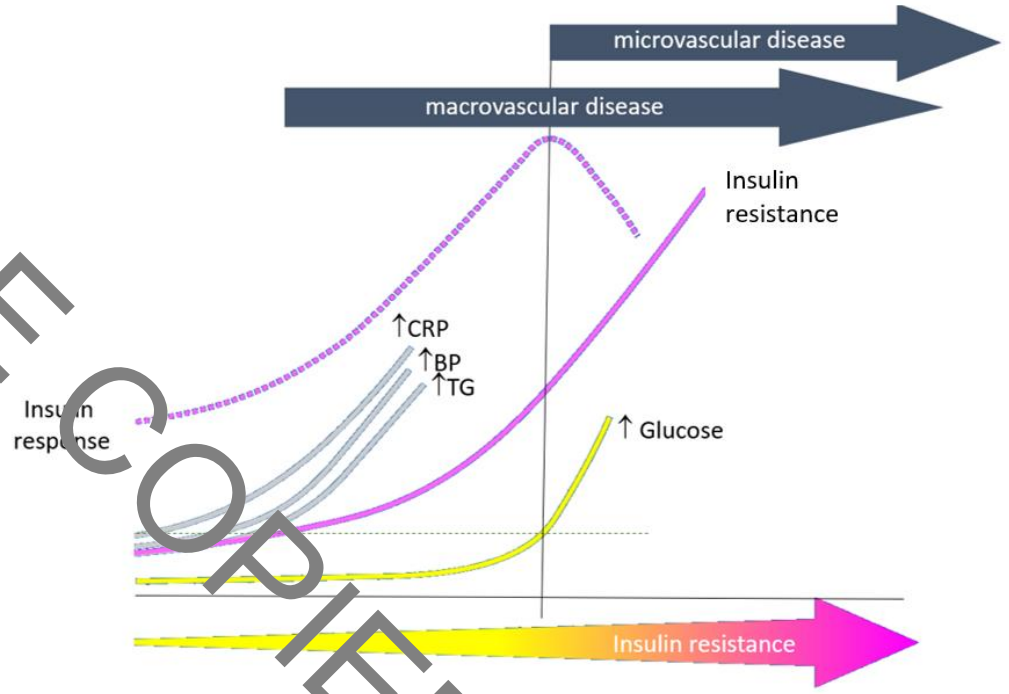
Adapted from Bailey CJ *et al. Int J Clin Pract* 2004; 58:867–876.

Development of Type 2 diabetes

At the time the blood glucose level rises and remains elevated , small vessel disease happens (leading to eye , kidney and nerve damage)

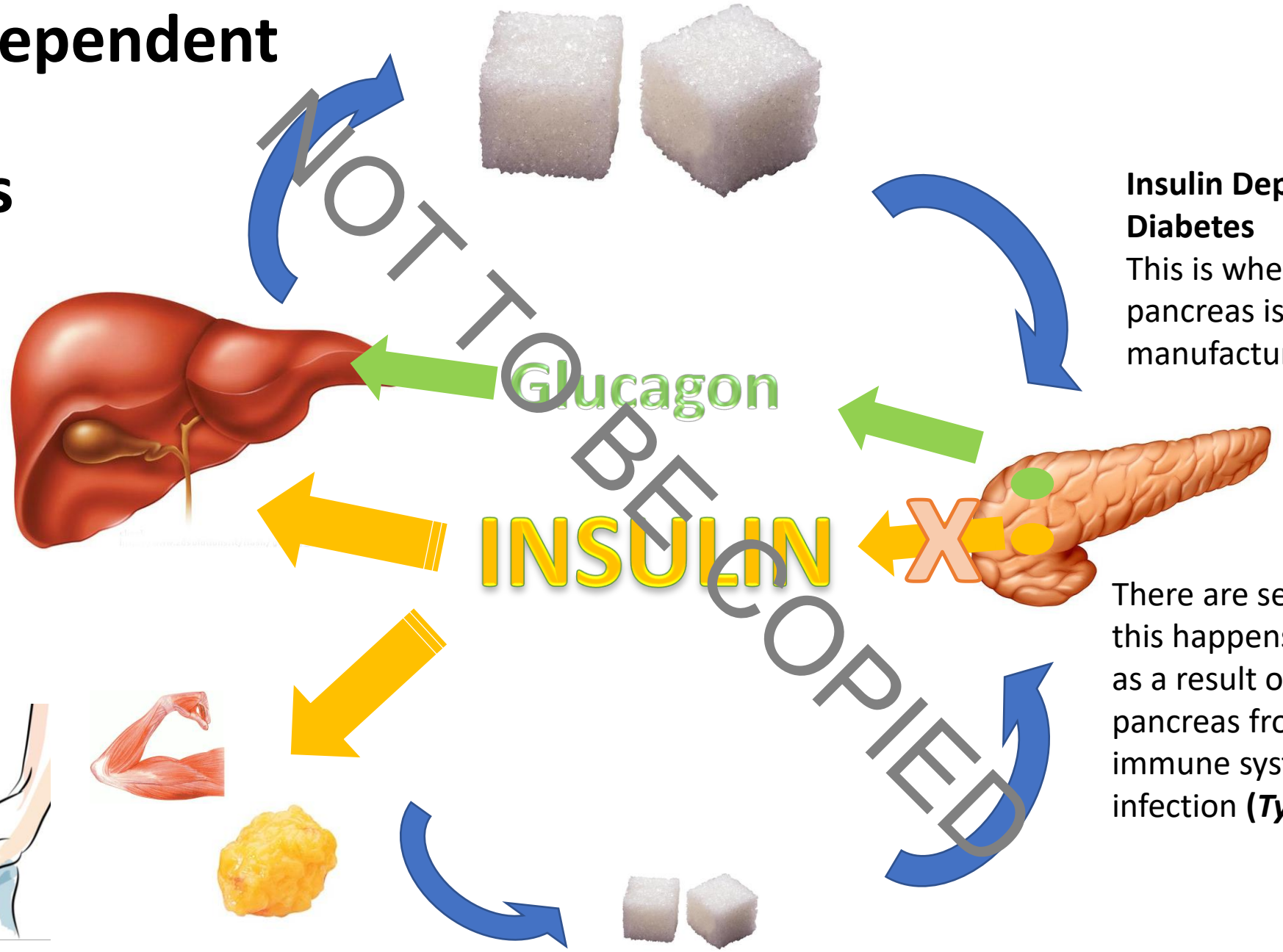
It is before the elevation in blood glucose , at the start of insulin resistance that the increase in insulin is associated with inflammation within the blood. This lead to atheroma and narrowing of the larger blood vessels resulting in an increased risk of stroke and heart attack.

Prevention of diabetes and weight gain is important to address early on in people who are at risk.



1. Beck-Nielsen H & The EGIR. *Drugs* 1999; **58** (Suppl 1): 7–10. Modified from Sattar N. *Clin Lab International* 2005; **29**: 7–11.

Insulin Dependent
(TYPE 1)
Diabetes



Insulin Dependent Diabetes
This is where the pancreas is unable to manufacture insulin

There are several causes why this happens . Normally it is as a result of damage to the pancreas from the body's immune system ***(Type 1)*** or infection **(*Type 3c)***

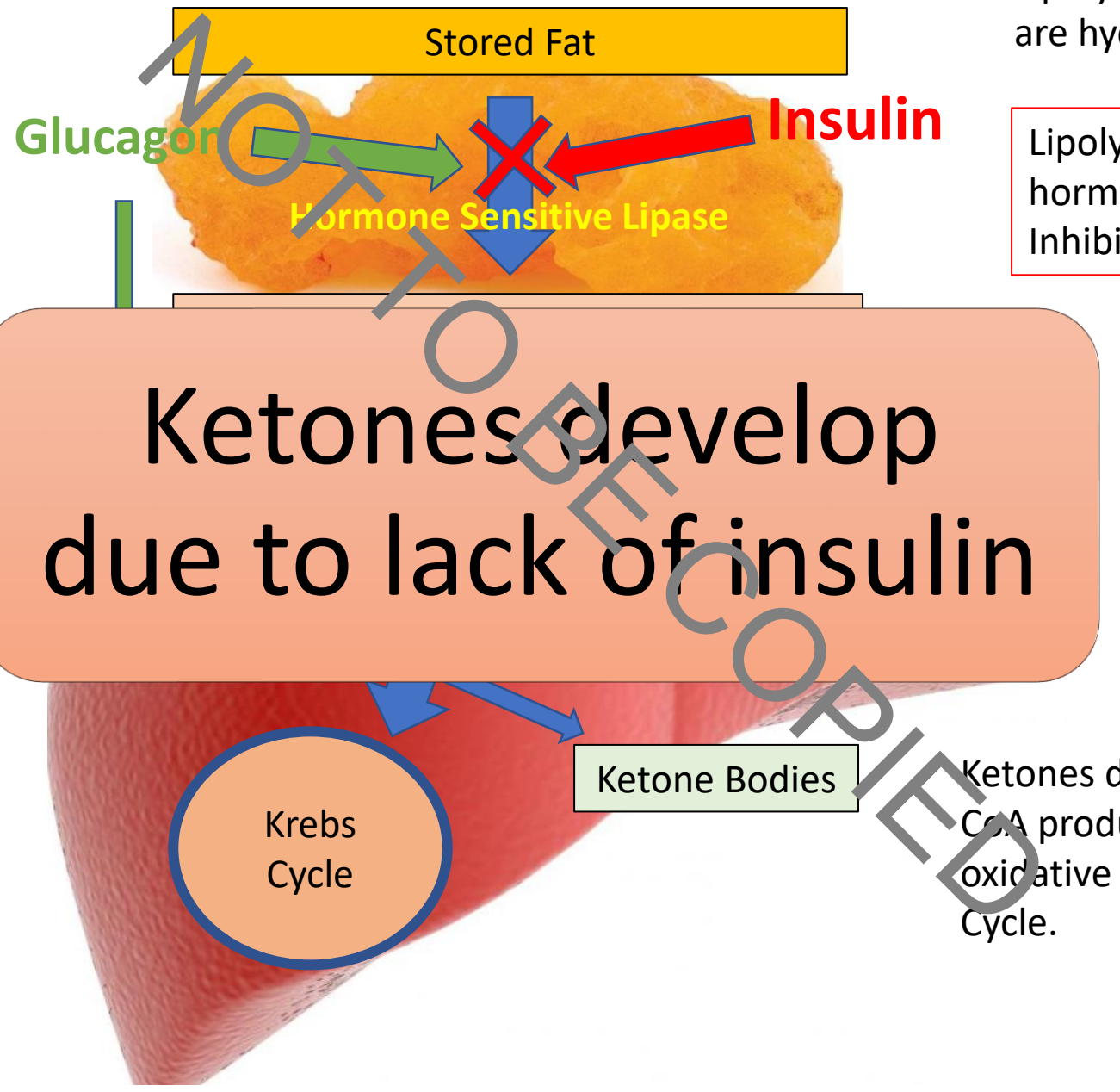
The treatment for Type 1 diabetes is to give Insulin

Lipolysis – process by which Tg. are hydrolysed to fatty acids

Lipolysis – controlled by a hormone sensitive lipase
Inhibited by insulin

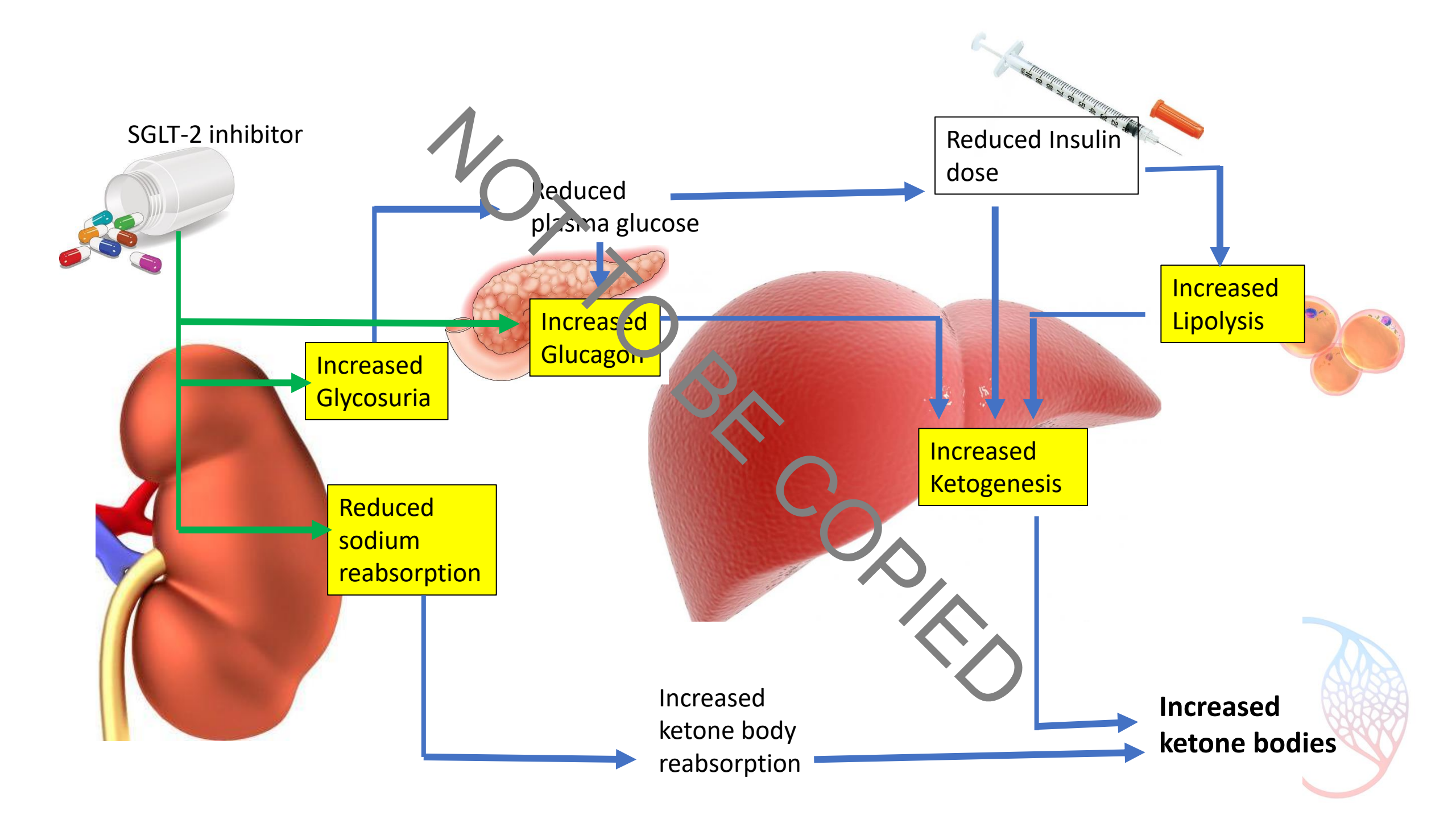
Glucagon
- Stimulates Hormone sensitive Lipase in adipocytes

-acts on Acetyl CoA carboxylase , stimulates fatty acid uptake by mitochondria and ketogenesis

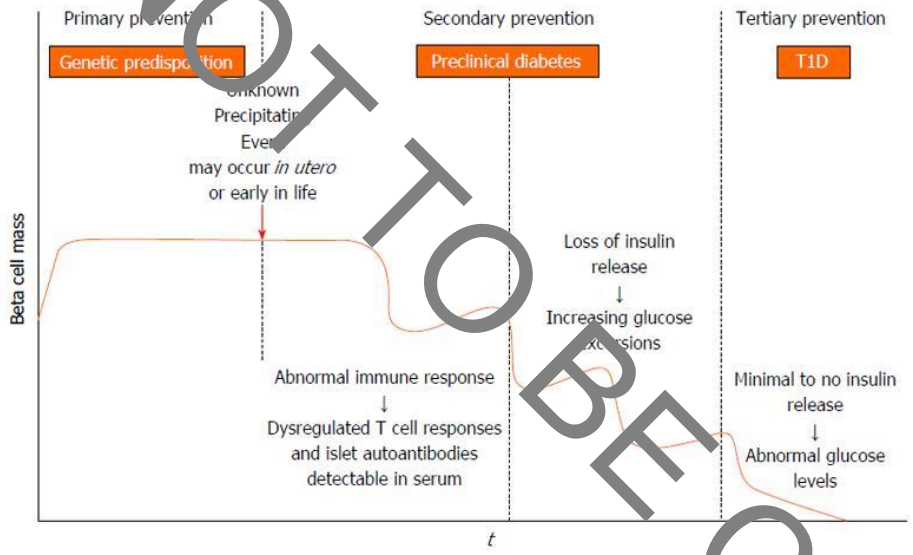


Ketones develop due to lack of insulin

Ketones develop when Acetyl CoA production exceeds the oxidative capacity of the Krebs Cycle.


SGLT-2 inhibitor
Reduced plasma glucose
Reduced Insulin dose
Increased Glucagon
Increased Glycosuria
Increased Lipolysis
Increased Ketogenesis
Reduced sodium reabsorption
Increased ketone body reabsorption
Increased ketone bodies
NOT TO BE COPIED

T1D is a chronic autoimmune disorder that develops in stages



In genetically predisposed individuals (those with DR4/DQ8 and/or DR3/DQ2 haplotypes) there is an environmental trigger that leads to a break in immunologic tolerance and loss of beta cell mass.

- Over time, usually years, there is autoimmune destruction of insulin producing beta cells that is marked by the presence of serum islet autoantibodies .
- The process continues, very likely in a relapsing and remitting manner, with a loss of glucose stimulated insulin release, and eventually insulin deficiency such that overt hyperglycaemia results and clinical T1D is diagnosed

Simmons KM, Michels AW. Type 1 diabetes: A predictable disease. *World J Diabetes* 2015; 6(3): 380-390 [PMID: 25897349 DOI: 10.4239/wjd.v6.i3.380]

LADA

Latent autoimmune diabetes in adults (LADA) is considered a subgroup of type 1 diabetes and is often misdiagnosed because of a lack of both awareness and standardized diagnostic criteria .

LADA is characterized by adult-onset diabetes and circulating autoimmune antibodies

- the autoimmune process seems to be milder and the progression of beta-cell failure slower;
  - this is evidenced by the fact that LADA patients consistently display higher levels of C-peptide as indicator of insulin secretion
- Whereas type 1 diabetes typically is characterized by a clustering of different islet autoantibodies (Regnell and Lernmark, 2017), LADA patients tend to be positive primarily for GADA

Patients may present clinically with characteristics of both type 1 and type 2 diabetes

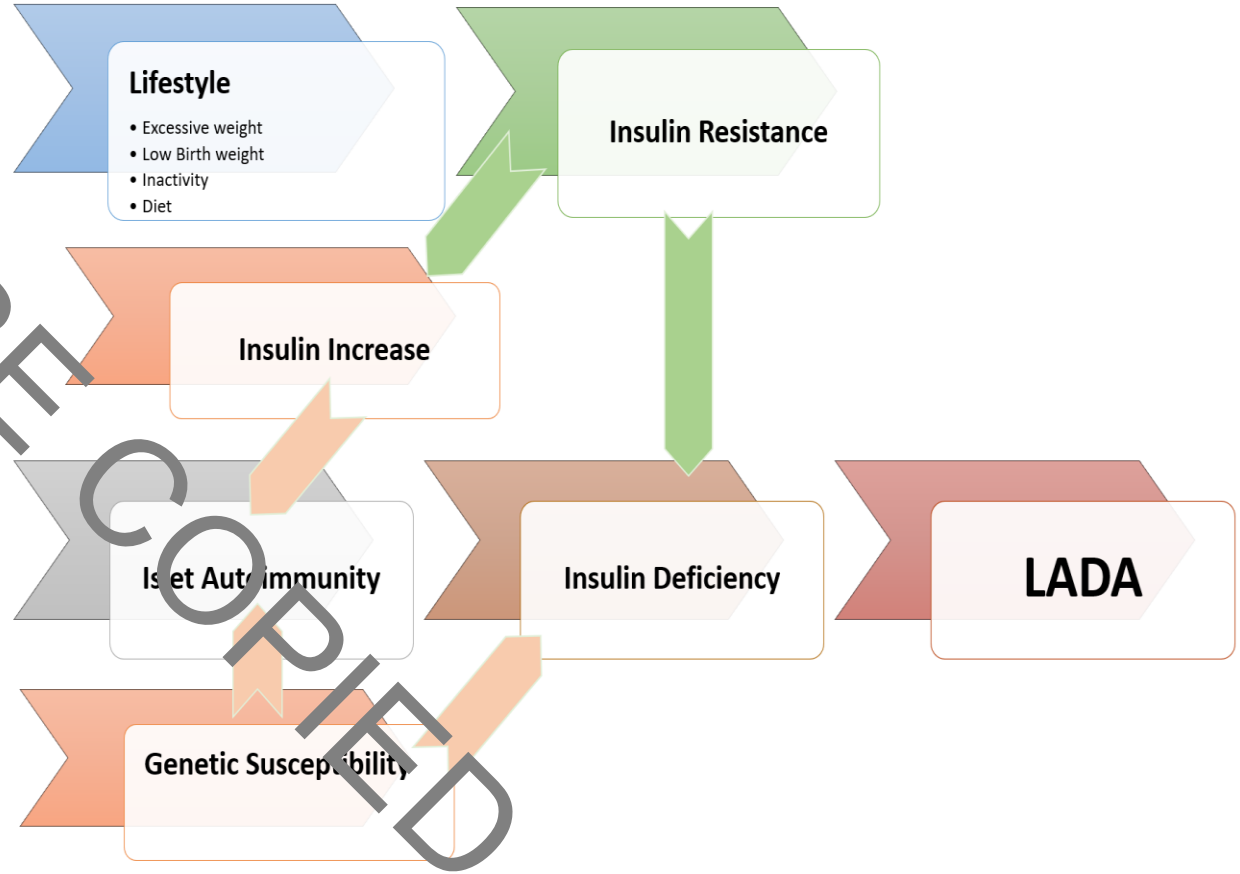
The Pathogenesis of LADA

The pathogenesis of LADA involves the presence of autoantibodies and the progressive deterioration of the beta-cell function

Patients with LADA share insulin resistance with type 2 diabetic patients but display a more severe defect in maximally stimulated B-cell capacity (1)

At diagnosis, both ICA and GAD antibodies were shown to be predictors of insulin dependency, but GAD antibodies appeared to have higher sensitivity as predictors than ICA (2)

Data from the UKPDS (3) has shown that in diabetic patients aged between 35 and 45 years, who test positive for both GAD and ICA progress rapidly toward insulin dependency



1) Carlsson A, Sundkvist G, Groop L, Tuomi T: Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA). J Clin Endocrinol Metab 85:76–80, 2000
2) Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nisse´n M, Ehmstro¨m B, Forse´n B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC: Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 48:150–157, 1999 24.
3) Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R, for UK Prospective Diabetes Study (UKPDS) Group: UKPDS 25: Autoantibodies to islet cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. Lancet 350:1288–1293, 1997

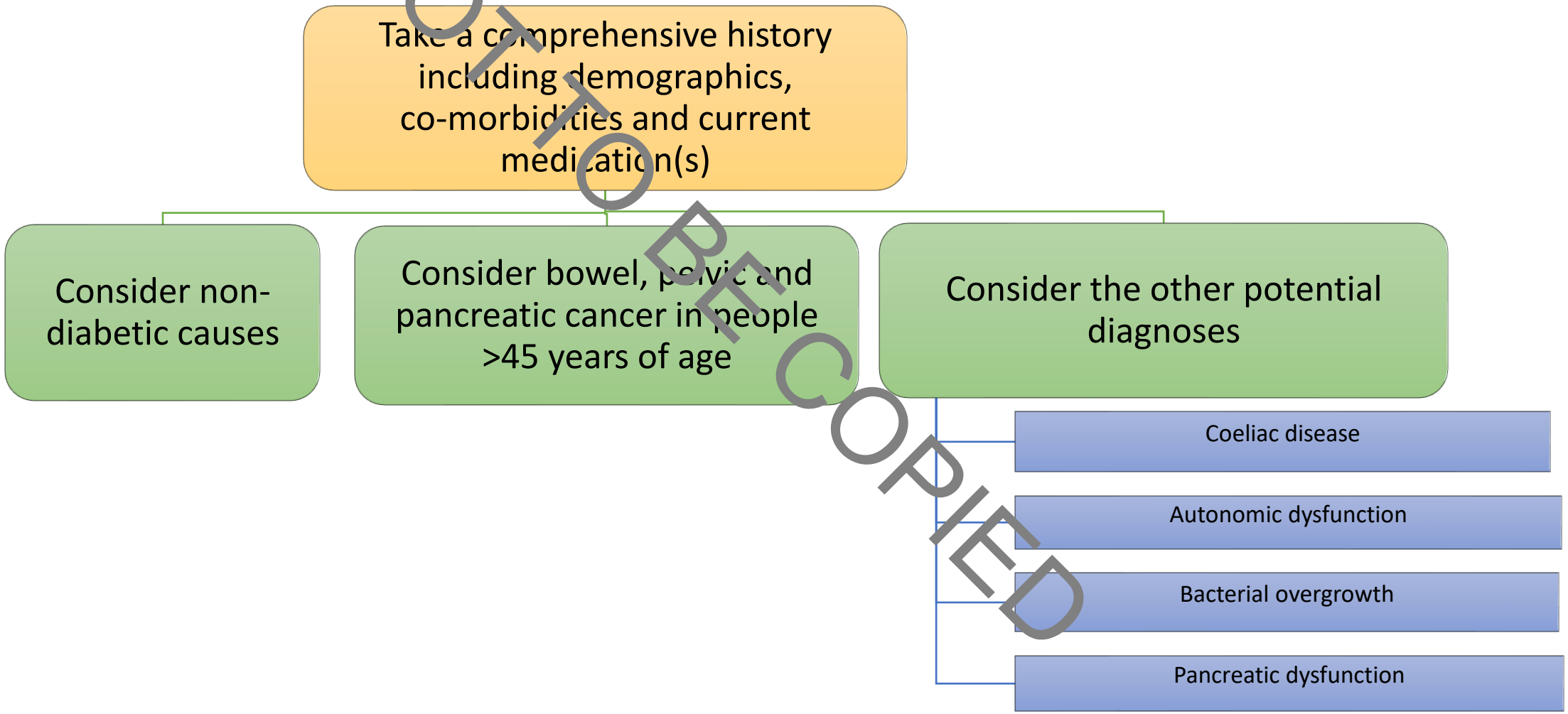
LADA

Criteria for LADA

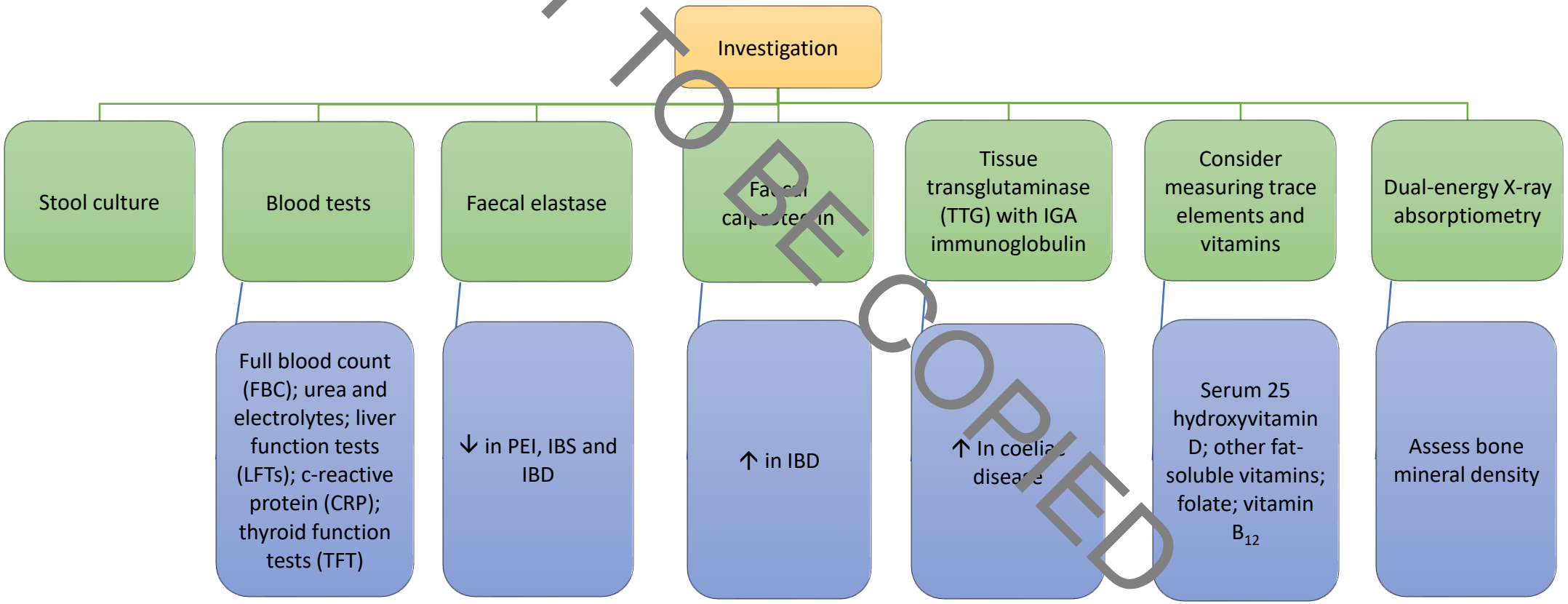
- Aged >30yr
- Antibody positive
- May initially respond to OHA
- Free from insulin for first 6 months from diagnosis
  - Progress within months/ years to insulin dependence
- 20% non-obesity related type 2 diabetes may have LADA
- Ketosis prone

GASTRIC

Clinical work up



Investigations



Be vigilant for pancreatic cancer

Symptoms	Risks	Tests
New-ons		ypical of easuring
Pain in a back pa		
Unexpla appetite in stool		c aphy; T scan

Pancreatic Cancer UK suggests considering pancreatic cancer as a diagnosis in patients with:

- ✓ A new diagnosis of diabetes in those aged > 60 years
- ✓ Diabetes control suddenly becomes erratic
- ✓ Gastrointestinal symptoms that do not improve with treatment
- ✓ New onset mechanical back pain, especially if the person also has gastrointestinal symptoms

Be vigilant for pancreatic cancer

Symptoms	Risks	Tests
New-onset diabetes	Diabetes; pancreatitis	Blood tests; liver function tests (typical of obstructive jaundice); consider measuring CA19-9
Pain in abdomen and/or mechanical back pain	Age; family history of pancreatic cancer	Radiology: ultrasound, CT or MRI, endoscopic ultrasound; endoscopic retrograde cholangiopancreato-graphy; magnetic resonance cholangiopancreatography; PET-CT scan
Unexplained weight loss, loss of appetite, nausea, indigestion, changes in stool	Being overweight; smoking	

Autonomic Neuropathy

Gastrointestinal symptoms are relatively common in patients with diabetes and often arise from diabetic gastrointestinal autonomic neuropathy

- Up to 76% of outpatients with diabetes experience at least one gastrointestinal symptom, most commonly constipation

The vagus - the longest autonomic nerve - accounts for about 75% of all parasympathetic activity

- Therefore, diabetic autonomic neuropathy typically occurs as a system-wide disorder affecting all parts of the ANS
- Gastric emptying largely depends on the vagus nerve
- About 50% of outpatients with chronic diabetes show delayed gastric emptying

Gastroparesis

Gastroparesis in diabetes is usually asymptomatic; however, severe gastroparesis is one of the most debilitating diabetic gastrointestinal complications[5]

Food in the stomach after an 8- to 12-hour fast in the absence of obstruction is diagnostic of gastroparesis

Gastroparesis is associated with the development of bezoars (solid mass of indigestible material)

Major clinical features of gastroparesis in diabetes[5]
Anorexia
Bloating
Early satiety
Epigastric discomfort
Erratic blood glucose control
Nausea and vomiting, which may be persistent (last days or months) or be cyclical

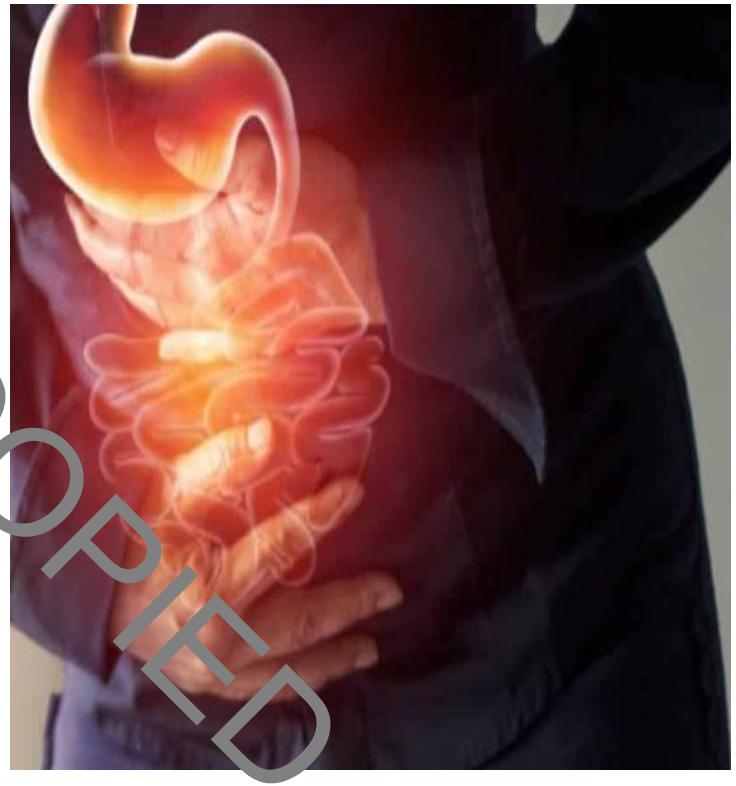
Gastroparesis

Suspect gastroparesis in people with erratic blood glucose control

Gastroparesis interferes with nutrient delivery to the small bowel and, in turn, disrupts the relationship between glucose absorption and administration of exogenous insulin or oral hypoglycaemic drugs

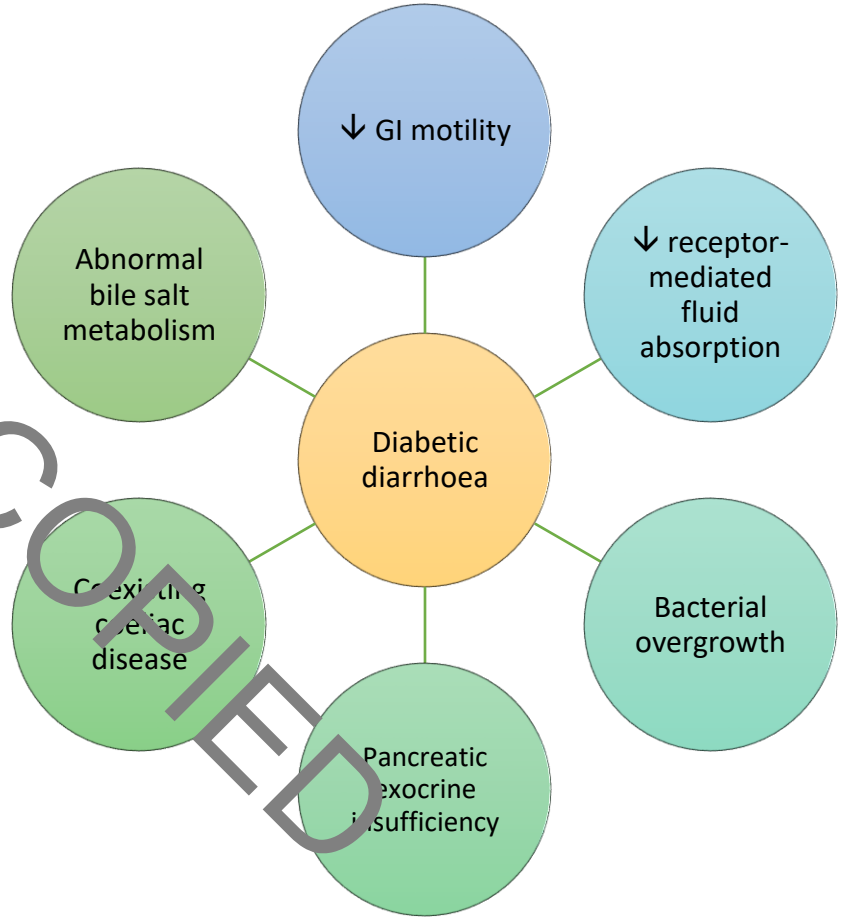
- This can result in wide swings of glucose levels and unexpected episodes of postprandial hypoglycaemia and apparent “brittle diabetes”

NICE guidelines suggest considering gastroparesis in any patient with unexplained poor glycaemic control



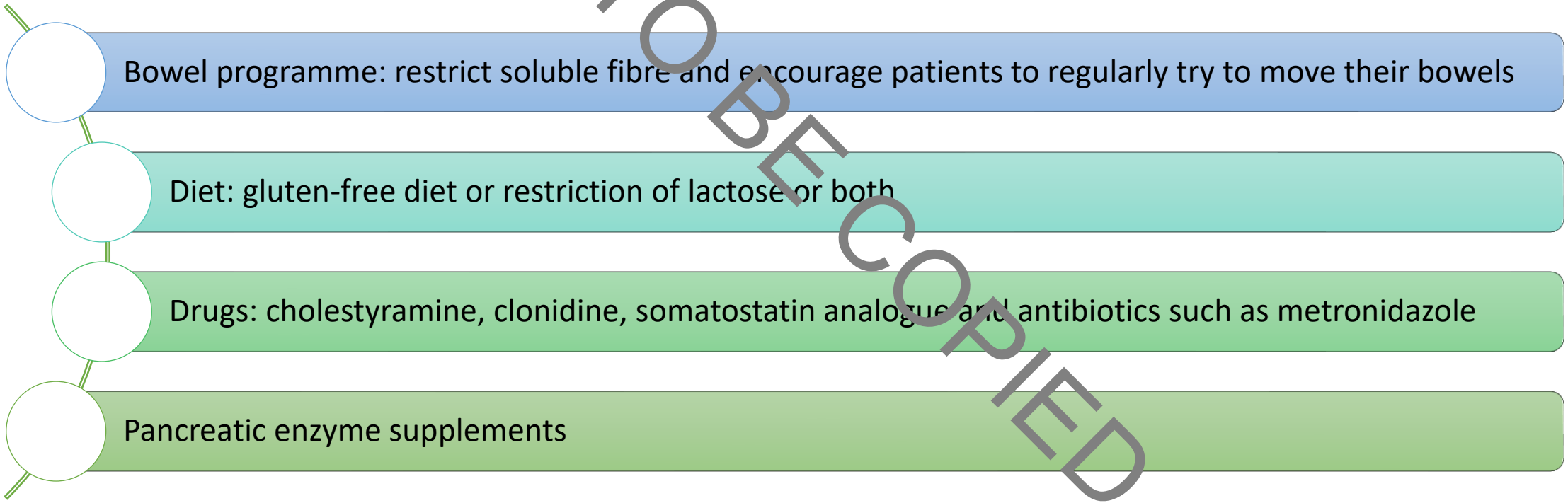
Diabetic Diarrhoea

- ✓ Diabetic diarrhoea is typically profuse, watery and nocturnal
- ✓ Diabetic diarrhoea can last for hours or days, is commonly associated with abdominal discomfort and frequently alternates with constipation
  - Severe constipation may be complicated by perforation and faecal impaction
  - Constipation is the most common symptom of diabetic gastrointestinal dysfunction and affects almost 60% of people with diabetes
- ✓ Diabetic gastrointestinal neuropathy can cause faecal incontinence due to anal sphincter incompetence or reduced rectal sensation
- ✓ The severe and intermittent nature of diabetic diarrhoea complicates treatment and assessment



Diabetic Diarrhoea - treatment

- Consider trial of one or more of the following



Pancreatic Exocrine Insufficiency

Type 1 diabetes

- ✓50% of patients show some degree of PEI
- ✓Co-existing PEI in type 1 and 2 diabetes is probably a different clinical entity to type 3c diabetes

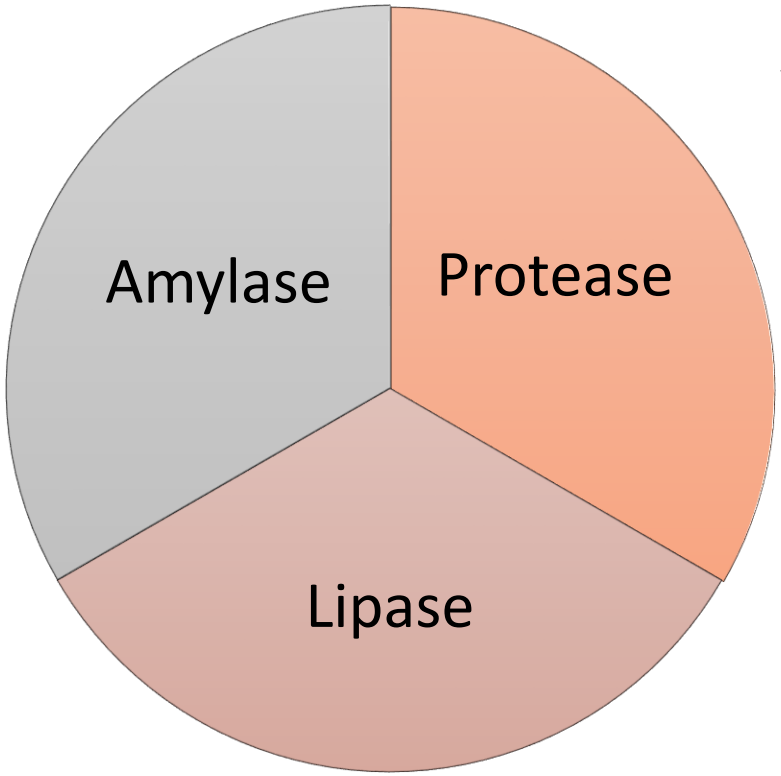
Type 2 diabetes

- ✓30-50% of patients show some degree of PEI
- ✓Type 3c diabetes is often misclassified as type 1 and 2 diabetes

Type 3c (pancreatic) diabetes

- ✓Type 3c diabetes refers to diabetes caused by pancreatic disease or injury; affects endocrine and exocrine function
- ✓5-10% of people in western populations with diabetes have type 3c diabetes, which is associated with chronic pancreatitis

PEI is characterised by a deficiency in three major groups of pancreatic enzymes



Leading to

- ✓ Impaired digestion
- ✓ Abnormal food breakdown
- ✓ Nutrient malabsorption and malnutrition

Importance of recognising 3c

To ensure appropriate medical treatment.

Insulin may be required earlier.

Awareness of “brittle diabetes” and risk of hypoglycaemia through loss of counter-regulatory hormone response.

Need for pancreatic enzyme replacement therapy (PERT).

- Malabsorption of fat-soluble vitamins.
- Risk of vitamin D deficiency and osteoporosis.

Increased risk of pancreatic carcinoma.

To avoid incretin-based therapies where there is a history of pancreatitis.

Recognising 3c

Classic symptoms of diabetes: thirst, polyuria, weight loss, fatigue, recurrent infection may be present.

Consider type 3c as cause of diabetes if history of upper abdominal pain, steatorrhoea, bloating and weight loss.

Pancreatic enzyme insufficiency (PEI) usually pre-dates onset of diabetes.

There is no definitive diagnostic test for type 3c diabetes.

Investigation	Pancreatogenic diabetes
HbA1c , fasting /random glucose	Diagnose diabetes
Antibodies	Absent Type2 and 3c
C-Peptide	Low in Type 1 and 3c ? Raised in Type 2
25 hydroxy Vitamin D	Often low in Type 3c
Faecal Elastase-1	Low in Type3c – indicate exocrine insufficiency
Pancreatic Imaging	? Pancreatic Pathology

Management

There are no specific guidelines.

- Treatment goals are derived from randomised controlled trials from type 1 and type 2 diabetes, and expert opinion.
- Insulin may be the safest management

Metformin

- Lactic-acidosis risk with high alcohol intake

SGLT2i

- Ketosis risk

Incretin therapies (GLP1-RSA / DPP4i

- Pancreatitis associations

Diet and lifestyle

Reducing cardiovascular risk (as per type 1 and type 2 diabetes)

YOUNG

YOUNG

Systematic Case Finding of type 2 diabetes in under 40 years

- BMI > 35 kg/m^2
  - (> 32.5 in South Asian, Asian, Middle Eastern, Black African or African Caribbean background)
- Strong family history
- Previous gestational diabetes
- Previous prediabetes
- Symptoms of diabetes
- Periodontal disease
- Other features of metabolic syndrome
- Early cardiovascular or renal disease
- Severe mental illness
- Learning disability

Young Type 2 diabetes

- Need special consideration

Mental / social stress

Fertility

longevity

- Longer glycaemic burden

Cardiovascular / renal issues

- Younger and for longer

Young Type 2

- Metformin
- SGLT2i
- GLP

Management

Concerns

Cardiovascular / diabetes risks

Weight

Fertility

- Increased fertility (Metformin)
- OCP efficicay (GLP)

Potential pregnancy

- Medication safety in pregnancy
- Pregnancy risks post cessation GLP (Weight / miscarriage / DM/ Pre-eclampsia)

GLP - considerations

The Positives

- Cardiovascular risk reduction
- Renal decline reduced
- Weight loss
- Liver
  - Reduction progression steatosis
- Reduction cognitive decline

The Concerns

GLP - considerations

The Concerns

Eyes
- Worsening retinopathy
- Macular degeneration
- Anterior ischaemic changes

Thyroid cancer
- Medullary cell carcinoma

Precipitation of gall stones

Pancreatitis

GORD

Sarcopenia

Weight rebound

Malabsorption

Contraception / HRT management

Poor pregnancy outcomes

Progression of existing retinopathy
NAION
Neovascular AMD

Eye Health and GLP

GLP-1 receptor agonists have been associated with an increased risk of certain eye diseases, particularly diabetic retinopathy and non-arteritic anterior ischemic optic neuropathy (NAION)

GLP-1 RAs among patients with diabetes was associated with a 2-fold higher risk of incident nAMD (neovascular AMD) development than among similar patients with diabetes who did not receive a GLP-1 RA.(1 ,2)

- AMD is the leading cause of irreversible vision loss in older adults

The evidence remains conflicting: some articles in fact suggest protective effects of GLP-1 RAs on ocular health, citing their anti-inflammatory and neuroprotective mechanisms (3)

1. Shor R, Mihalache A, Noori A, Shor R, Kohly RP, Popovic MM, et al. Glucagon-Like Peptide-1 Receptor Agonists and Risk of Neovascular Age-Related Macular Degeneration. JAMA Ophthalmol. 2025; 143(7):587-594
2. Anderer S. GLP-1 Drugs Linked to Higher Risk of Age-Related Macular Degeneration. JAMA. 2025; 334(5):383
3. Allan KC, Joo JH, Kim S, Shaia J, Kaelber DC, et al. Glucagon-like Peptide-1 Receptor Agonist Impact on Chronic Ocular Disease Including Age-Related Macular Degeneration. Ophthalmology. 2025; 132(7):748-757.

Eye Health and GLP prescribing

Exercise caution and explore potential options.

These could include :-

- integrating eye health into conversations around GLP-1 drugs.
- implementation of enhanced retinal screening for patients starting GLP-1 RAs,
  - particularly for those with AMD risk factors such as smoking, family history or early retinal changes .
- Clearer patient information on possible ocular side effects integrated into informed consent and prescribing discussions

GLP - considerations

The Concerns

- **Eyes**
  - Worsening retinopathy
  - Macular degeneration
  - Anterior ischaemic changes
- **Thyroid cancer**
  - Medullary cell carcinoma
- Precipitation of gall stones
- Pancreatitis
- GORD
- Sarcopenia
- Weight rebound
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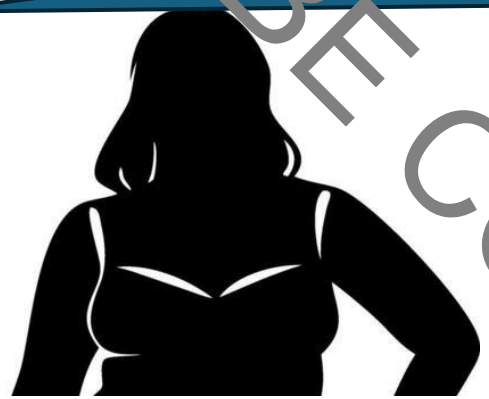
- Contraception / HRT management
- Poor pregnancy outcomes



Medullary Cell Cancer (Associated with calitonin and calcium)

GLP - considerations

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- **Malabsorption**
- **Contraception / HRT management**
- **Poor pregnancy outcomes**

GLP-1RAs have been associated with an increased risk of gallbladder disease, including cholelithiasis and cholecystitis, (Especially with prolonged use and higher doses)

GLP-1RAs reduce postprandial release of CCK, resulting in inadequate emptying of the gallbladder after meals. This impaired contractility contributes to bile stasis increasing the likelihood of cholesterol crystallization and gallstone formation.

Ramírez-Mejía MM, Ponciano-Rodriguez G, Eslam M, Méndez-Sánchez N. GLP-1 receptor agonists and gallbladder disease risk: insights into molecular mechanisms and clinical implications. Ther Adv Endocrinol Metab. 2025 Dec 23;16:20420188251406456. doi: 10.1177/20420188251406456. PMID: 41459016; PMCID: PMC12739101.

GLP - considerations

The Concerns

- Eyes
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  - Macular degeneration
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  - Medullary cell carcinoma
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weight loss associated predominantly comprises a reduction in FM, although significant heterogeneity exists between studies.
In over half of the studies identified, the proportion of LBM reduction ranged between 20% and 50% of total weight lost

A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans
JA Sargeant, J Henson, JA King, T Yates, K Khunti, MJ Davies
Endocrinology and Metabolism, 2019

GLP - considerations

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- **Poor pregnancy outcomes**

Weight regain within 18 months of stopping GLP-1RAs

J Obes. 2024 May 10;2024:8056440. doi: 10.1155/2024/8056440

Mechanism of weight regain

Hormonal imbalance of incretins and other hormones associated with satiety

Dysregulation of pathway and lack of appropriate feed back mechanisms in overweight people

Beta cell dysfunction due to continued stimulation by GLP leading to impaired insulin regulation

Alteration in gut microbes

Sarcopenia and GLP

<40% loss of lean body mass

Weight regain within 18months of cessation

Sarcopenia - Reducing the Risks
Emerging evidence suggests that GLP therapies will cause <38% lean mass weight loss **- "No further titration of GLP therapy once HbA1c target has been achieved without appropriate review"** **• -Dietary assessment regarding increase protein intake** **• -review activities and ensure appropriate exercise is being undertaken to preserve muscle mass** **• -if any concerns , refer weight management service for the appropriate level of support**

GLP - considerations

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Nutritional complications from use of GLP-1 agonists.

- Severe thiamine deficiency causing Wernicke's encephalopathy, which can lead to an irreversible dementia.
- Metabolic acidosis resulting from anorexia
- severely low magnesium levels.

US adverse event reporting has also noted harmful "starvation" and low glucose as well as other metabolic and nutritional adverse effects

Fallows E. Malnutrition with use of GLP-1 agonists is an underestimated real world harm *BMJ* 2025; 390 :r1512 doi:10.1136/bmj.r1512

GLP - considerations

The Concerns

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- **Contraception / HRT** management
- Poor pregnancy outcomes

Contraception efficacy
HRT and progesterone protection

Women's Health and GLP

Avoid pregnancy

- 1month if taking daily GLP
- 3 months if taking weekly GLP

Contraception

- Reduced efficacy on initiation and titration of Tirzepatide for first 4 weeks – extra contraception advised

HRT

- Either increase oral progesterone or alternative non-oral progesterone if taking Tirzepatide to ensure adequate protection of endometrium

Fertility

Fertility		
Women who are of fertile age should take precautions to avoid pregnancy when being prescribed GLP therapy		
Planning a pregnancy	**Daily GLP 1**	**Stop 1 month prior to conception**
	Weekly GLP 1	**Stop 3 months prior to conception**
Contraception choice	Ideally LARC	
	Tirzepatide	**Barrier methods needed at initiation and dose increase for 4 weeks**
	Lixisenatide Exenatide	Efficacy affected unless contraception taken 1 hour before injection
	Oral Semaglutide – not clear on interaction	

GLP - considerations

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GLP1-Ras were associated with an increased risk of preterm birth,

(the risk was only present when the medication was used for diabetes treatment, and not for weight management)

Kathrine Vauvert R. Hviid et al. Periconceptional GLP-1 receptor agonist exposure and obstetric outcomes: a Danish nationwide cohort study, *Human Reproduction Open* (2026). DOI: 10.1093/hropen/hoag015

Discontinuation of (GLP-1 RAs) before conception or during early pregnancy was associated with greater gestational weight gain and increased risks of preterm delivery, gestational diabetes, and hypertensive disorders of pregnancy

Vinaya J, Patel D, Fu Y, et al. Gestational Weight Gain and Pregnancy Outcomes After GLP-1 Receptor Agonist Discontinuation. *JAMA.* 2025;334(24):2186–2196. doi:10.1001/jama.2025.20951

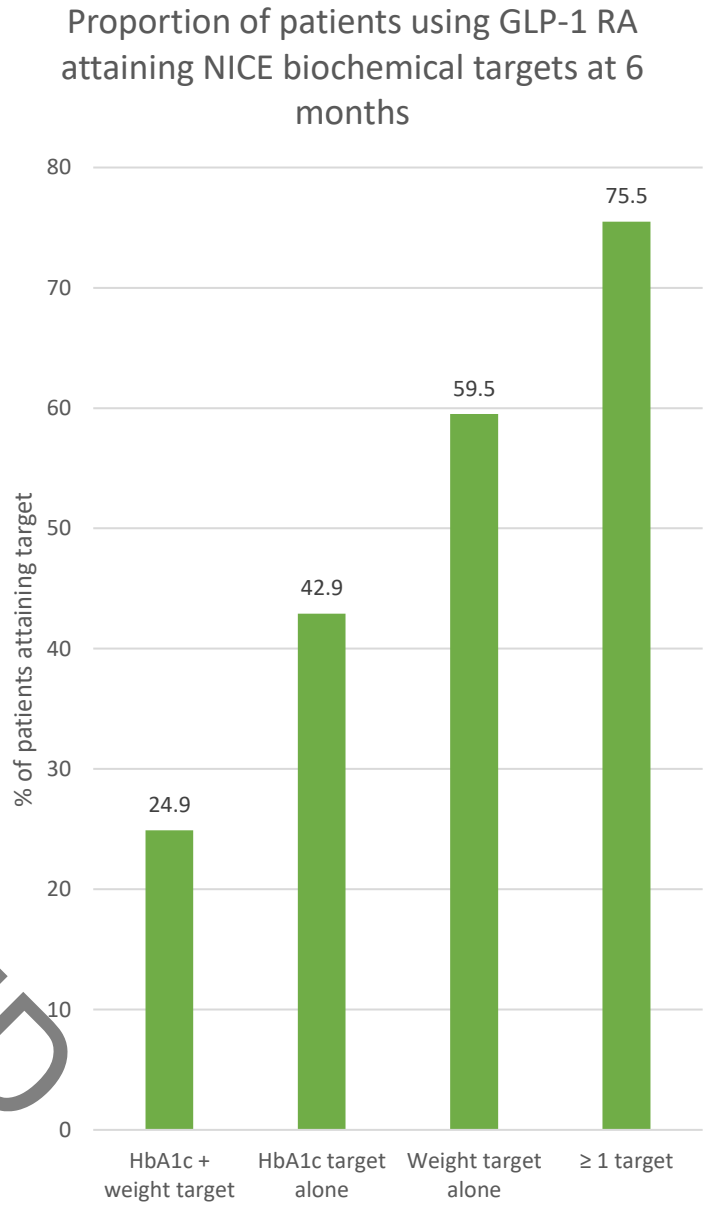
Poor pregnancy outcomes

Pregnancy risk and GLP

- Weight regain during pregnancy
- Increased risk gestational diabetes (if been taking for weight loss alone)
- Feotal malformation
- miscarriage

Only a quarter of patients who start a GLP-1 RA achieve both NICE targets

- In a retrospective study of 1123 people, **68% completed 6-months treatment with GLP-1 RA;** of those with a weight and HbA_{1c} record at 6 months **only 25% achieved both NICE criteria for a beneficial metabolic response**



Poor Responders

Genetic

- More research needed to define who responds

Ethnicity

- Poorer response with Afro-Caribean

Gender

- Women respond better than men

Age

- Younger age respond better

Compliance

Other metabolic conditions

Poor Responders

HbA1c reduction no weight loss	**Consider** - **Compliance with therapy** - **Compliance with lifestyle**	**Offer review and support** **? refer weight management**
	Review other medications that can cause weight gain	Beta Blocker Antidepressants Opioids Steroids Insulin Sulphonylureas
	Consider underlying cause - Hypothyroid - Fluid overload	Check TFT & treat appropriately Check renal / cardiac and liver bloods
Weight loss but no HbA1c reduction	**Consider** - Compliance with therapy - Compliance with lifestyle	If no improvement, ? stop medication.
	Consider underlying condition	Endocrine (Thyroid -toxicity) Malabsorbtion Underlying cancer etc
No improvement in weight / HbA1c	**Consider** - Compliance with therapy - Compliance with lifestyle	Consider stopping therapy if no improvement. Consider continuing therapy if no worsening but perceived CVD / CKD / Hepatic benefits
HbA1c at target but weight remains high	Refer weight management service to ensure proper support regarding diet and exercise to avoid loss of lean mass (sarcopenia risk) GLP should not be up titrated by diabetes team	

GLP and pre-operative concerns

Aspiration risk

- -To be stopped before surgery
- - Use a cuffed tube and head-up table for anaesthesia