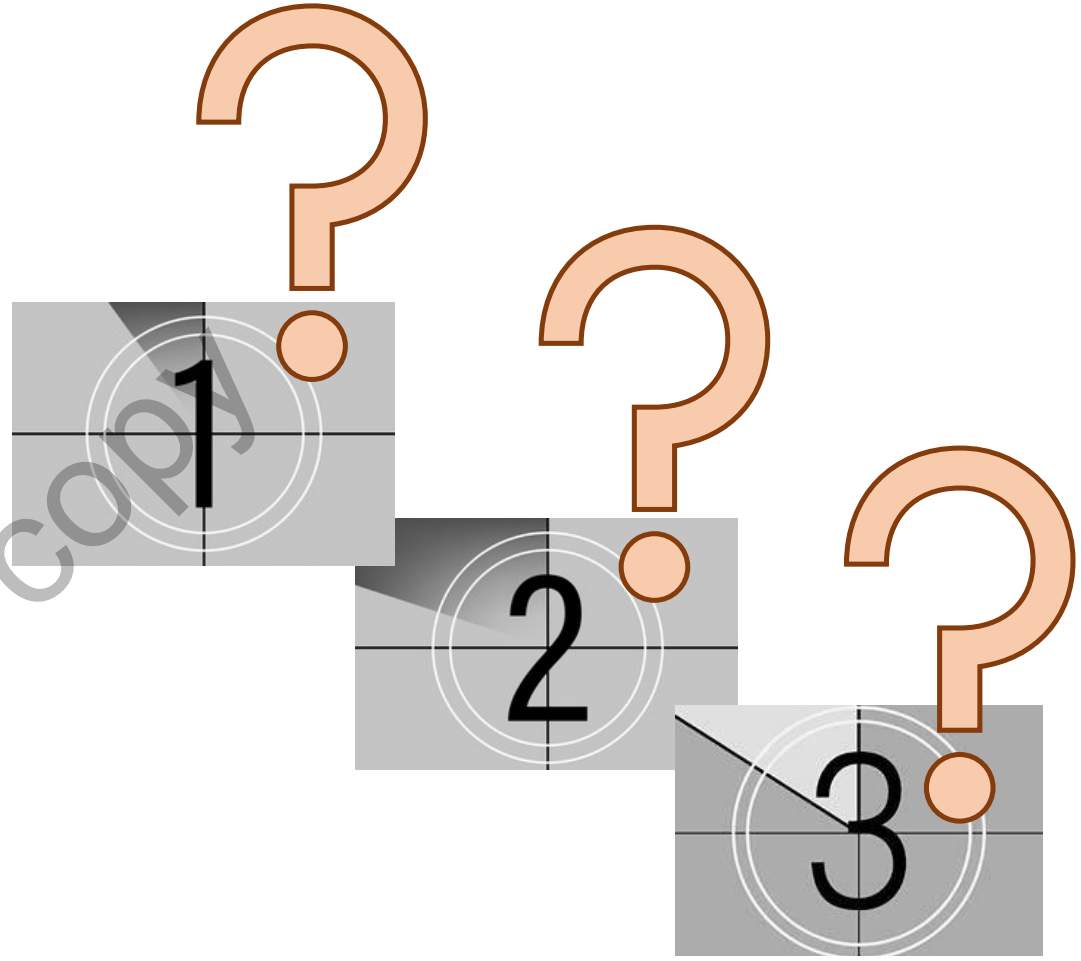
Diabetes Type



"Not Everything is as it seems"

Charles Westmoreland

Classification of Diabetes

There are many different types of diabetes

- **Type 1**
- **Type2 (Non insulin dependent)**
- **MODY (Maturity onset diabetes of the Young)**
- **LADA (Latent Autoimmune Diabetes in Adults)**
- **Iatrogenic Diabetes (eg. Steroid Induced)**
- **Associated Diabetes (eg. Cystic Fibrosis)**
- **Diseases of Exocrine pancreas (Type 3c)**
  - Infection / inflammation / toxins / neoplasia
- **Endocrine associated Diabetes**
  - Cushing's , Acromegally , Pheochromocytoma , Glucagonoma , Somatostatinoma
- **Immune Diabetes**
- **Genetic Diabetes**
- **Gestational Diabetes**
- **Protein Deficient Pancreatic Diabetes (Malnutrition Modulated)**

Type 3 Diabetes

Type 3a diabetes

- any forms of diabetes caused by **genetic defects to beta cells**

Type 3b diabetes

- any form of diabetes caused by **genetic defects that affect the action of insulin**.

Type 3c diabetes

- also known as **'pancreatogenic diabetes',** is a form of secondary diabetes, that may occur as a result of the pancreatic disorders such as pancreatitis, cystic fibrosis,
- hemochromatosis, pancreatic cancer, pancreatomy and some neonatal diabetic cases caused by pancreatic agenesis.

Type 3d diabetes

- any form of diabetes that **results from hormone disorders**.

Type 3e diabetes

- any diabetes that has been **induced by chemical or drugs**. For example, high doses of steroids, taken for an extended period of time, can lead to diabetes developing.
- Steroid-induced diabetes is therefore a form of type 3e diabetes.

Type 3f diabetes

- diabetes that develops as the **result of an infection**.

Type 3g diabetes

- less common **immune-mediated diabetes**.

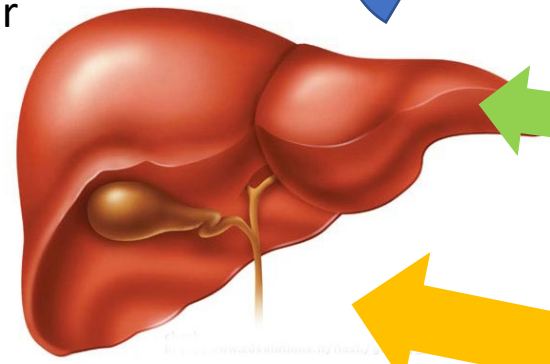
Type 3h diabetes

- other **genetic syndromes** that may be associated with diabetes occurring.

Blood glucose level rise

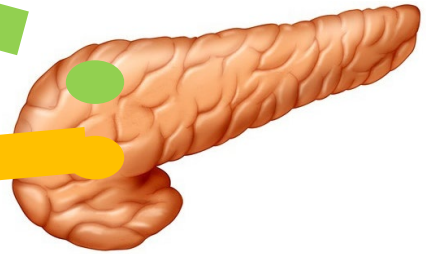
Glucose enters the body by the ingestion of carbohydrates. These are converted to glucose in the gut and the glucose is absorbed into the blood stream.

Glucagon acts by stimulating the release of glucose that has been stored in sites such as the liver



Glucagon

The beta cells in the pancreas are stimulated to make insulin



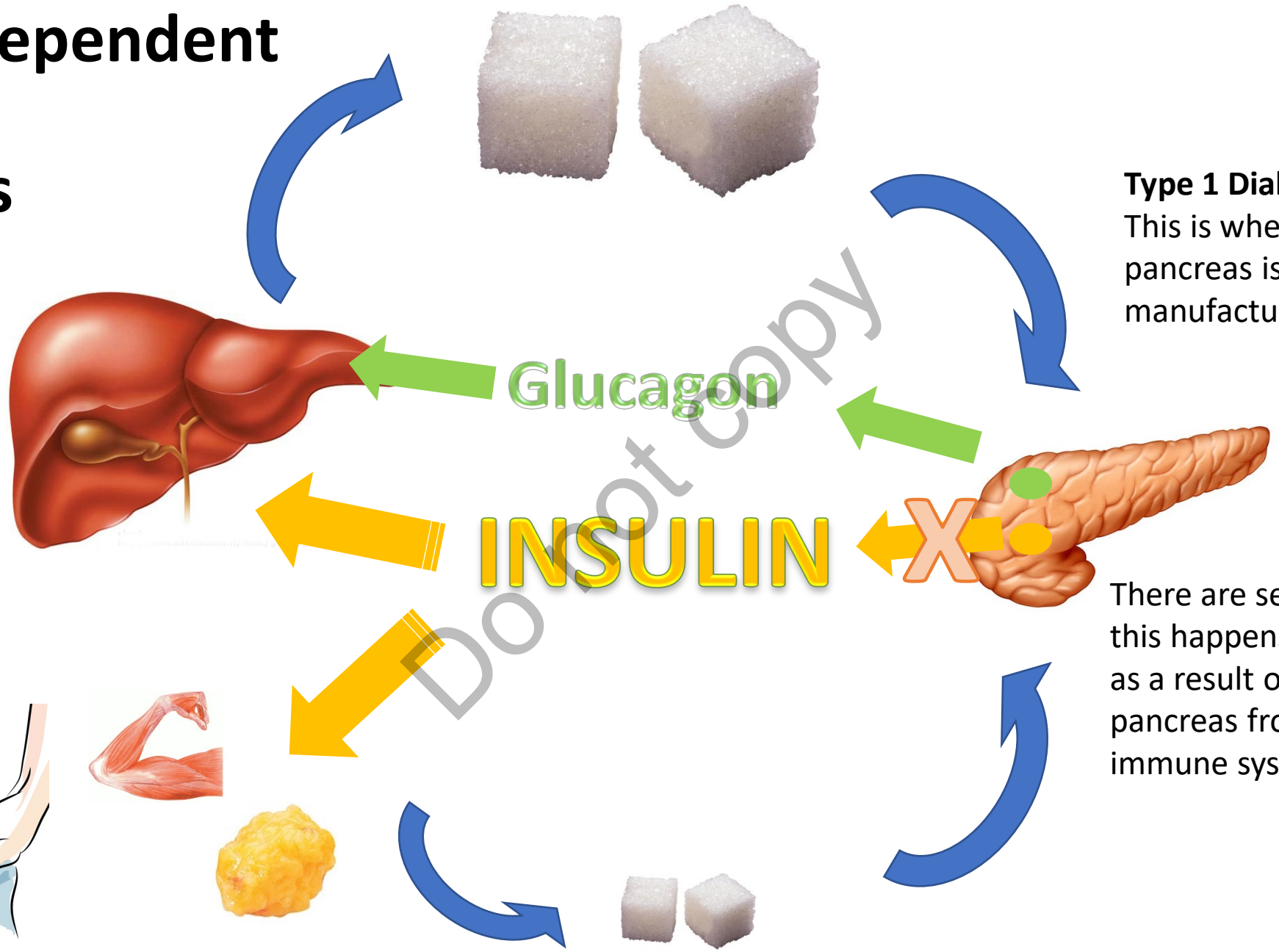
INSULIN

Insulin when released helps in the recognition of glucose by the liver , fat and muscle cells . The glucose is taken into the cells and is either used as a fuel source or stored.

Glucose levels in the blood fall

The drop in blood glucose stimulate alpha cells in the pancreas to make Glucagon

Insulin Dependent (TYPE 1) Diabetes



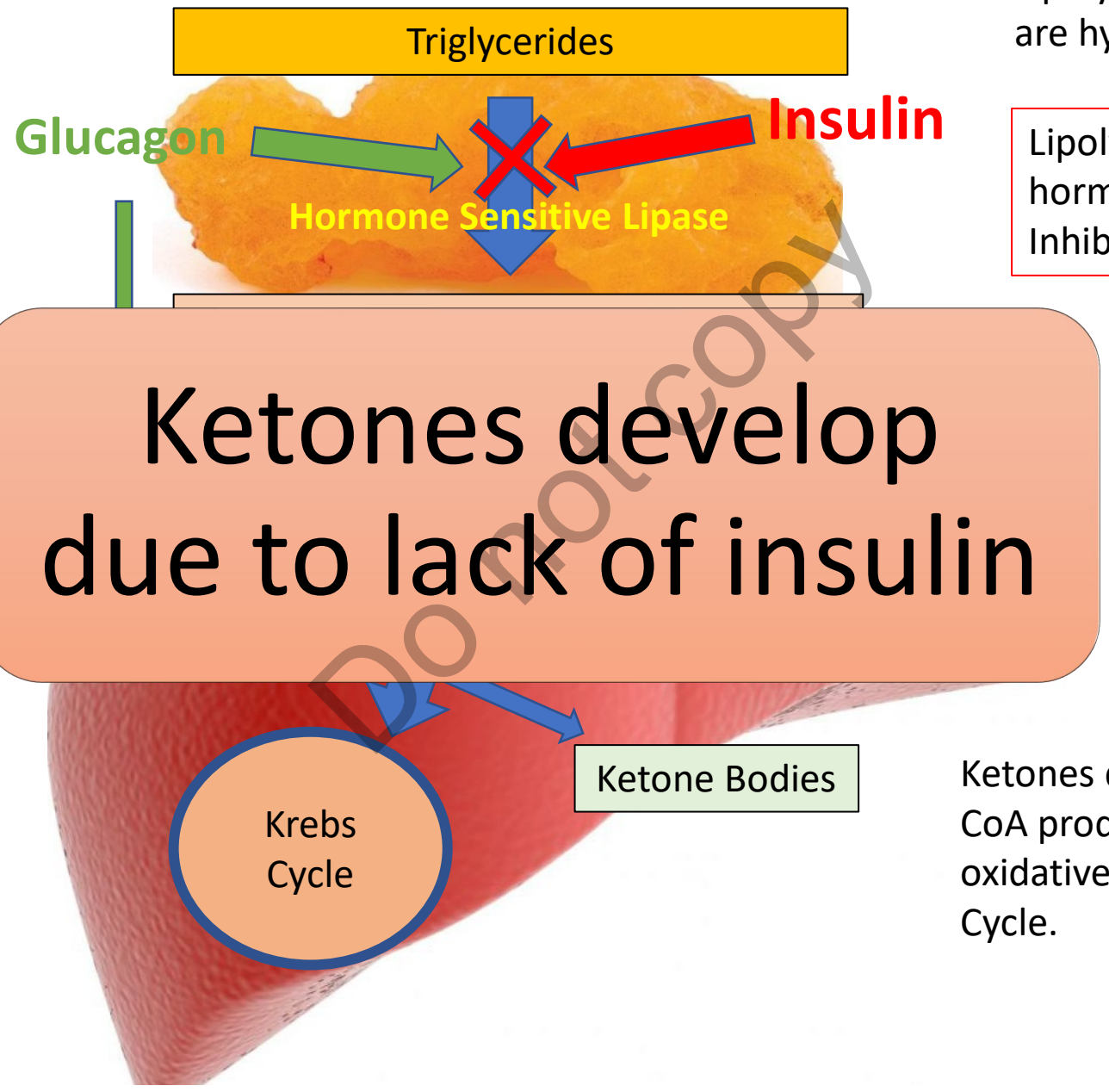
Type 1 Diabetes
This is where the pancreas is unable to manufacture insulin

There are several causes why this happens . Normally it is as a result of damage to the pancreas from the body's immune system or infection

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

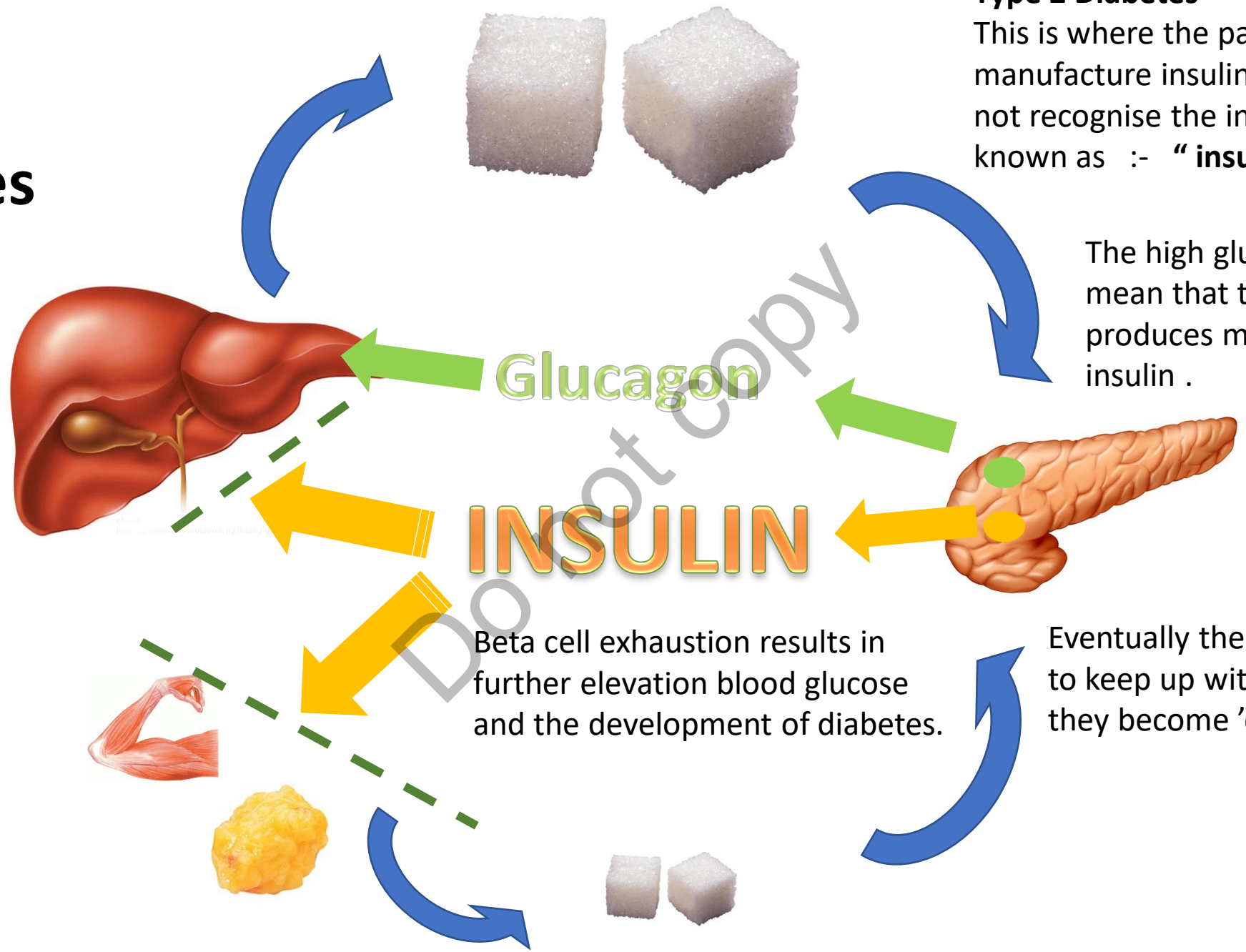
-acts on Acetyl CoA carboxylase , stimulates fatty acid uptake by mitochondria and ketogenesis

Ketones develop due to lack of insulin

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

TYPE 2 Diabetes

Type 2 diabetes has also been shown to have elevated Glucagon levels. This results in the stored glucose being released from the liver and further elevating the blood glucose.



Type 2 Diabetes
This is where the pancreas is able to manufacture insulin but the cells do not recognise the insulin . This is known as :- **“ insulin Resistance “**

The high glucose levels often mean that the pancreas produces more and more insulin .

Eventually the beta cells are unable to keep up with the demand and they become ’exhausted’.

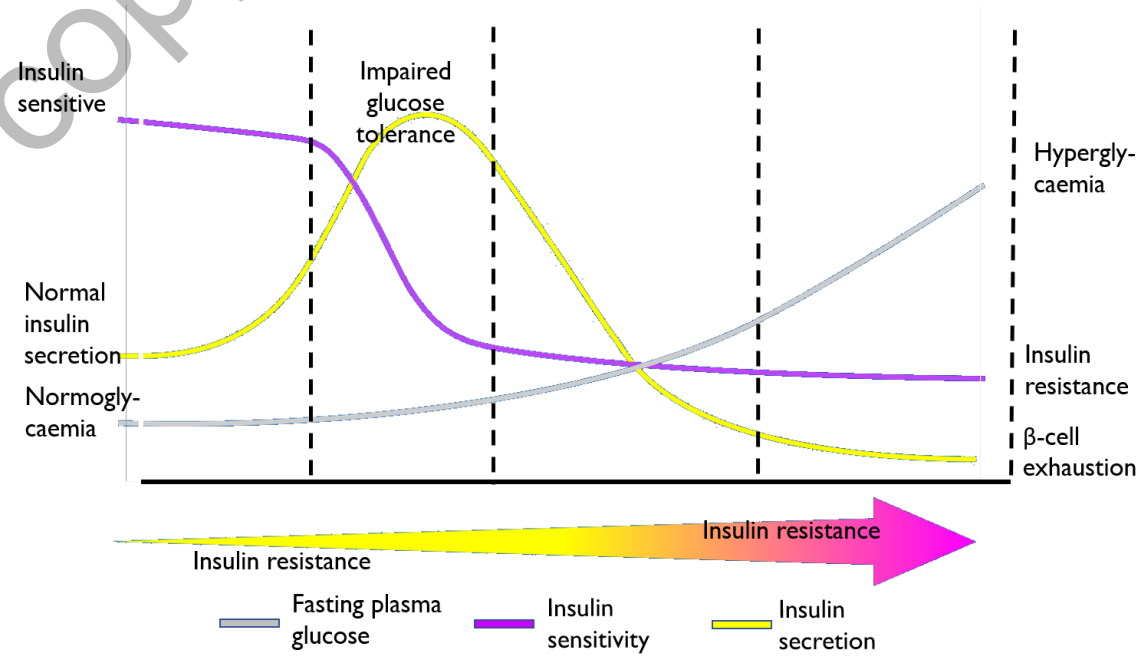
Beta cell exhaustion results in further elevation blood glucose and the development of diabetes.

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.

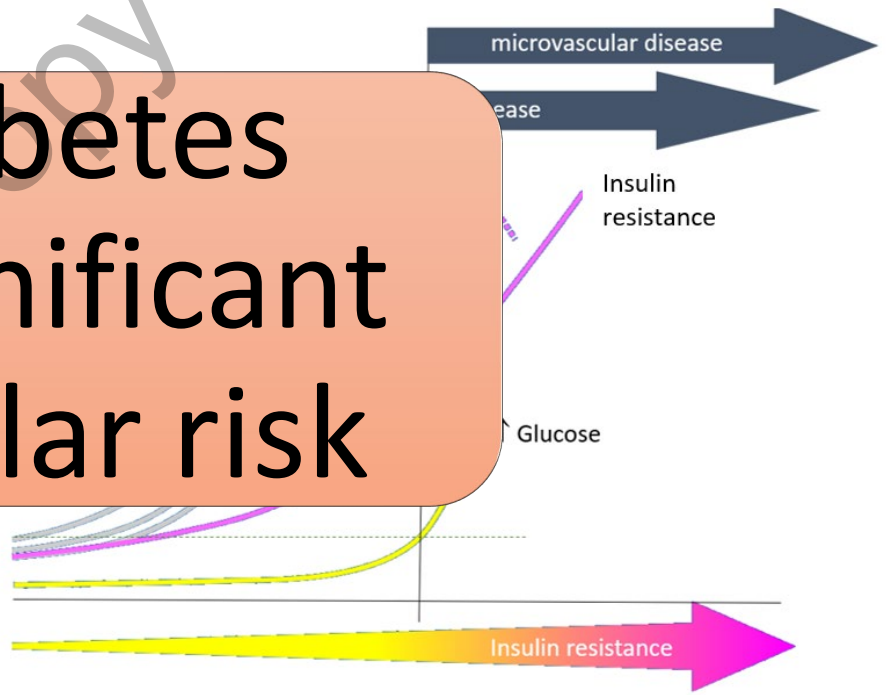
Development of Type 2 diabetes

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 b
insulin resistance that the inc
with inflammation within the
and narrowing of the larger bl
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.

Type 2 diabetes carries a significant cardiovascular risk



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Characterising Diabetes

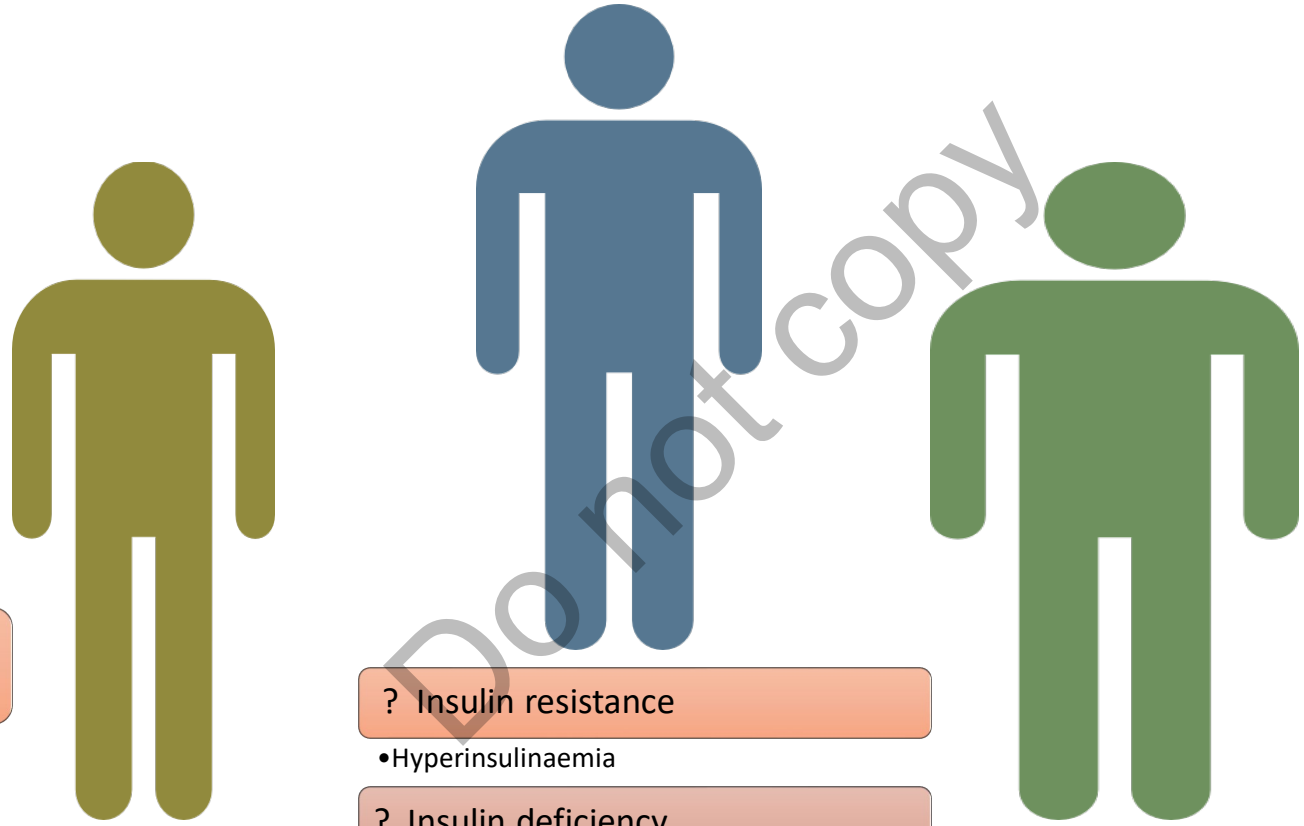
Acute onset

Weight loss

Osmotic Symptoms

? Autoimmune disease

Weak Family History



Slow onset

Overweight

Few symptoms

Metabolic issues

- **Hypertension**
- **Waist Circumference**
- **Dyslipidaemia**

Strong Family History

Insulin deficiency

- Congenital
- Autoimmune
- Infection
- Toxic
- Other endocrine

? Insulin resistance

•Hyperinsulinaemia

? Insulin deficiency

•B-cell exhaustion / down-regulation /Autoimmune

? Hepatoglucogenesis

•Glucagon excess

? Reduced renal glucose clearance

Insulin resistance

•Hyperinsulinaemia

Insulin deficiency

•B-cell exhaustion / down-regulation

Hepatoglucogenesis

•Glucagon excess

? Reduced renal glucose clearance

Tests to identify Diabetes

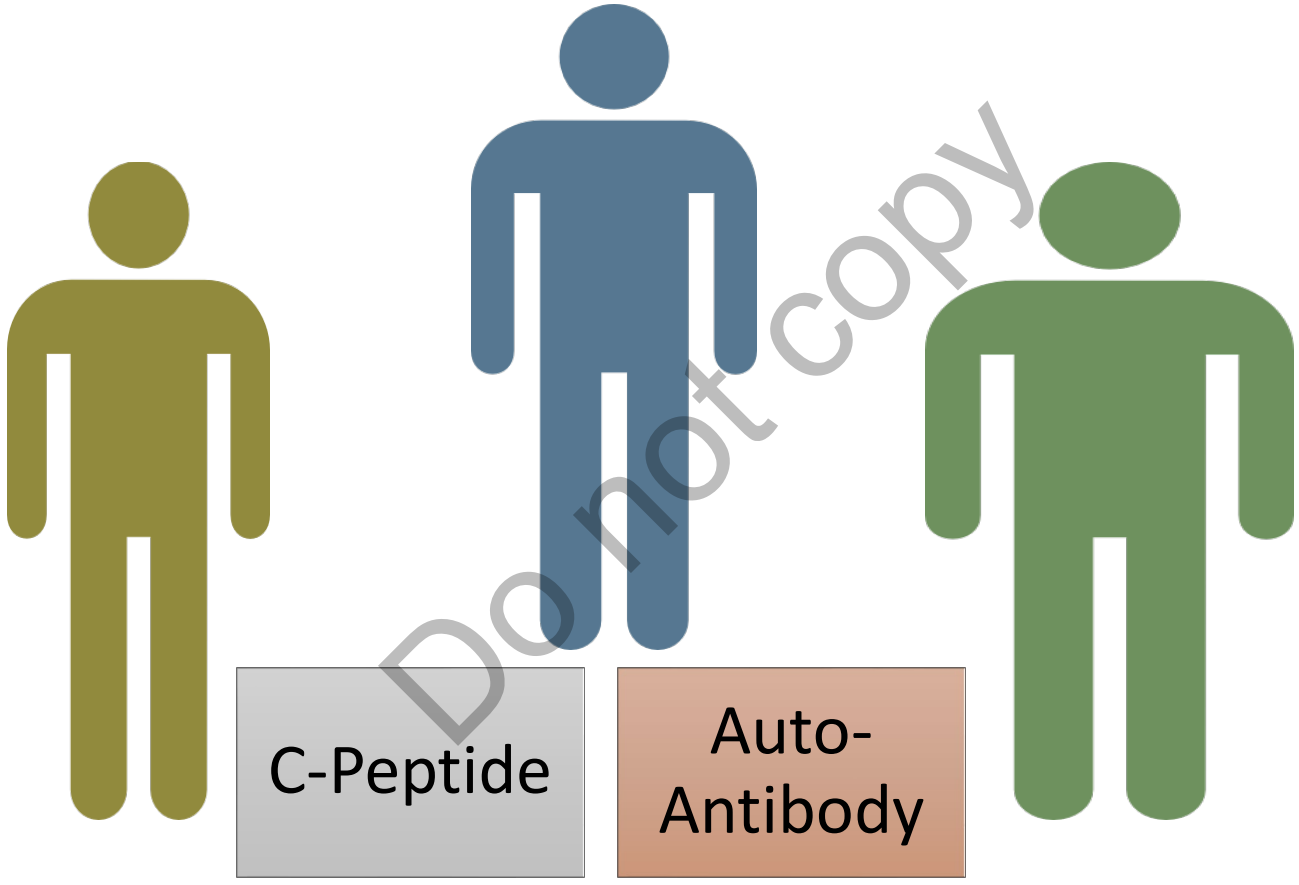
Acute onset

Weight loss

Osmotic Symptoms

Autoimmune disease

Weak Family History



Slow onset

Overweight

Few symptoms

Metabolic issues

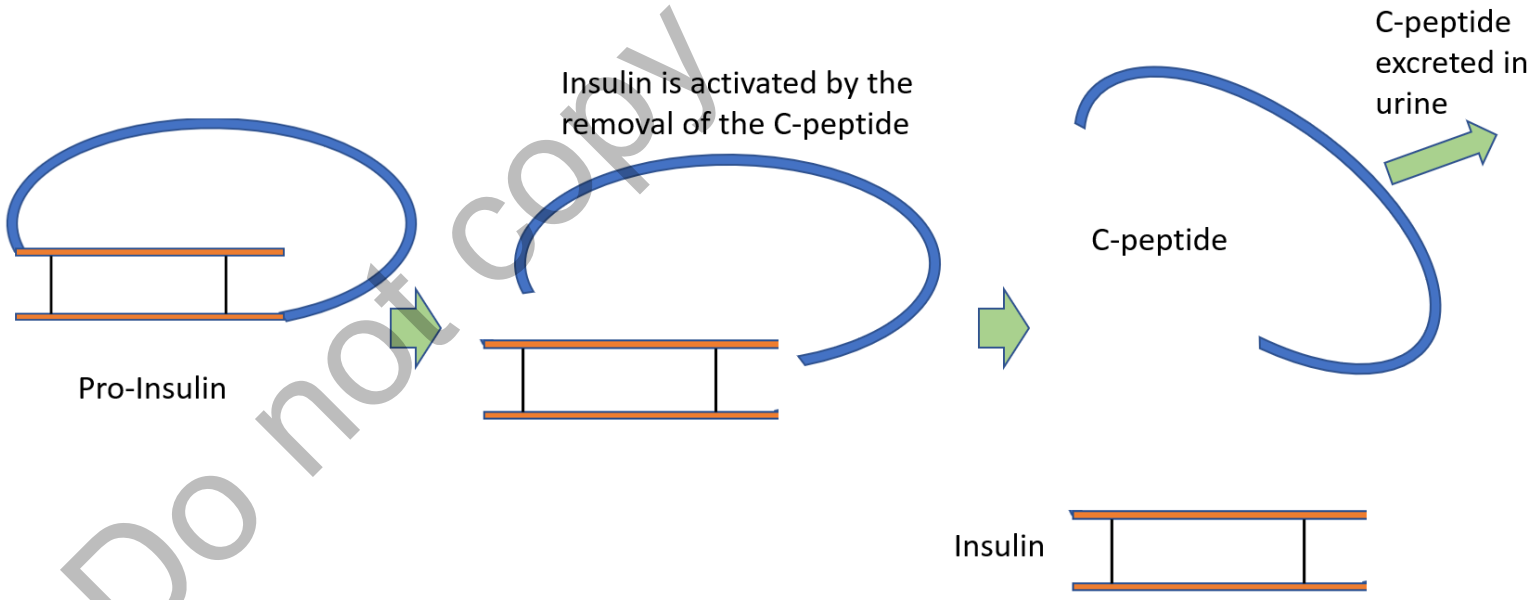
- **Hypertension**
- **Waist Circumference**
- **Dyslipidaemia**

Strong Family History

C-Peptide

C-peptide is a useful indicator of beta cell function, allowing discrimination between insulin-sufficient and insulin-deficient individuals with diabetes.

The urinary C-peptide creatinine ratio (UCPCR) result is best measured on a post prandial sample taken approximately two hours after a meal stimulus.



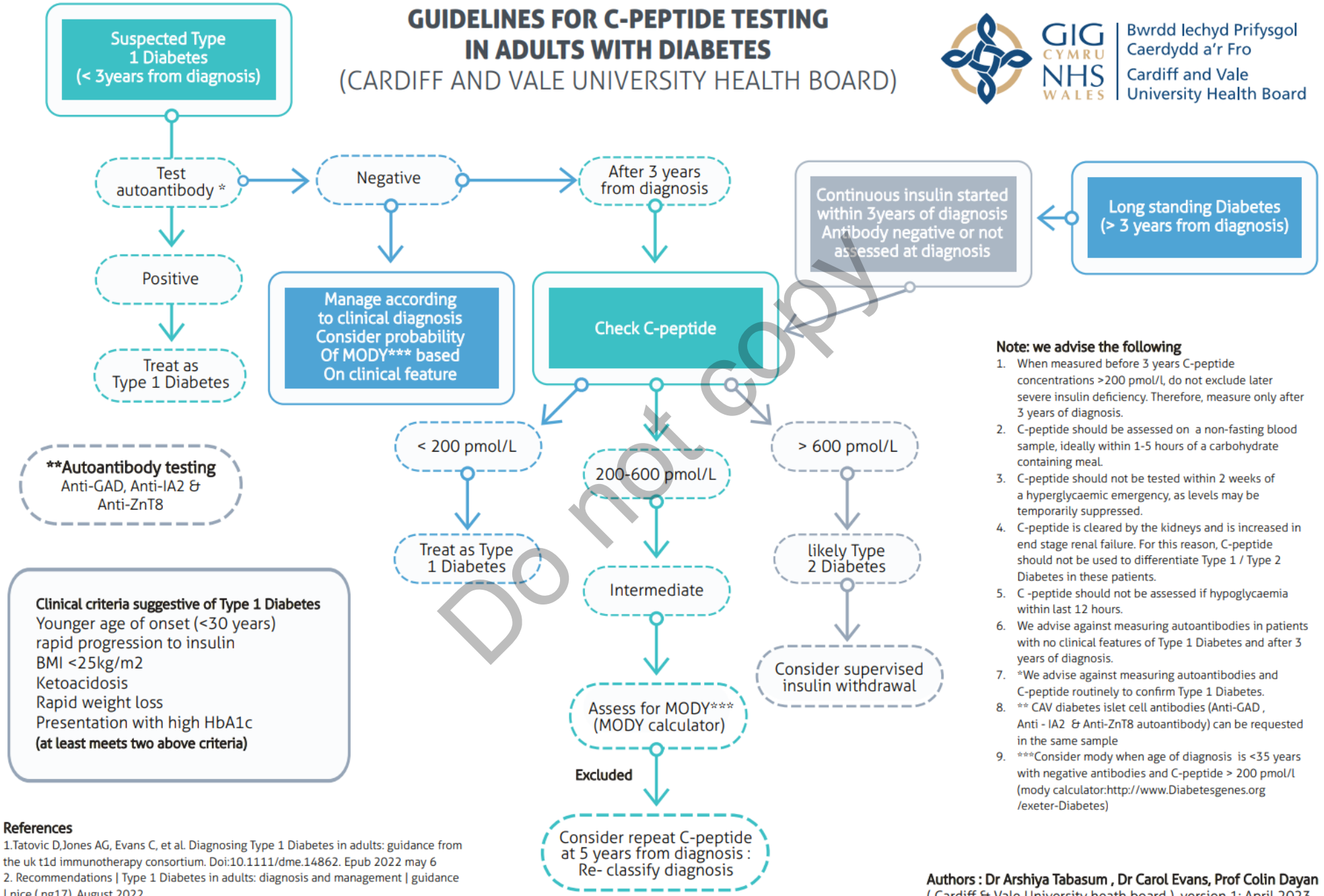
C-peptide

- correlates with diabetes type, duration of disease, and age of diagnosis.
- is associated with microvascular complications.

GUIDELINES FOR C-PEPTIDE TESTING IN ADULTS WITH DIABETES

(CARDIFF AND VALE UNIVERSITY HEALTH BOARD)

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board



****Autoantibody testing**
Anti-GAD, Anti-IA2 & Anti-ZnT8

Clinical criteria suggestive of Type 1 Diabetes
Younger age of onset (<30 years)
rapid progression to insulin
BMI <25kg/m2
Ketoacidosis
Rapid weight loss
Presentation with high HbA1c
(at least meets two above criteria)

Note: we advise the following

1. When measured before 3 years C-peptide concentrations >200 pmol/l, do not exclude later severe insulin deficiency. Therefore, measure only after 3 years of diagnosis.
2. C-peptide should be assessed on a non-fasting blood sample, ideally within 1-5 hours of a carbohydrate containing meal.
3. C-peptide should not be tested within 2 weeks of a hyperglycaemic emergency, as levels may be temporarily suppressed.
4. C-peptide is cleared by the kidneys and is increased in end stage renal failure. For this reason, C-peptide should not be used to differentiate Type 1 / Type 2 Diabetes in these patients.
5. C -peptide should not be assessed if hypoglycaemia within last 12 hours.
6. We advise against measuring autoantibodies in patients with no clinical features of Type 1 Diabetes and after 3 years of diagnosis.
7. *We advise against measuring autoantibodies and C-peptide routinely to confirm Type 1 Diabetes.
8. ** CAV diabetes islet cell antibodies (Anti-GAD , Anti - IA2 & Anti-ZnT8 autoantibody) can be requested in the same sample
9. ***Consider mody when age of diagnosis is <35 years with negative antibodies and C-peptide > 200 pmol/l (mody calculator:http://www.Diabetesgenes.org /exeter-Diabetes)

References

1.Tatovic D,Jones AG, Evans C, et al. Diagnosing Type 1 Diabetes in adults: guidance from the uk t1d immunotherapy consortium. Doi:10.1111/dme.14862. Epub 2022 may 6

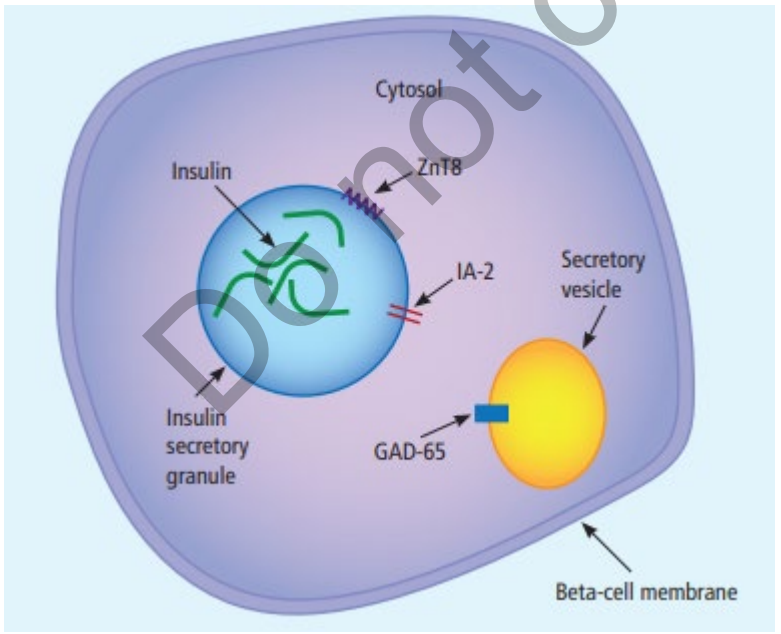
2. Recommendations | Type 1 Diabetes in adults: diagnosis and management | guidance | nice (ng17), August 2022

Authors : Dr Arshiya Tabasum , Dr Carol Evans, Prof Colin Dayan
(Cardiff & Vale University heath board), version 1: April 2023

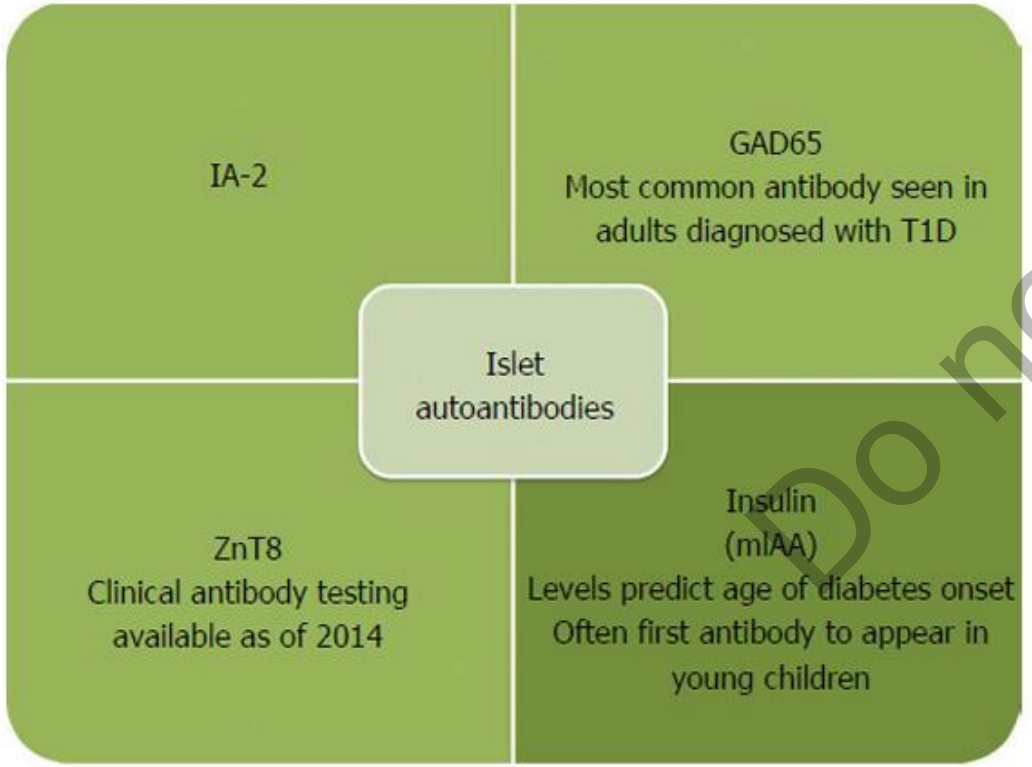
Threshold if Stimulated blood (pmol/L)	Threshold if UCPCR (nmol/mmol)	Interpretation
<200	<0.2	Severe insulin deficiency • Expected in longstanding type 1 diabetes (>3-5 years depending on age of onset) • Associated with an absolute requirement for insulin, high glycaemic variability and high hypoglycaemia risk • Manage as type 1 diabetes • MODY unlikely • Patients with neonatal monogenic diabetes (onset in the first 6 months of life) may have C-peptide in this range but may not require insulin if treated with sulphonyureas
≥200-<600	≥0.2-<0.6	Intermediate insulin secretion • MODY should be considered where a patient with young onset 'type 1' diabetes has C-peptide in this range >3 years from diagnosis • <3% of adolescent onset and <6% of adult onset type 1 diabetes will have persisting C-peptide in this range after 5 years from diagnosis • Most patients with type 2 diabetes will have a C-peptide above this range.
≥600	≥0.6	Substantial endogenous insulin secretion • Associated with type 2 diabetes and MODY and absence of absolute requirement for insulin • May occur in type 1 diabetes in the honeymoon period, particularly if a patient is obese • If >3-5 years from diagnosis Type 1 diabetes unlikely – consider alternative diagnoses

Antibodies

Pancreatic autoantibodies form against components of the pancreatic beta-cell and may be detected in people with type 1 diabetes.



Antibodies



Type 1 diabetes;

- **GAD65: Glutamic decarboxylase;**
- **IA-2: Islet antigen 2;**
- **ZnT8: Zinc transporter 8**

Insulin autoantibodies are often the first antibody to develop in young children.

Adults most often are **GAD65 and IA-2 autoantibody** positive at diagnosis.

The **ZnT8 antibody** is the most recently identified autoantibody with commercial testing now available.

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]

Antibody testing

Children presenting with diabetes should be assumed to have type 1 diabetes at diagnosis, so that there are no delays in initiating life-sustaining insulin treatment.

- Routine pancreatic autoantibody testing is not recommended and is reserved for cases where there may be uncertainty around diagnosis

It is important to test several pancreatic autoantibodies, as a proportion of individuals may be negative to one but positive to another.

- When testing antibodies in adults,
  - 60% of individuals were positive to GAD only;
  - 80% were positive to GAD and/or IA-2.2

Antibody Test results

Positive Test

Not necessarily diagnostic of type 1 diabetes, but may support a clinical diagnosis.

A proportion of individuals have background antibody positivity

- GAD-65 positivity has been reported in between 0.4–4.7% of people who did not develop diabetes over the time period assessed, but had an affected relative

Negative Test

A negative result does not exclude type 1 diabetes.

A proportion of people who have type 1 diabetes clinically do not have antibodies when measured at diagnosis.

Pitfalls of testing

- A positive titre may not be diagnostic of type 1 diabetes
- A negative result does not exclude type 1 diabetes
- When tested after diagnosis, initial positive titres may become negative
- Many laboratories do not offer a panel of autoantibodies and less than complete testing may miss people who are positive to another antibody
- Assays that measure pancreatic autoantibodies may not be standardised
- The significance and interpretation of pancreatic autoantibodies are understudied in people from non-white ethnic groups

Simple recommendations for safe testing

Consider one key question before requesting the test:

- **"how will this result change management of the patient ?"**
- If the answer is that it won't and there is confidence around the diagnosis of type 1 diabetes, it is not worth undertaking the test.

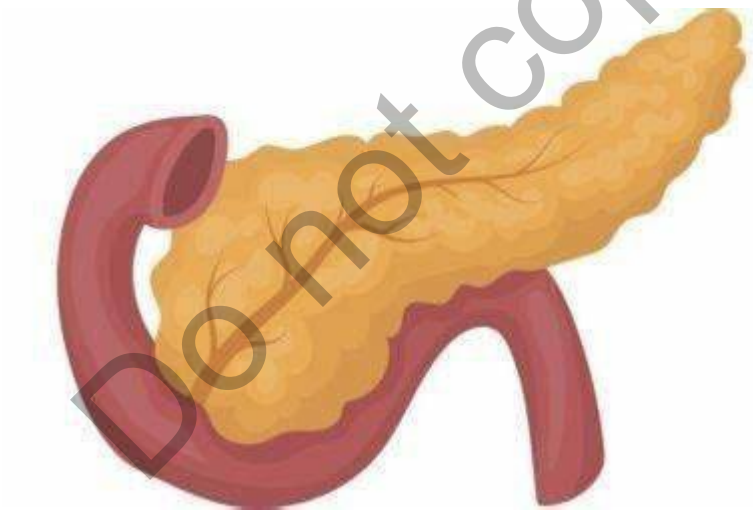
Decision-making around commencing and replacing insulin therapy should primarily be based on clinical parameters.

- If type 1 diabetes is suspected clinically, but the antibody results are negative, do not be put off: remember that insulin remains a safe and appropriate treatment in the majority of cases.

The antibody results should be supporting a diagnosis, directing a treatment pathway or stratifying people for genetic testing.

Test all three antibodies to ensure accuracy in diagnosis

Type 3c



Pancreato-genic **(type 3c)** diabetes

Causes of pancreato-genic diabetes

- Pancreatitis (acute or chronic)
- Pancreatectomy
- Trauma
- Pancreatic carcinoma (can develop early in the disease)
- Cystic fibrosis
- Haemochromatosis (for information, visit www.haemochromatosis.org.uk)

Prevalence 3c

In Western populations estimates vary

- as many as 5–10% of all individuals with diabetes may have type 3c diabetes.

Type 3c diabetes is frequently misclassified (often as type 2 diabetes) and so prevalence is underestimated in practice.

Chronic pancreatitis accounts for around 75% of all cases.

- Alcohol is a common cause of pancreatitis.
- Other causes include smoking, toxic chemicals, autoimmune disease, genetic causes and pancreatic duct obstruction

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-hyroxy 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.

Diet and lifestyle

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

Management

Glycaemic control

- Increased risk of hypoglycaemia and need for blood glucose monitoring. May need to accept higher HbA1c levels.

Metformin:

- first-line therapy for mild hyperglycaemia; low risk of hypoglycaemia; possible protective effect against pancreatic carcinoma.

Sulfonylureas/glinides:

- less effective as beta-cell function declines in type 3c diabetes; risk of hypoglycaemia.

Pioglitazone:

- option if intolerance or contraindication to metformin

DPP-4 inhibitors and GLP-1 receptor agonists:

- generally avoided because of concerns over pancreatitis and pancreatic carcinoma. GLP-1 RA properties of reducing appetite and weight loss not desirable in type 3c diabetes.

SGLT2 inhibitors:

- little evidence but potentially useful; can increase risk of DKA.

Insulin:

- ultimately needed in most cases to deal with insulin deficiency; may be required from outset if HbA1c markedly elevated; treatment of choice in cystic fibrosis-related type 3c diabetes

Management

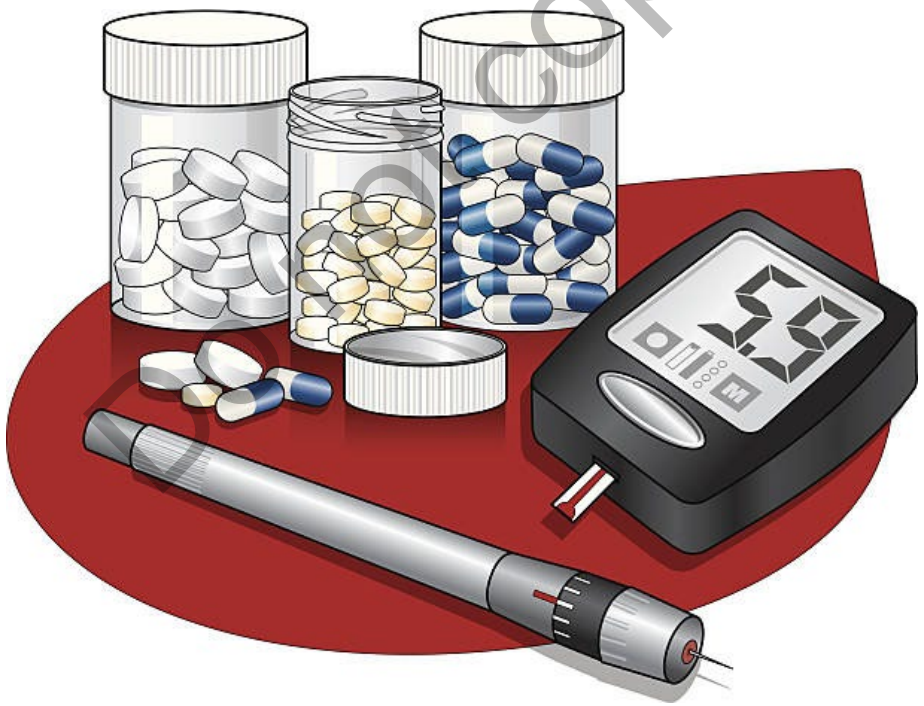
Exocrine issues

- Pancreatic enzyme replacement therapy (PERT; e.g. Creon, Nutrizym, Pancrease, Pancrex) with meals if PEI.
  - Judge response by relief of steatorrhoea, weight gain.

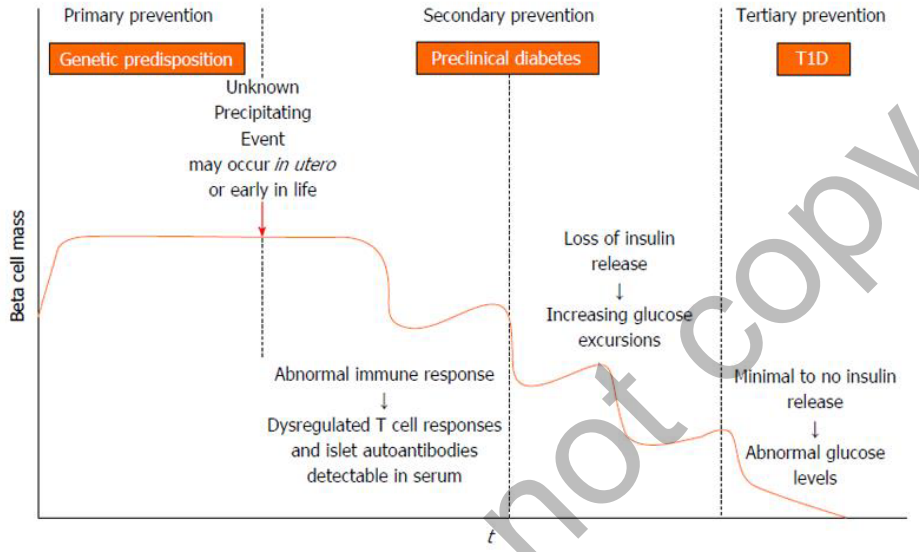
  - PERT can improve digestion of carbohydrates and increase glucose levels.
  - PERT may unmask diabetes in an individual with previously normal HbA1c.

- Vitamin D supplements if proven deficiency.
  - Consider investigations for osteoporosis

LADA



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

Type 2 overlap

Despite the autoimmune nature of LADA and clear genetic overlap with type 1 diabetes, studies on lifestyle and LADA risk indicate that factors such as overweight and physical inactivity that are associated with insulin resistance and type 2 diabetes may also promote LADA.

- This indicates that insulin resistance may play a key role in the pathogeneses of LADA together with autoimmune destruction of the insulin producing beta-cells.

LADA patients tend to have worse glycaemic control than patients with type 2 diabetes

- which may be due to the limited endogenous insulin production.

The combination of poor glycaemic control and insulin resistance, together with other features of the metabolic syndrome may put individuals with LADA at higher risk of complications.

- Evidence indicates that the risk of both micro- and macro vascular complications is at least as high in LADA as in type 2 diabetes patients, in spite of their generally healthier metabolic profile.

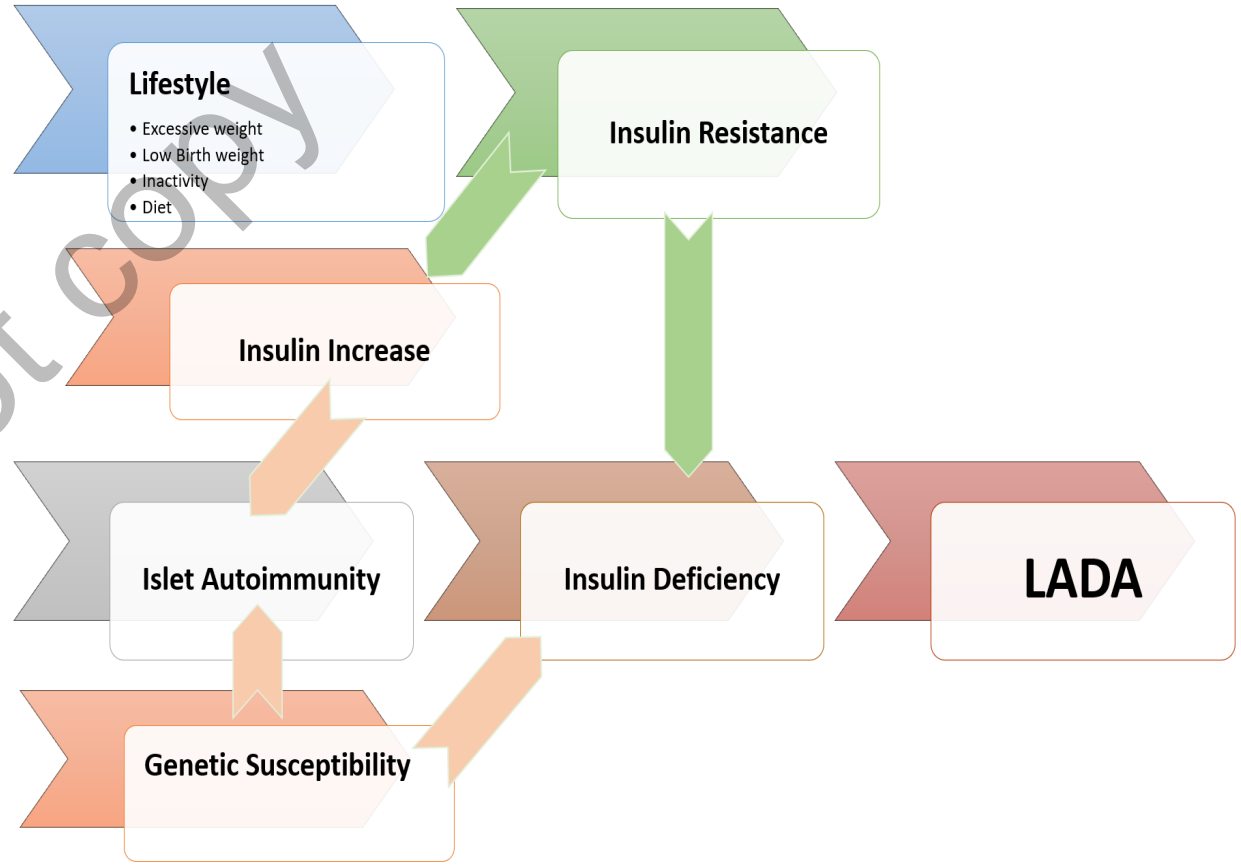
The Pathogenesis of LADA

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



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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

LADA treatments

Sulphonylurea

- SUs are good first-choice agents in type 2 diabetic patients, and LADA.
  - Initially controlling blood glucose, such treatment of LADA might favour early exhaustion of B-cell function because of the stimulatory effect of insulin secretion mediated by SUs.
  - May speed the progression toward B-cell destruction and the need to introduce insulin therapy to control hyperglycaemia.

LADA Treatments

Metformin

- does not stimulate insulin secretion or induce hypoglycemia and does not promote weight gain.
  - Gluconeogenesis is suppressed, and stimulation of peripheral glucose uptake is increased
- does not interfere with the pathogenic process leading to B-cell destruction.
  - By controlling blood glucose levels, metformin may be able to protect B-cells from continuous hyperstimulation of insulin secretion

LADA treatments

Glitazones

- Has primary effect on peripheral insulin action . The glitazones have the potential to preserve endogenous insulin secretory reserve (1).
- There is evidence that glitazones increase insulin synthesis and the insulin content of islet cells as well as improve the secretory response of islets (2)
- Potential anti-inflammatory properties, (reduction of cytokines such as tumour necrosis factor-a and g-interferon)(3)
  - may explain why troglitazone protects animals from development of diabetes(4)

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LADA Treatments

Insulin

- Early intervention with insulin may be protective to the B-cells
  - Allowing B-cell rest
  - High antigen exposure is associated with insulin output

Monogenic Diabetes

Monogenic forms of Diabetes

3b

Forms Associated with Insulin resistance

- Mutation in insulin receptor gene
  - Type A insulin resistance
  - Leprechaunism
  - Rabson-Medenhall Syndrome
- Lipoatrophic Diabetes
- Mutations in PPAR gamma gene

3a

Forms associated with defective insulin secretion

- Mutation in insulin / pro-insulin genes
- Mitochondrial gene mutations **(MIDD)**
- Maturity onset diabetes of the young **(MODY)**

Atypical Diabetes – consider Monogenic forms

Features atypical for type 1 diabetes mellitus including:

- Absence of pancreatic antibodies, especially when measured at diagnosis
- Low insulin requirement for treatment that will persist (more than 3-5 years)
- Lack of ketoacidosis when insulin omitted from treatment

Features atypical for type 2 diabetes mellitus including:

- Onset of diabetes before age 45 years with a normal or low body mass index
- Lack of acanthosis nigricans
- Normal triglyceride levels and/or normal or elevated high-density lipoprotein cholesterol (HDL-C) seen in HNF1A-MODY.

MODY Characteristics

Family history of diabetes with parent affected by MODY monogenic diabetes

Early-onset diabetes in adolescence or young adulthood

- (typically : young age , Mild, stable fasting hyperglycaemia that does not progress or respond appreciably to pharmacologic therapy

Extreme sensitivity to sulfonylureas

Extra-pancreatic features

- (eg, renal, hepatic, gastrointestinal)

A personal history or family history of neonatal diabetes or neonatal hypoglycaemia

A family history of diabetes consistent with autosomal dominant inheritance

this contrasts with type 1 diabetes and type 2 diabetes in the following ways:

- Type 1 diabetes can run in families but is often sporadic: only 2–6% of individuals with type 1 diabetes have an affected parent
- Type 2 diabetes often runs in families with shared environment and risk alleles

- Family history that helps distinguish MODY are onset of diabetes before age 35 years with lack of obesity (in MODY) compared to onset of diabetes after age 45 years associated with obesity

MODY screening

A thorough history,
physical examination,

3+ multigenerational
family history

NO → **MODY- monogenic diabetes unlikely**

YES

Blood testing

- [HbA1c], - normally low diagnostic range
- [GADA], [IA-2A], [ZnT8] antibodies. undetected

NO → **MODY- monogenic diabetes unlikely**

YES

Genetic testing

- Should be performed before attempting specific treatments in most cases.

Additional supportive testing

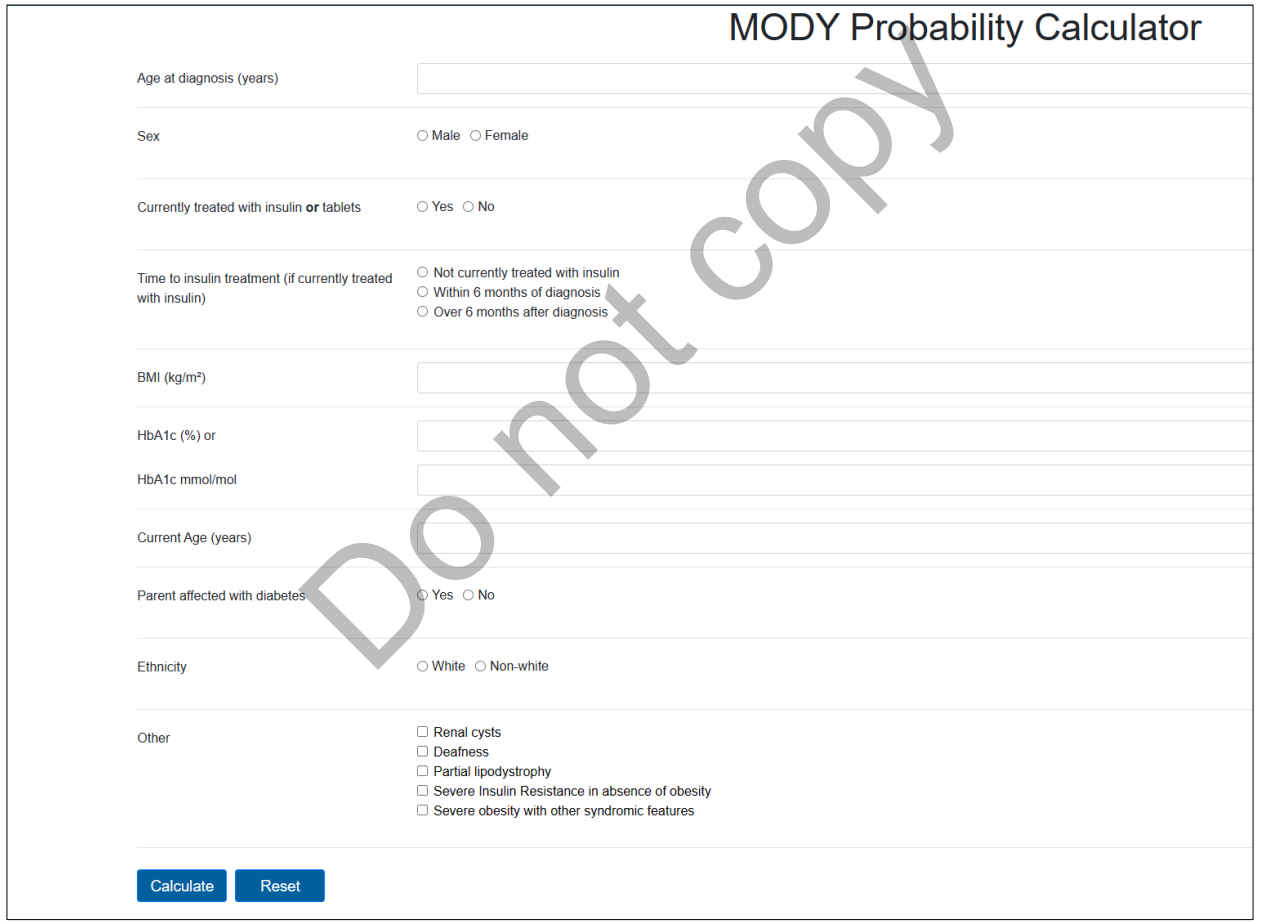
- Preserved C-Peptide at 3-5 years after presentation

High hsCRP (suggestive of *HNF4A*-MODY)

2 hour postprandial UCPCR >0,2mml/mol (distinguishes *HNF1A* and *HNF4A*-MODY from Type 1 diabetes)

Clinical Risk Calculator >25%PPV

MODY Probability Calculator

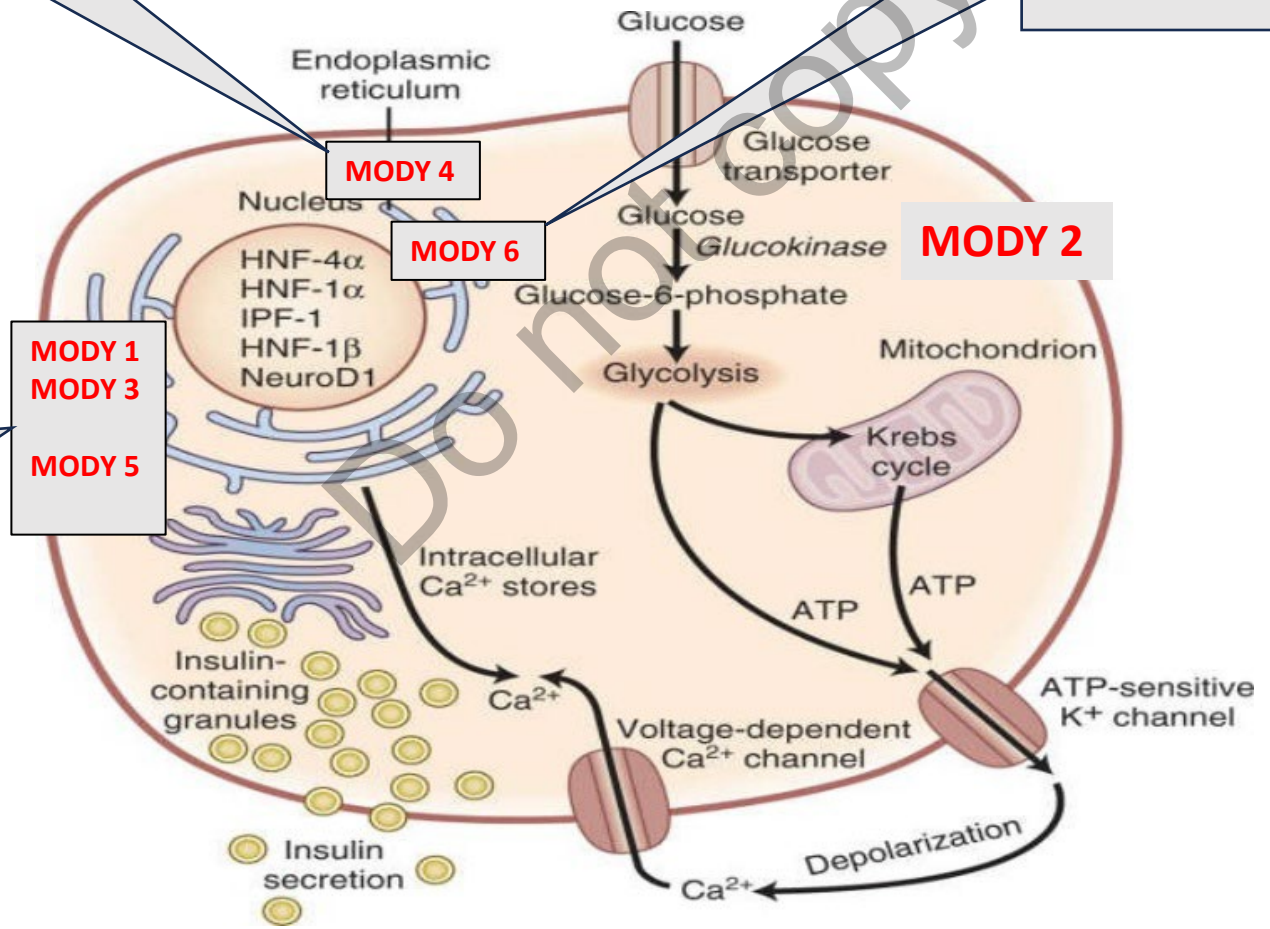


MODY types

glucose-induced stimulation of insulin gene transcription

Activates transcription of insulin gene

Mutations result in defects of insulin secretion response to glucose



MODY – Genetic Testing

Only definitive way to confirm MODY

- Blood / saliva

Not all mutations cause diabetes

50% chance of inheritance (autosomal dominance)

50% chance of gene carriage by 1st degree relatives

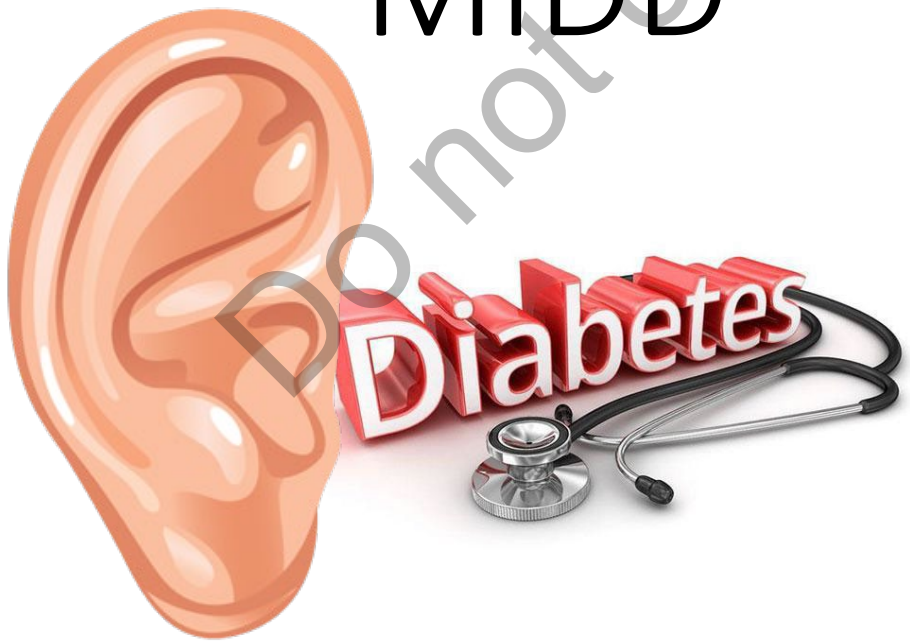
- >95% chance of developing MODY at some time in their life

https://www.diabetesgenes.org/training/find-your-nearest-genetic-diabetes-nurse-and-or-monogenic-clinic/Leanne.Jenkins@wales.nhs.uk

MODY vs Type 2 Diabetes

	MODY	Type 2 Diabetes
Inheritance	Monogenic Autosomal Dominant	Polygenic
Age of onset	Childhood Adolescence Adult <25years	Usually 40-60 Occasionally obese children / adolescence
Pedigree	Multigenerational	Rarely multigenerational
Penetrance	80-95%	Variable 10-40%
Body habitus	Not obese	Usually obese
Dys-metabolic syndrome	absent	Usually present

MIDD



MIDD

- **Maternally inherited diabetes and deafness**

Dominant inheritance

Defect in mitochondrial function

Presents , 40yrs

Defect in beta cell function

- Normal insulin sensitivity
- May respond to diet and oral therapy but usually needs insulin < 2 years
- .....(Metformin interferes with mitochondrial function so probably best avoided)

Often associated with other organ involvement

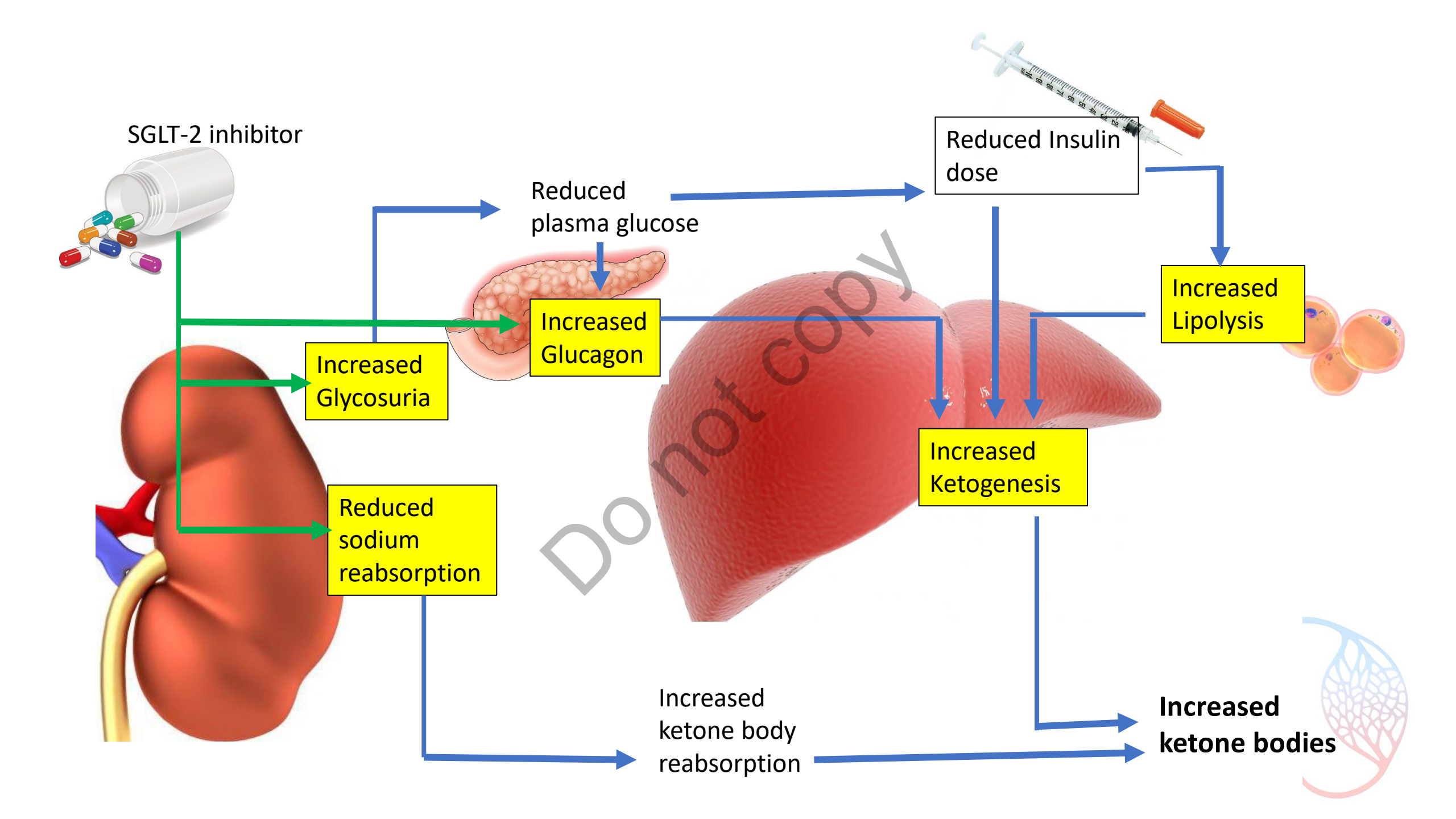
- Pigmented retina
- Liver / renal abnormalities

Ketone Prone Type 2 diabetes

Euglycaemic DKA and SGLT-2 inhibitors

Mechanisms

- **1) Dose reduction of insulin** when used in combination leading to relative insulin deficiency
  - Lower dose of insulin may be insufficient to suppress lipolysis and ketogenesis
- **2) SGLT-2 expressed in alpha cells**
  - SGLT-2 inhibitors promote Glucagon secretion
- **3) SGLT-2 and renal**
  - SGLT-2 inhibitors reduce urinary excretion of ketone bodies
    - Sodium / glucose exchange causes decreased Na+ absorption driving carrier mediated reabsorption of positively charged ketone bodies
      - **(using urinary ketones as a detection method for DKA is not recommended if on SGLT-2 inhibitor)**


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
Do not copy

James

- 48yr business man
- NIDDM for 10 years
- Weight gain over past 4 years (BMI 31Kg/m2)
- FH – Mother and sisters with NIDDM

- HbA1c 67mmol/mol
- Cholesterol 5.4mmol/l

Unwell with chest infection for past week

Random BG 26mmol/l

Urinary Ketones +++

Metformin 1g bd
Gliclazide 80mg bd
Atorvastatin 20mg

FLATBUSH Diabetes

Ketone Prone Type 2 diabetes

Ketone Prone Type 2 diabetes

Ketones - Traditionally believed to be caused by absolute deficiency of insulin and seen in type 1 diabetes

In type 2 diabetes , there is always believed to be enough insulin to suppress lipolysis and prevent ketogenesis

Some people with type 2 can develop ketones

- Acute reduced production coupled with insulin resistance
  - ‘ ketone prone type 2’
  - ‘Flatbush’ or ‘type 1b diabetes ‘
- Particularly seen in Afro Caribbean (20-50% presenting with DKA will have type 2 diabetes) and non-white ethnicity

Umpierrez et.al Ketosis prone type 2 diabetes mellitus , Ann Intern Med 2006:144;350-7

Aetiology of DKA risk

Polymorphism of key transcription factors involved in islet cell development

Glucose 6 phosphate dehydrogenase deficiency

- Leading to reduced B cell function at times of oxidative stress

Differs from Type 1 as endogenous insulin recovers over a relatively short period of time

Long term Outcomes

Consensus from specialist centres suggest that following admission with DKA , all patients should be discharged on insulin

- Studies have shown 70% will have further DKA <2yr if treated with diet and lifestyle alone (1)
- Oral agents seem to reduce recurrence
  - SU reduced by 72% (2)
  - Pioglitazone reduced by 68% (3)

1)Mauvais-Jarvis et.al. Diabetes 2004.53:645-653
2)Umperiez et.al. Diabetes Care.1997; 20:479-483
3)Sanarji et.al. Diabetes.1995:45;337-341

Recognising Ketone prone type 2

Should be considered in all non-white presenting with DKA

- But has been reported in white ethnicity (1)

Generally

- Older
  - But 20-30% type 1 present over the age of 20years (2)
  - Ketone prone type 2 has been found in children
- More overweight
- Family history of type 2

1)Umiperriez GE Ketosis prone type 2 diabetes . Time to revise the classification of diabetes. Diabetes Care 2006:29;2755-7
2) Sidley D et.al. update on diagnosis . Pathogenesis and management of ketosis prone type 2 diabetes. Diabetes Manag 2011;11:589-600

Management

Autoimmunity and B cell function should be assessed 1-3 weeks post DKA

- C-peptide levels will recover in weeks to months
  - (hall mark of Ketone prone type 2)
- Glucagon stimulated C-Peptide is currently the best predictor of long-term insulin independence [1]

Balasubramaynyam et.al Diabetes Care. 2006:29; 2575-2579

Factor	Type1	Ketone prone type 2	Type2
Primary abnormality	Insulin deficiency	Temporary reduced insulin secretion and sensitivity	Insulin resistance and B cell dysfunction
Course	Fast & progressive decline in insulin secretion	Relapsing remitting course	Progressive insulin resistance and insulin secretory defect
Development of ketones	Due to absolute insulin deficiency	Acute lack of insulin action	Relative insulin deficiency likely to prevent ketosis
Age			
Ethnicity	Non discriminatory	Mainly Afro-Caribbean / Hispanic	Non discriminatory
Presentation	Hyperglycaemia +/-DKA	Hyperglycaemia +/-DKA	Hyperglycaemia +/- HONK
Duration of symptoms	Days - weeks	weeks	months
Family history	30%	80-100%	30-80%
Treatment with orals	Needs insulin	Can be maintained on oral agents for a time	First line oral
Autoantibodies	present	absent	absent
C peptide at follow up	Absent / reduced	Preserved	Preserved

Other Diabetes

Classification

Diseases of exocrine pancreas

- Pancreatitis
- Trauma / surgery
- Pancreatic destruction
  - Cystic fibrosis
  - Haeamchromatosis
- Neoplasia

Endocrinopathies

- Cushing's
- Acromegally
- Pheochromocytoma
- Glucagonoma
- Hyperthyroidism
- Somatostatinoma

Other Diabetes

Classification

Genetic Syndromes

- Down's Syndrome
- Klinefelter
- Lawrence-Moon-Biedl Syndrome
- Prader-Willi
- Wolfram (DIDMOAD)

Drug induced

Gestational Diabetes

Genetic Defects of insulin action

“Not Everything is as it seems”

Charles Westmoreland