Review of Diabetes

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Definition of Diabetes

Diabetes mellitus, or simply Diabetes, is a group of metabolic diseases in which a person has high blood glucose, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced

Types of Diabetes

- Type 1 Diabetes results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump / previously referred to as “insulin-dependent diabetes mellitus” (IDDM) or “juvenile diabetes”

- Type 2 Diabetes results from insulin resistance sometimes combined with insulin deficiency / previously referred to as “non insulin-dependent diabetes mellitus” (NIDDM) or “adult-onset diabetes”

- Gestational Diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level

Classification of glycaemic states and diagnosis of diabetes

Diagnosis	Timing	Plasma glucose (mmol/L)
Normal physiology	fasting	< 6.1
	2 hr post meal	< 7.8
Impaired fasting glucose	fasting	6.1-7.0
	2 hr post OGTT	< 7.8
Impaired glucose tolerance (↑ CV risk)	fasting	< 7.0
	2 hr post OGTT	7.8-11.0
Diabetes mellitus (↑ CV risk)	fasting	> 7.0
	2 hr post OGTT	>11.1

Diagnosis of Diabetes

- Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl)

- Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test

- HbA1c ≥ 6.5% (48 mmol/mol)

- Diagnosis of diabetes is based on

❖ **2** positive findings from the list above (this can include a repeat fasting blood glucose on a different day)

OR

❖ Symptoms of hyperglycemia and random plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

COMPLICATIONS IN DIABETES

- Acute
  - Diabetic ketoacidosis (DKA)

    Type 1 diabetes
  - Hyperosmolar hyperglycaemic state (HHS)

    (previously known as HONK)

    Type 2 diabetes Elderly
  - Hypoglycaemia

- Chronic
  - Microvascular
  - Macrovascular

DIABETIC KETOACIDOSIS (DKA)

DKA PATHOPHYSIOLOGY

- Complete lack of insulin signals starvation
- Compensatory hormones are secreted
  - glucagon
  - catecholamines
  - cortisol
  - growth hormone
- Ketone bodies are produced FRUITY SMELL
- Acidosis develops RAPID, DEEP BREATHING (AIR HUNGER)

DKA PATHOPHYSIOLOGY

- Hyperglycaemia results in glycosuria
- Glycosuria causes an osmotic diuresis
- There is depletion of water, sodium, potassium, chloride, calcium, phosphate and magnesium DEHYDRATION

INVESTIGATIONS

- Blood glucose
- Urinary ketones
- Arterial blood gases
- Electrolytes
- Osmolality
- Lactate
- FBC
- ECG
- Cardiac enzymes
- Amylase
- CXR
- Blood Cultures
- MSU

LABORATORY FINDINGS

- Blood glucose 25-40 mmol/l
- Ketonuria
- ABGs
  - pH < 7.3
  - HCO_3^- < 20 mmol/l
  - CO_2 low
  - O_2 high / normal

- Na^+ 130-135 mmol/l
- K^+ 4.8-6 mmol/l
- Urea 10-15 mmol/l
- Osmolality 310-330 mOs/l
- Lactate 4.5-5 mmol/l

DKA MANAGEMENT

- Fluid replacement
- Insulin replacement
  – sliding scale and early dose of background insulin
- Potassium replacement
- Heparin if immobile or unconscious
- Find and treat cause if possible

HYPEROSMOLAR HYPERGLYCAEMIC STATE (HHS)

HHS PATHOPHYSIOLOGY

- Marked hyperglycaemia (usually > 50mmol/l), without significant ketosis or acidosis
- Osmotic diuresis

SEVERE DEHYDRATION

CONFUSION

↓ LOC

FOCAL NEUROLOGY

COMA

INVESTIGATIONS

- Blood glucose
- Urinary ketones
- Arterial blood gases
- Electrolytes
- Osmolality
- Lactate
- FBC
- ECG
- Cardiac enzymes
- Amylase
- CXR
- Blood Cultures
- MSU

LABORATORY FINDINGS

- Blood glucose 50-80 mmol/l
- pH ± normal
- HCO_3^- 15-19 mmol/l
- Na^+ 150-165 mmol/l
- K^+ 4.5-5 mmol/l
- Creatinine 50-520 mmol/l
- Osmolality 375-420 mOs/l

HHS MANAGEMENT

- This is the same as for DKA
- **BUT**
  - Less insulin requirement
  - More cautious fluid replacement
  - Low threshold for CVP line insertion
  - **MUST** use prophylactic s/c heparin

HYPOGLYCAEMIA

- Common side-effect of treatment with insulin or sulphonylureas
- Does not occur with metformin or diet alone
- Each year 25-30% of all insulin treated patients have one or more episodes of severe hypoglycaemia

HYPOGLYCAEMIA

- Predisposing factors
  - Inadequate food intake
  - Excess dosage, error by patient or doctor
  - Exercise
  - Weight loss
  - Alcohol
  - Adrenocortical, thyroid or pituitary failure
  - Renal failure

HYPOGLYCAEMIA MANAGEMENT

- Mild
  - Treat immediately with oral glucose (15-20g)
- If patient unable to swallow
  - IV 50% dextrose (30-50 ml)
  - IM glucagon (1mg)
- Patients should recover immediately
- Failure to recover may be due to cerebral oedema, postictal state or other causes of coma

HYPOGLYCAEMIA MANAGEMENT

- Hypoglycaemia induced by sulphonylureas may be very prolonged
- May need IV glucose for hours or even days

CHRONIC DIABETIC COMPLICATIONS

- Microvascular
  - Nephropathy
  - Retinopathy
  - Neuropathy

- Macrovascular
  - Heart disease
  - Stroke
  - Peripheral vascular disease
  - Hypertension

RISK FACTORS FOR CHRONIC DIABETIC COMPLICATIONS

- Hyperglycaemia
- Hypertension
- Dyslipidaemia
- Excess weight
- Smoking
- Disease duration
- Family history

DIABETES MANAGEMENT

- Dietary changes
- Exercise
- Smoking cessation
- Weight control
- Glycaemic control
- Blood pressure control
- Lipid control
- Foot care
- Screening for complications

SCREENING FOR COMPLICATIONS

- Screening for retinopathy

  Fundoscopy through dilated pupils, retinal photography and fluorescein angiography where indicated

- Screening for microalbuminuria

  Albumin/creatinine ratio in random spot urine sample

  24-h urine collection with creatinine

  Timed urine collection (4-h or overnight)

SCREENING FOR COMPLICATIONS

- Screening for neuropathy

  Examination of the feet for sensory loss, absent ankle reflexes, ulcers, calluses and deformities

  Inspection of footwear

  Examination for loss of heart rate variability with measurement of expiration-to-inspiration ratio and response to the Valsalva manoeuvre and standing

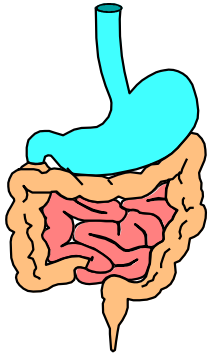
- Screening for macrovascular disease

  Examination of the feet for absent peripheral pulses

  Screening for macrovascular disease otherwise indicated only in symptomatic patients

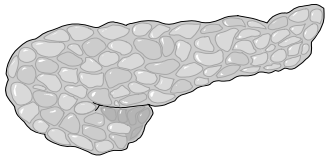
GLYCAEMIC CONTROL IN TYPE 2 DIABETES

Regulation of Blood Glucose in Type 2 Diabetes



Glucose Influx

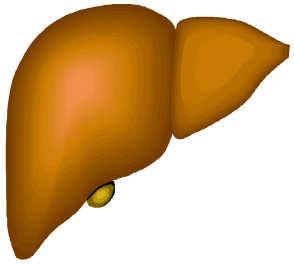
↑ Glucagon Secretion



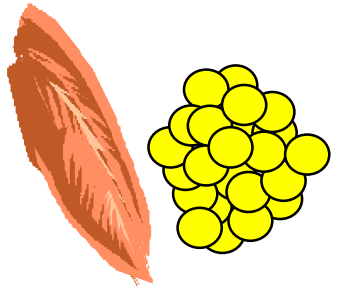
↑ Hepatic Glucose Output

Plasma Glucose

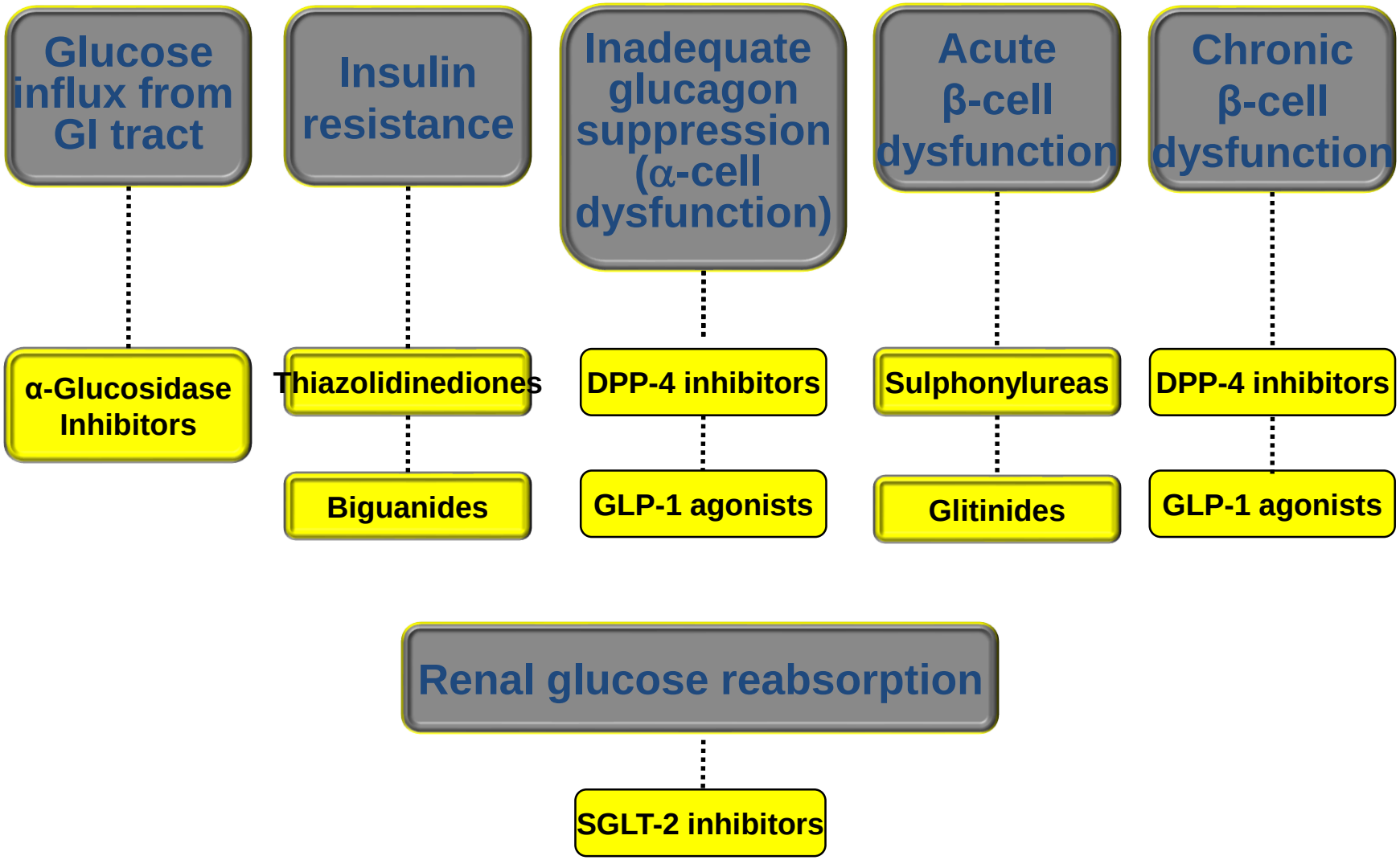
↓ Insulin Secretion



↓ Peripheral Glucose Uptake



Hypoglycaemic Agents Covering the Metabolic Needs of Type 2 Diabetes



α-Glucosidase Inhibitors (Acarbose)

- Decrease intestinal glucose absorption

- Advantages

  Do not cause hypoglycaemia when used as monotherapy

- Disadvantages

  Gastrointestinal side effects (abdominal discomfort, flatulence, diarrhoea)

  Contraindicated in intestinal diseases such as Crohn's disease and in autonomic neuropathy affecting the GI tract

Biguanides (Metformin)

- Decreases appetite and intestinal glucose absorption
- Decreases hepatic glucose output and increases muscle glucose uptake

Biguanides (Metformin)

- Advantages

  Does not cause hypoglycaemia when used as monotherapy

  Does not cause weight gain and may contribute to weight loss

- Disadvantages

  Gastrointestinal side effects (abdominal distension, nausea, diarrhoea)

  Lactic acidosis (1:35,000 patient-years)

  Should be withheld for 24h before and 48h after investigation requiring iv contrast administration

  Contraindicated in any severe organ failure

Insulin Sensitizers (Thiazolidinediones/Glitazones)

- Unique oral insulin sensitizing agents
- Decrease hepatic glucose output and increase muscle glucose uptake
- Change fat distribution by decreasing visceral fat and increasing peripheral fat

Insulin Sensitizers (Thiazolidinediones/Glitazones)

- Advantages

  Do not cause hypoglycaemia when used as monotherapy

  Preserve endogenous insulin secretory reserve

  Decrease glucose, insulin, triglycerides, LDL-C, blood pressure and increase HDL-C

- Disadvantages

  Weight gain, fluid retention, mild anaemia, upper respiratory tract infections, headaches

  Contraindicated in heart disease and liver disease

Sulphonylureas

- Stimulate insulin secretion by β-cells

- Advantages

  Potent in reducing blood glucose

  Reasonable gastrointestinal tolerability

  Variety of choices

  Newer 3rd generation agents less likely to cause hypoglycaemia and taken once a day therefore aiding compliance

Sulphonylureas

- Disadvantages

  Weight gain

  Hypoglycaemia with older generation agents especially in the elderly

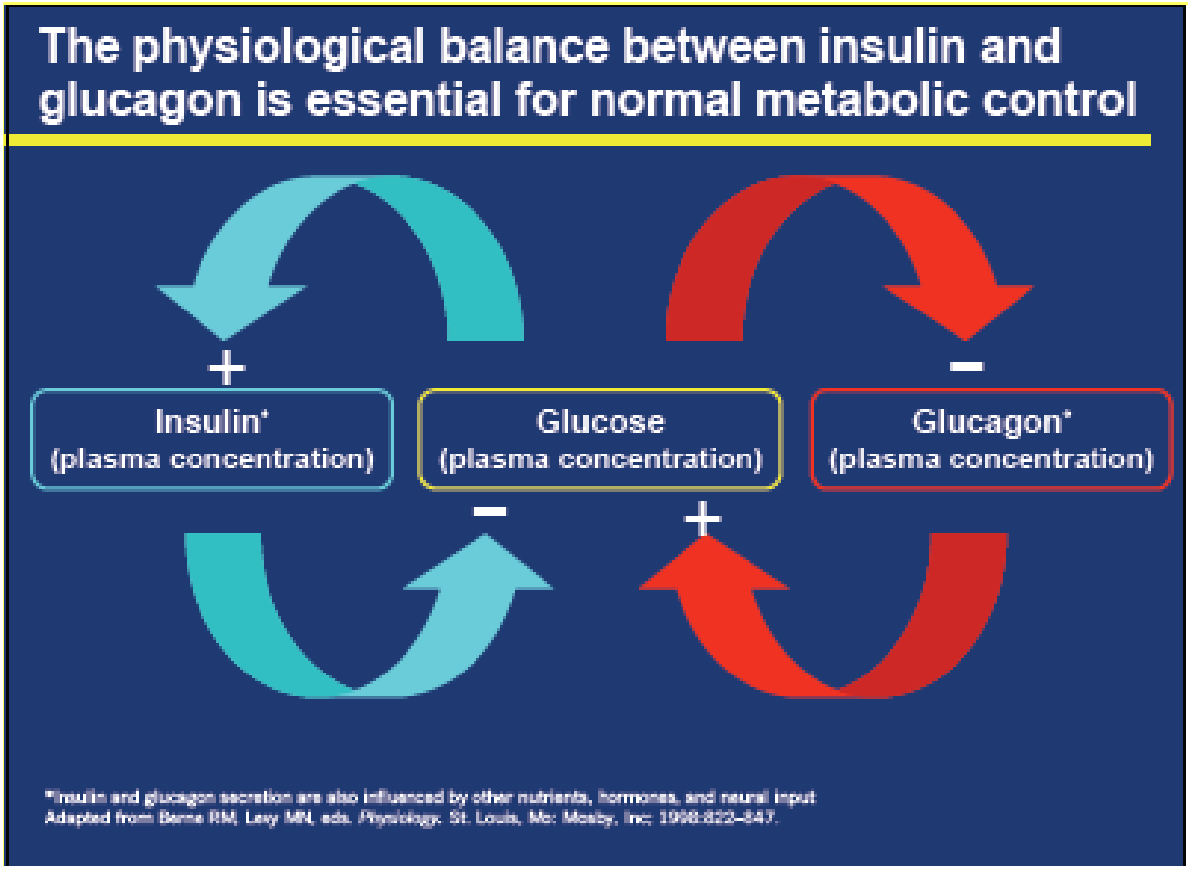
  Increase hyperinsulinaemia and insulin resistance

  Caution in renal failure

  Drug interactions

  Potency starts decreasing after 1 year

NEWER THERAPIES IN TYPE 2 DIABETES



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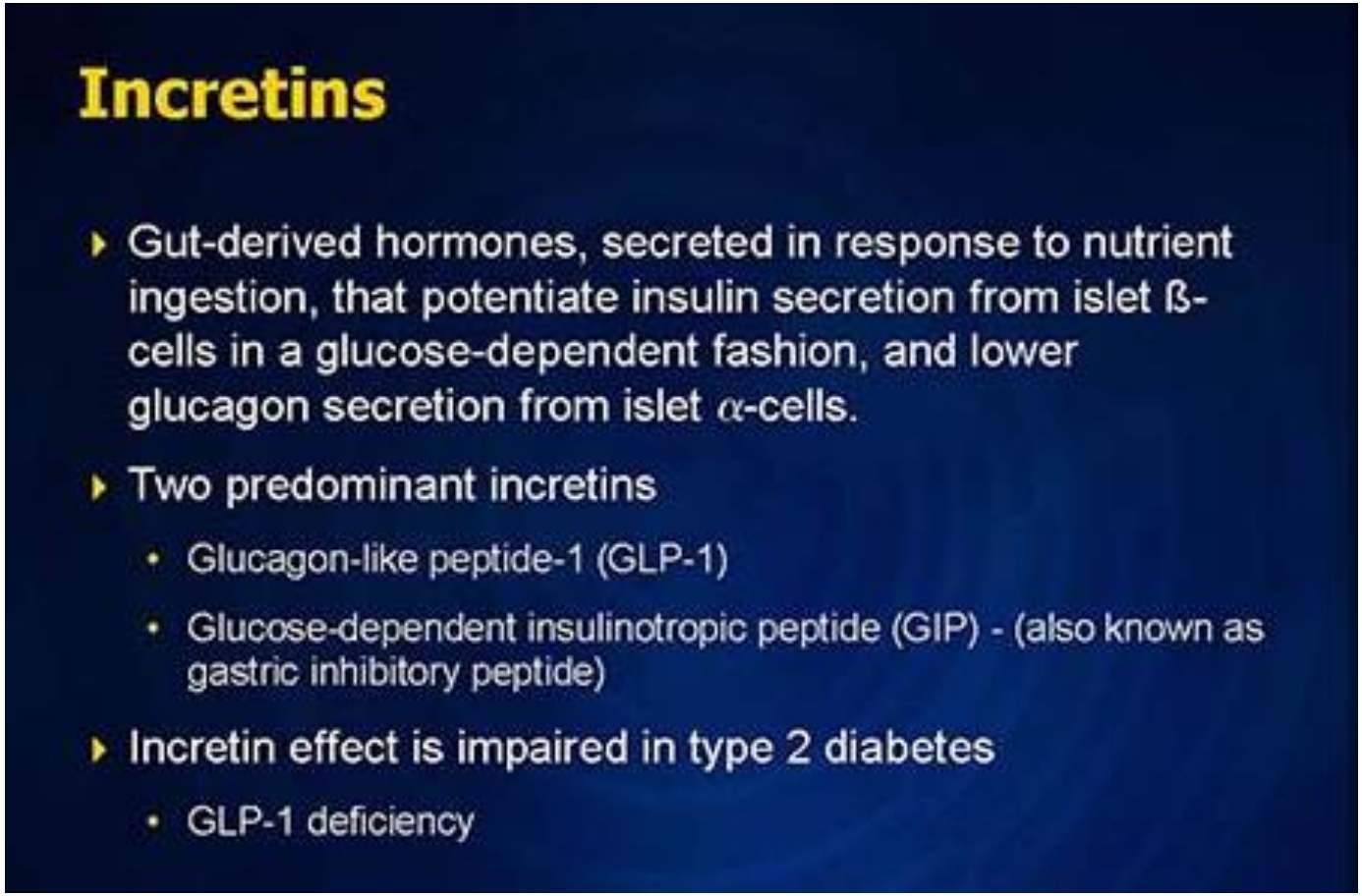

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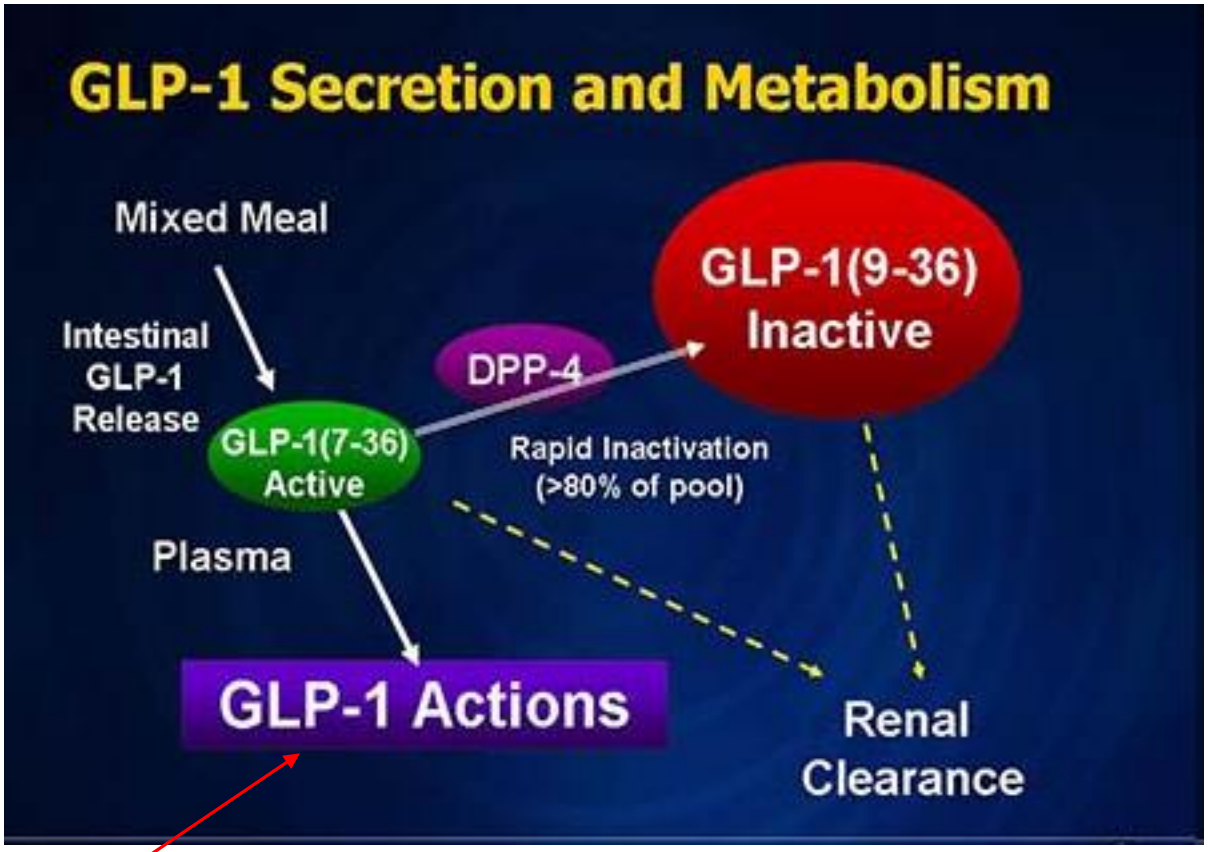
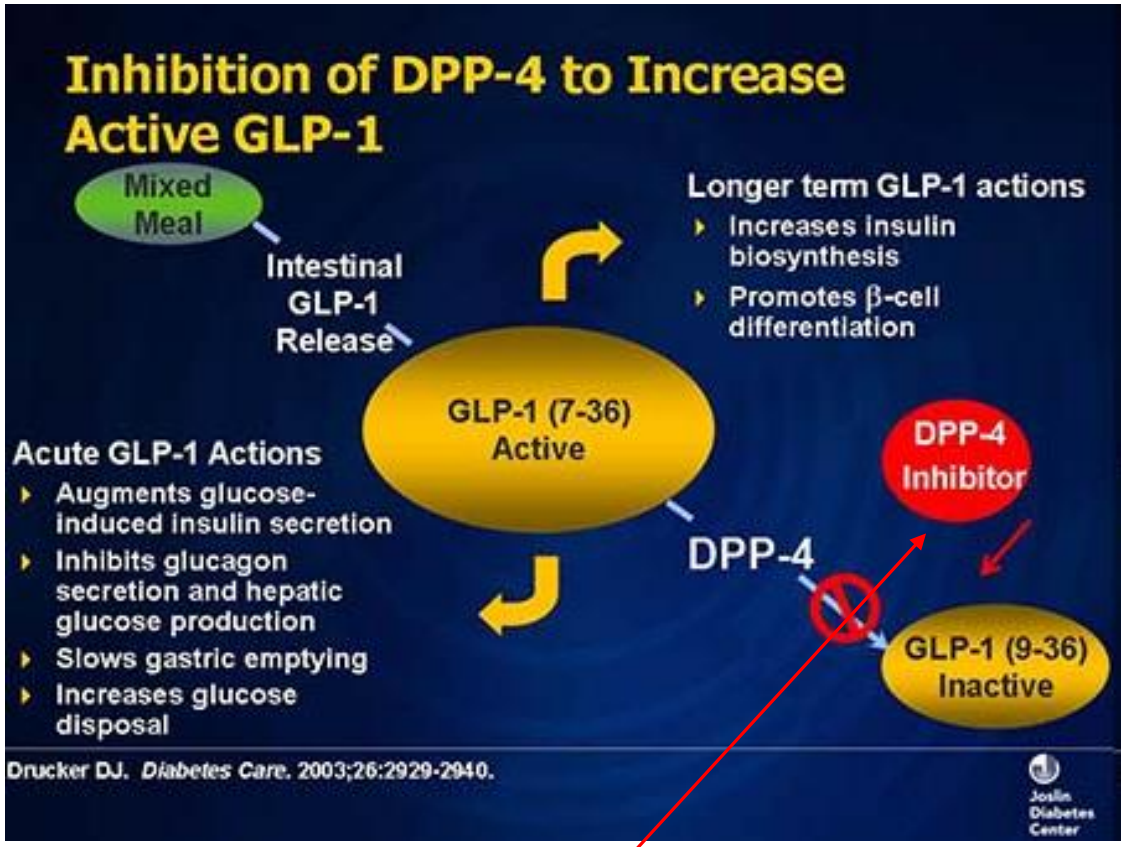


GLP-1 agonists

- **Control postprandial hyperglycaemia by increasing insulin, lowering glucagon and slowing gastric motility**
- **Administered by subcutaneous injection once a day or once a week**
- **Significant benefit in patients with cardiovascular disease**
- **Weight loss, nausea, pancreatitis**

NEWER THERAPIES IN TYPE 2 DIABETES



DPP-4 inhibitors

- **Oral administration**
- **May require dose reduction in renal impairment**
- **Weight neutral**
- **No gastrointestinal side effects**

SGLT-2 Inhibitors

- Act by inhibiting sodium-glucose transport protein 2 in the kidney therefore inhibiting glucose reabsorption and lowering blood glucose
- Reduce weight and blood pressure
- Significant benefit in patients with chronic kidney disease, cardiovascular disease and heart failure
- Increased risk of genital fungal infections and urinary tract infections

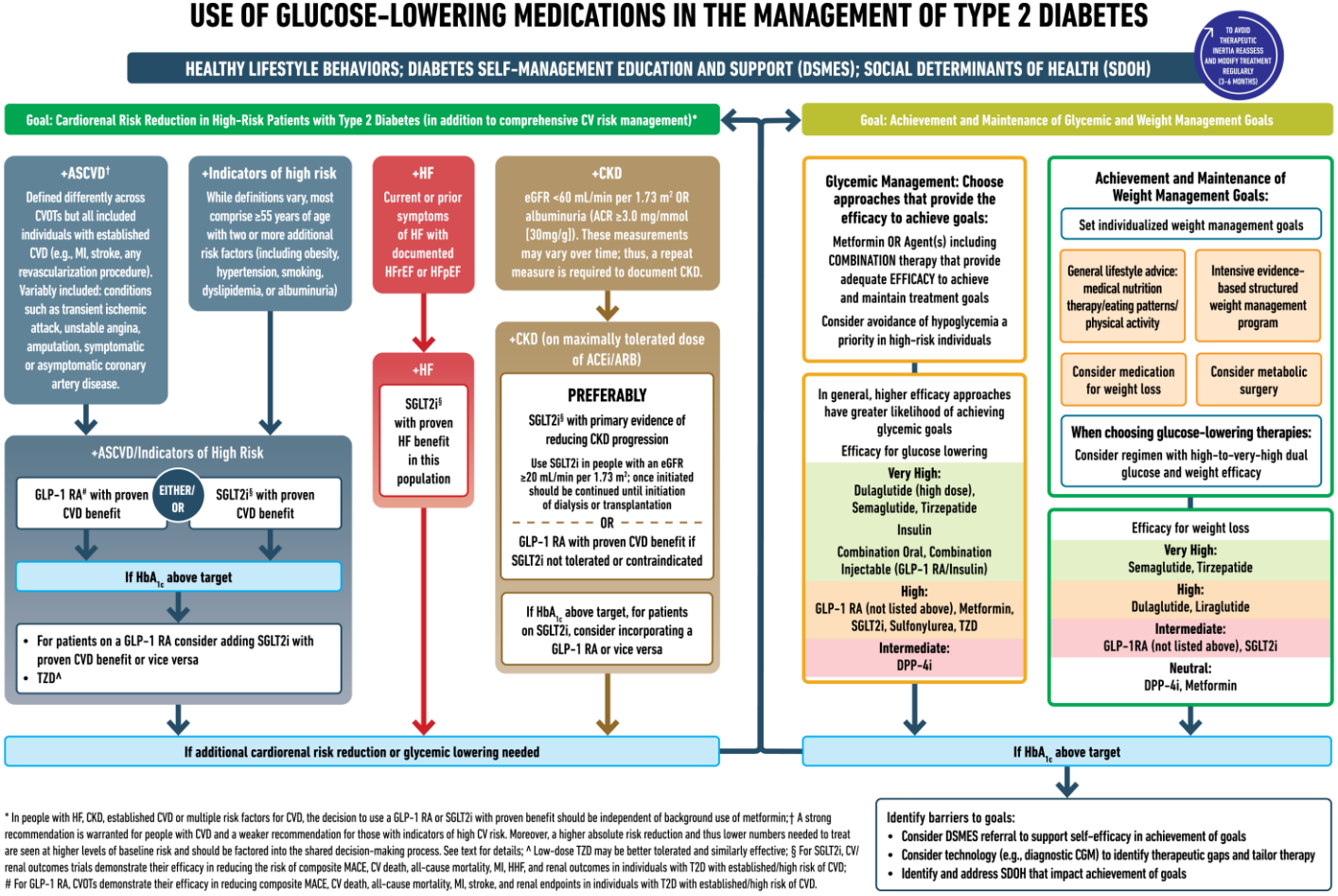
Insulin Therapy in Type 2 Diabetes

- Most patients with type 2 diabetes eventually need insulin
- Basal insulin is initially added to hypoglycaemic agents
- As insulin deficiency progresses, basal insulin and bolus insulin are combined, and hypoglycaemic agents are discontinued

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Diabetes Care. 2022;45(11):2753-2786. doi:10.2337/dci22-0034

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

GLYCAEMIC CONTROL IN TYPE 1 DIABETES

Type 1 Diabetes

Only treatment is insulin

Benefits of Insulin Analogues

- **Rapid-acting**

  Injection timing

  More predictable insulin levels

  Fewer hypoglycaemic episodes

  Quality of life

  Fewer snacks

- **Long-acting**

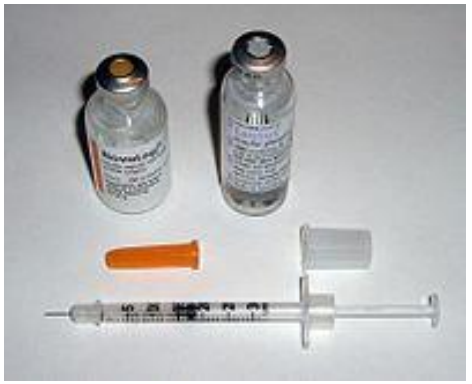
  Little peak activity

  Less variability in absorption

  Fewer hypoglycaemic episodes

Insulin Devices

- Syringes



- Pens

- Pumps