Type 1 and Type 2 Diabetes

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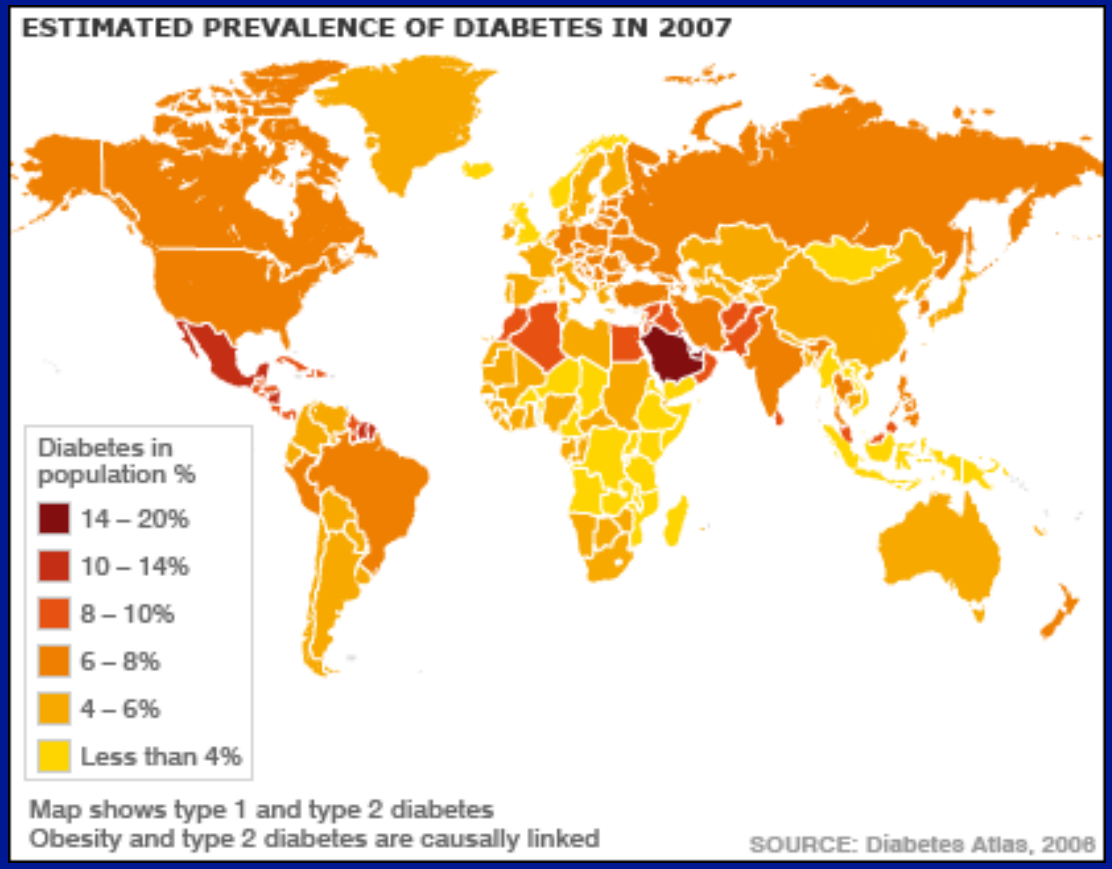
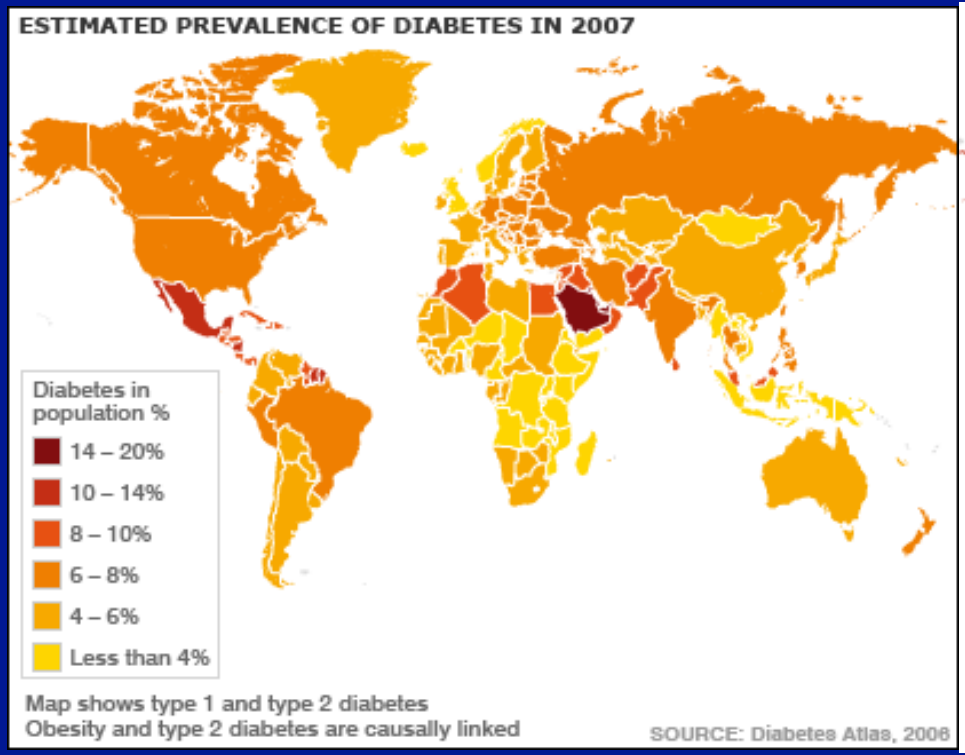
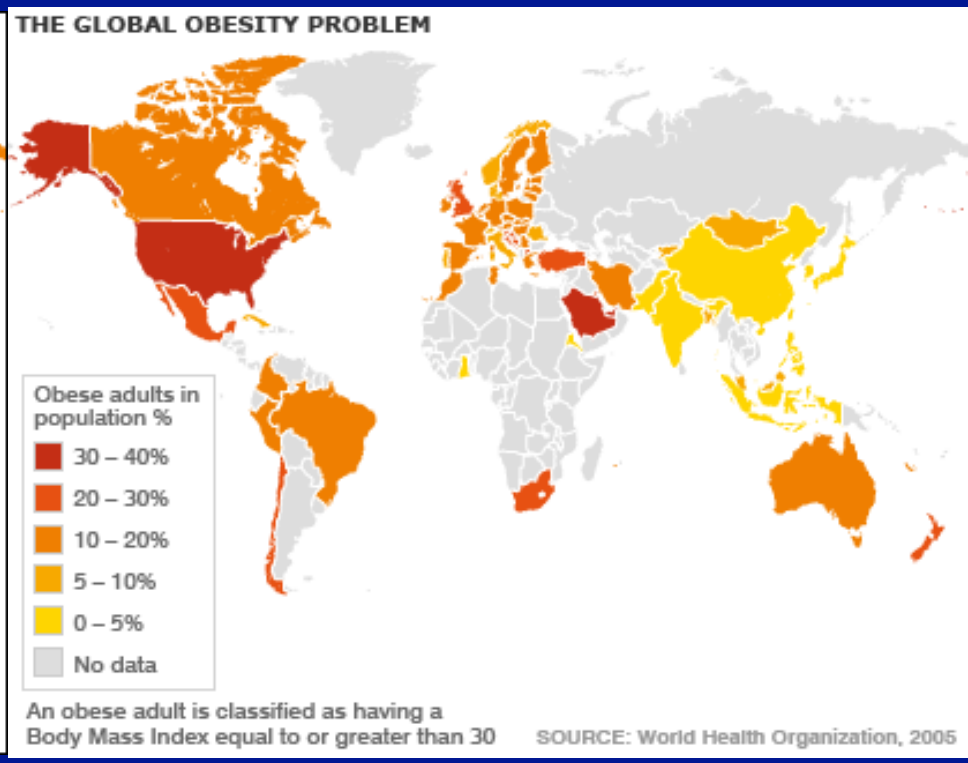
Worldwide, there are >170 million with diabetes mellitus
2.7 million in UK (nearly 1 in 20)



- This prevalence will double before 2030
- Worldwide 3.2 million deaths annually attributable to diabetes
- Commonest cause of end stage renal failure, blindness and non-traumatic amputations

Worldwide, there are >170 million with diabetes mellitus





- The increase in diabetes is linked strongly to the increasing prevalence of obesity
- 25% of UK obese, 32-42% overweight

Aims

- Acquire a basic understanding of:
  - clinical aspects of diabetes mellitus
  - its pathophysiology
  - Its subtypes
  - diabetes treatments
  - diabetes complications

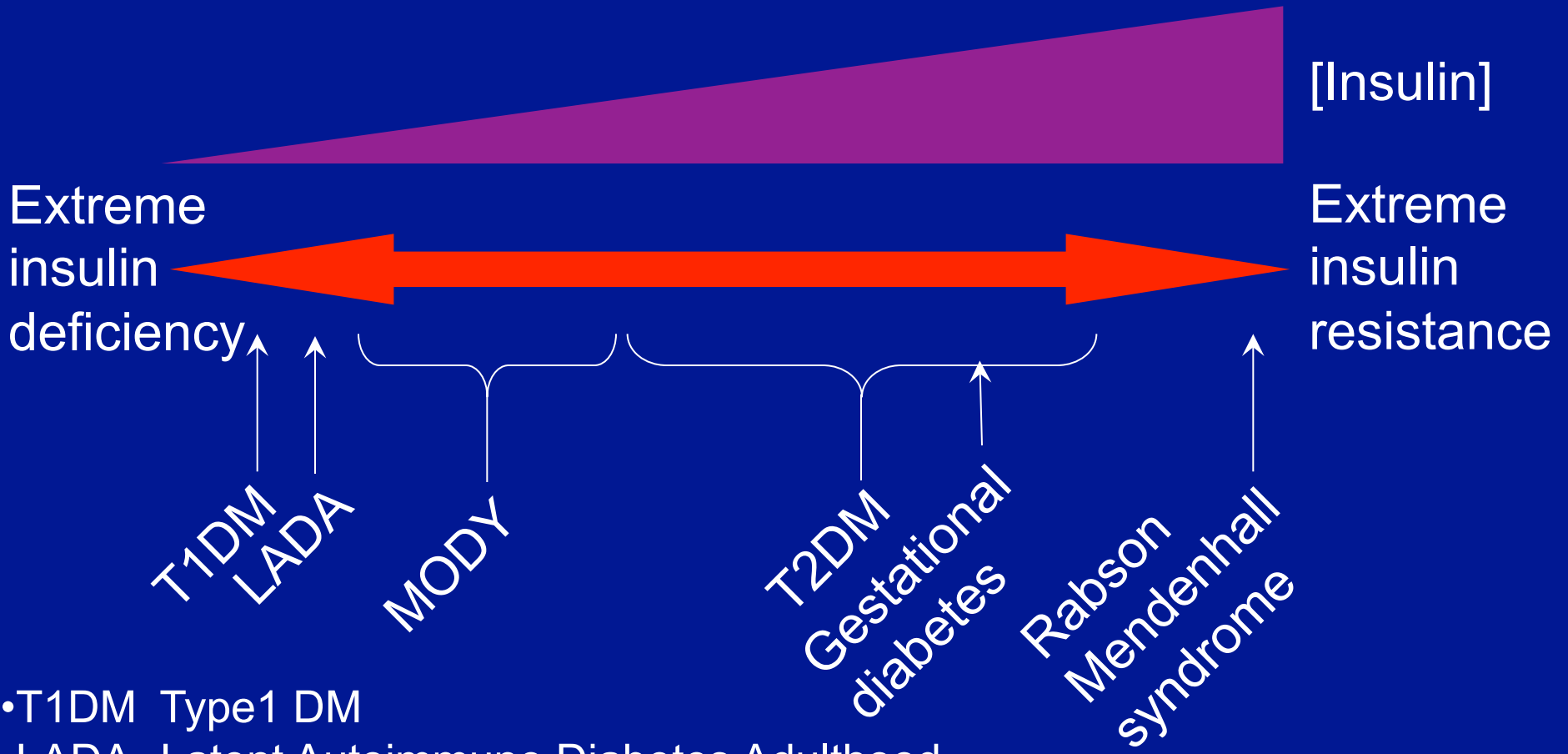
Learning outcomes

- List the signs and symptoms of DM
- Distinguish between T1DM and T2DM
- Understand their pathophysiology
- Know the treatment options appropriate to each type
- Classify types of complications
- Have a theoretical knowledge of managing diabetic emergencies

Compare and Contrast

	Type 1	Type 2
Age onset	Young	Mature
Insulin levels	Low (zero)	High
Aetiology	Insulin deficiency	Insulin resistance
Pathogenesis	Autoimmune	Obesity
Body Habitus	Thin	Normal/↑BMI
Hyperglycaemic crisis	DKA	HHS
Treatment	Mandatory insulin	Diet/OHAs/insulin
GAD Abs	+ve	-ve
C peptide	Low	High

In Reality



- T1DM Type1 DM
- LADA Latent Autoimmune Diabetes Adulthood
- MODY Maturity Onset Diabetes of Youth
- T2DM Type 2 DM
- Rabson-Mendenhall syndrome = severe genetic insulin receptor defect
- Others eg mitochondrial, secondary

Symptoms and Signs

- Polyuria, polydipsia, dehydration
- Blurring of vision
- Weight loss & cachexia
- Infections
- Ketotic foetor
- Glycosuria
- Delirium and coma

Pathophysiology of T2DM

- INSULIN RESISTANCE
  - Related to adipose tissue “dysfunction”
  - Visceral > Subcutaneous obesity
- plus β CELL FAILURE
- Associated with
  - Hypertension, dyslipidaemia, PCOS
- Stronger genetic component than T1DM
- Ethnically linked
  - S Asian Indians
  - Pima Indians in Arizona

Metabolic syndrome (WHO)

- One of:
  - T2DM / Imp gluc tolerance / Imp fasting gluc / Insulin resistance
- Plus two of:
  - BP ≥140/90
  - Trigs ≥1.695 and HDL ≤ 0.9(M) ≤1.0 (F)
  - Central obesity: waist:hip >0.90 (M) >0.85 (F) or BMI >30
  - Microalbuminuria: Alb:Creat ratio ≥30 mg/g

Pathophysiology of T1DM

- Autoimmune destruction of islets
- Combination of
  - genetic predisposition (HLA DR3 & 4)
  - viral infection (Coxsackie)
  - ➢ T-cell mediated ß cell destruction.
- 30-50% concordance in identical twins
- Geographic factors
  - Most common in European population
  - ?link to Vit D deficiency

Diagnosis of Diabetes

If symptoms, DM=

- Fasting plasma glucose ≥7.0 mmol/L
- Random PG or 2 hour OGTT ≥11.1

If no symptoms, DM=

- Two of above criteria

Impaired Gluc Tolerance=

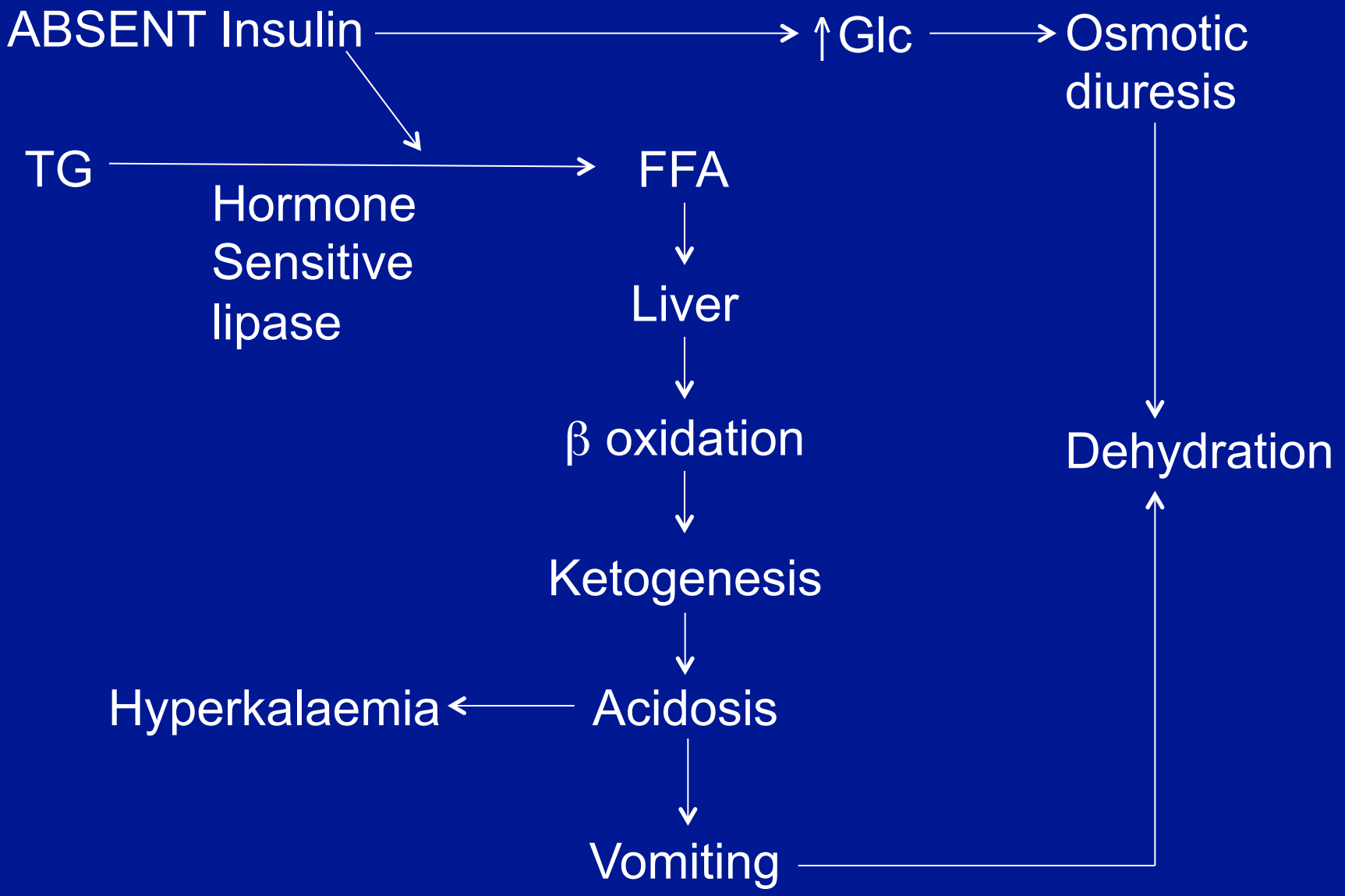
- Fasting PG <7.0, 2 hr OGTT ≥7.8 but <11.1

Impaired Fasting Gluc=

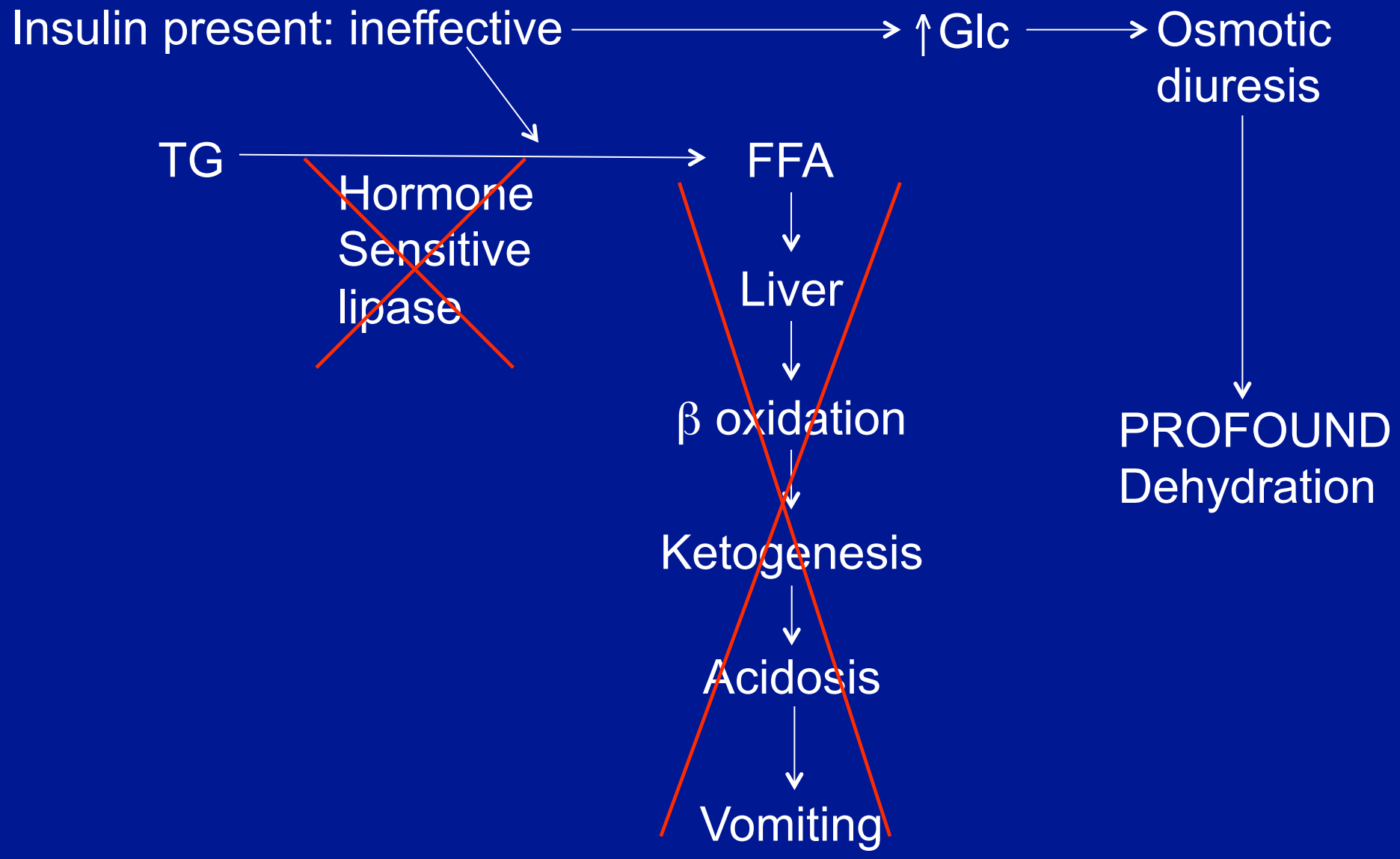
- Fasting PG ≥6.1 but <7.0

Complications

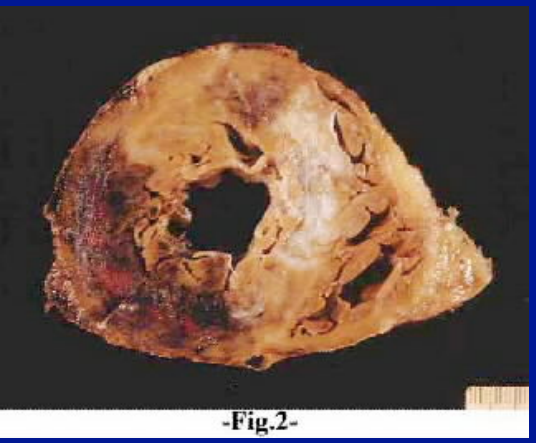
Diabetic Ketoacidosis

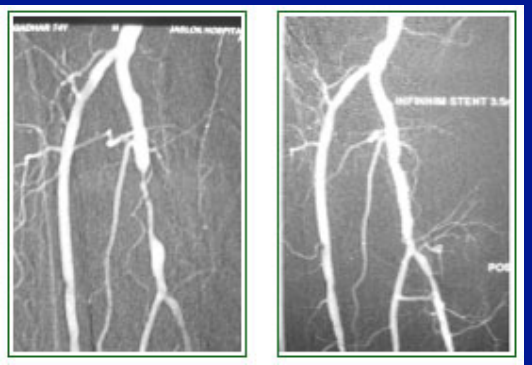


Hyperglycaemic Hyperosmolar State (HHS or "HONK")



Complications



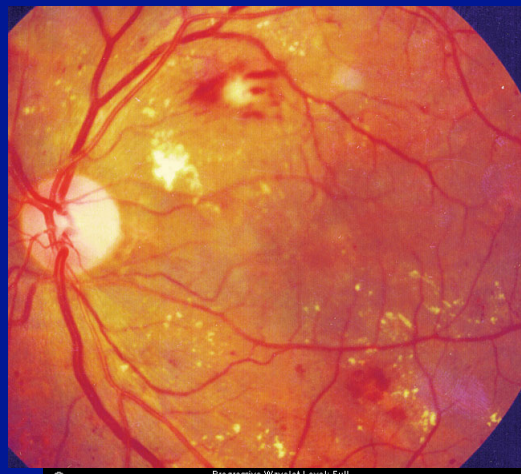


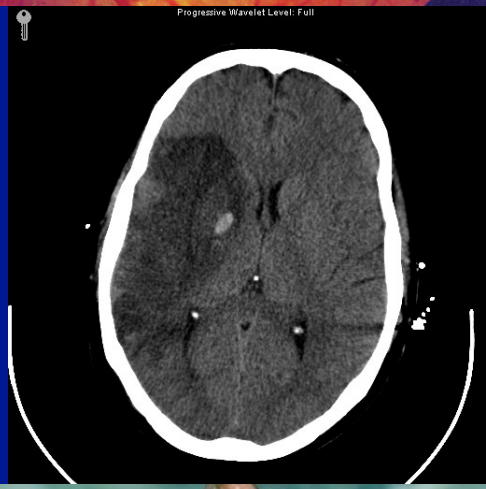
Microvascular

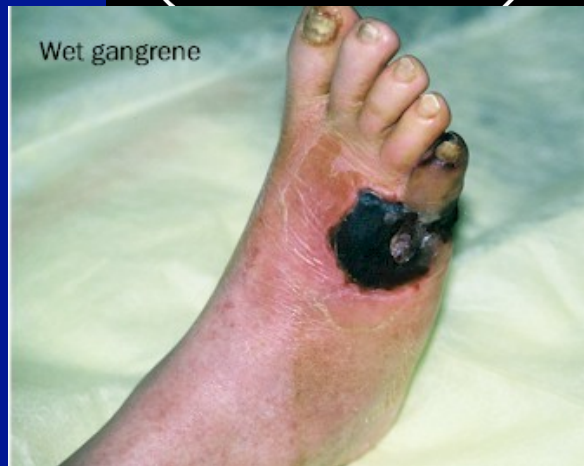
- Glycosylation of basement membrane proteins -> “leaky” capillaries
- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular

- Dyslipidaemia, hypertension
- IHD
- CVA
- Peripheral vascular disease







Treatment

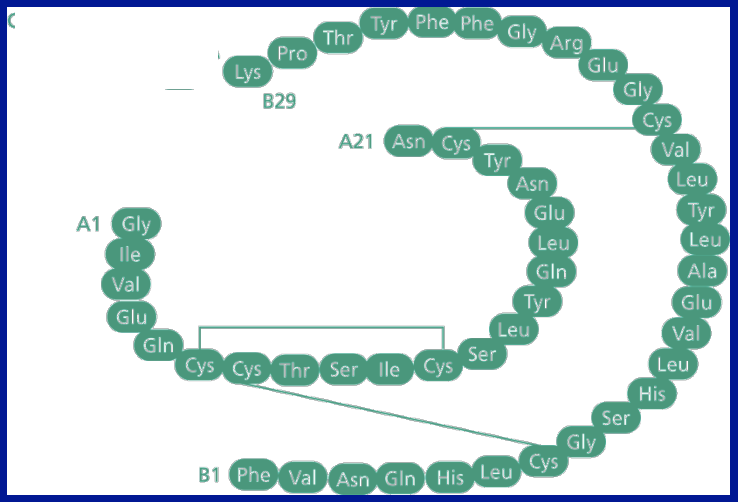
T2DM treatment

- Mediterranean diet
  - Olive oil, fruit & veg, fish, white meats
- Exercise
  - 3x 60 mins per week
  - Moderate physical activity
- Loss of weight
  - Bariatric surgery as new treatment?

T2DM Drugs

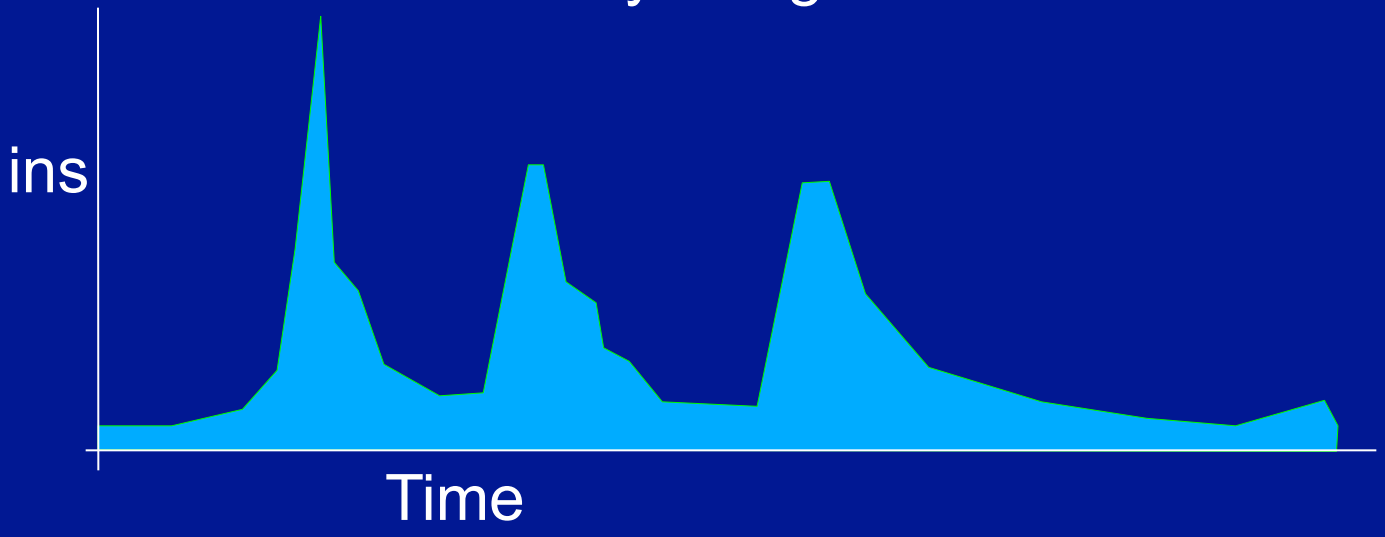
Example	Class	Mode of Action	Notes
Metformin	Biguanide	Insulin sensitizer	CKD, lactate
Gliclazide	Sulphonylurea	Secretagogue	Wt gain, hypo
Repaglinide	Meglitinide	Secretagogue	Not v useful
Acarbose	Glucosidase inhibitor	Retards CHO abs	Flatus+++
Pioglitazone	TZD	Insulin sensitizer	Arm #/CCF
Exenatide	GLP1-analogue	Secretagogue	Injections
Sitagliptin	DPP-IV inh	Secretagogue	New

Insulin Synthesis and Secretion

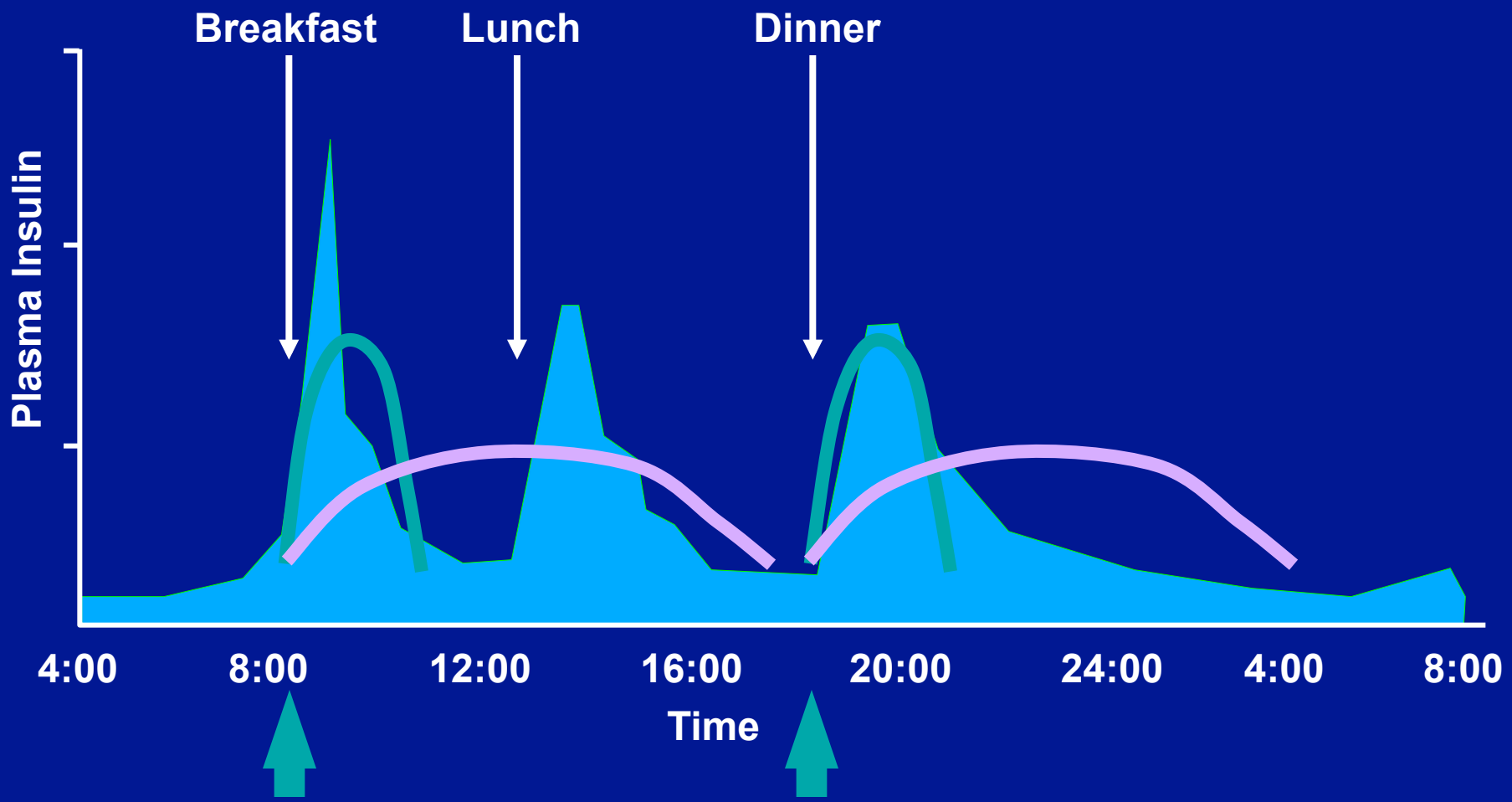


- 50 AA peptide, 3 intramolecular disulphide bridges, 5808 kDa
- Synthesised as preproinsulin
- ER peptidases cleave C-peptide
- Half life of insulin in the circulation = 6 minutes

Physiological Insulin Profile:



BD Mixed insulin



Advantage: fewer injections/day
simpler

Disadvantage: less flexibility

"Basal Bolus"

Breakfast Lunch Dinner

Plasma Insulin

Fast Acting

Long acting

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00

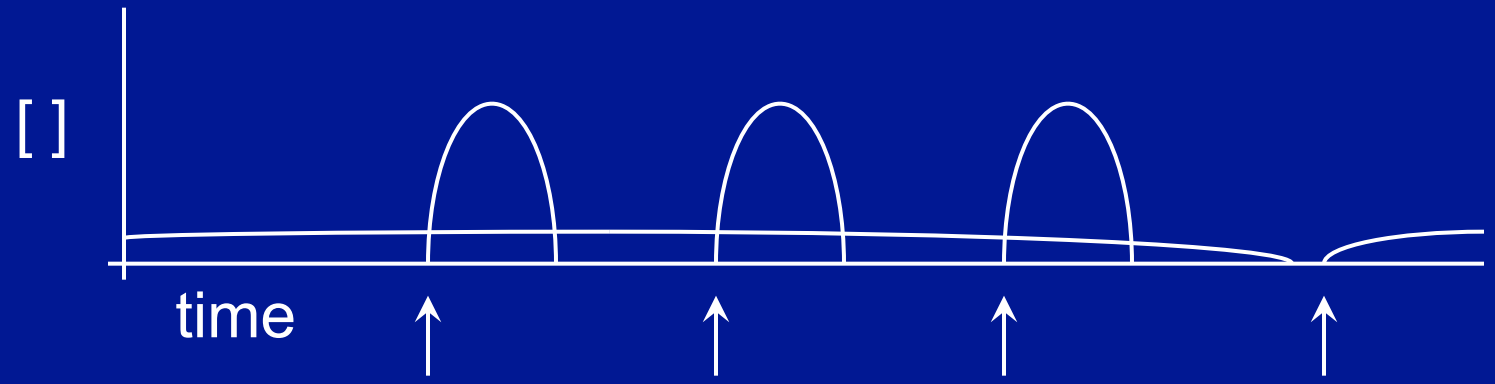
Time

Advantage: Flexibilty

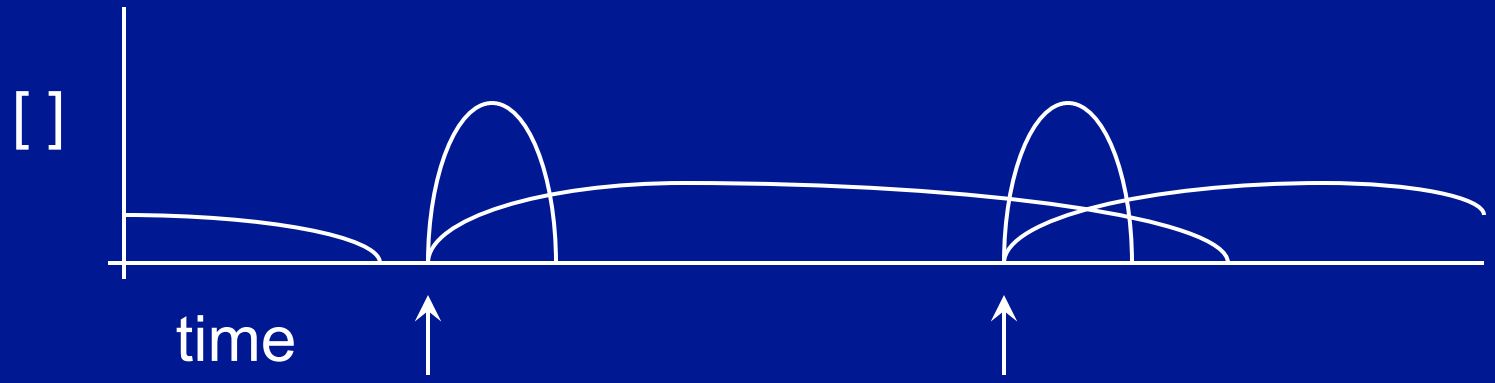
Disadvantage: 4 injections/day or needs pump

Insulin Regimens

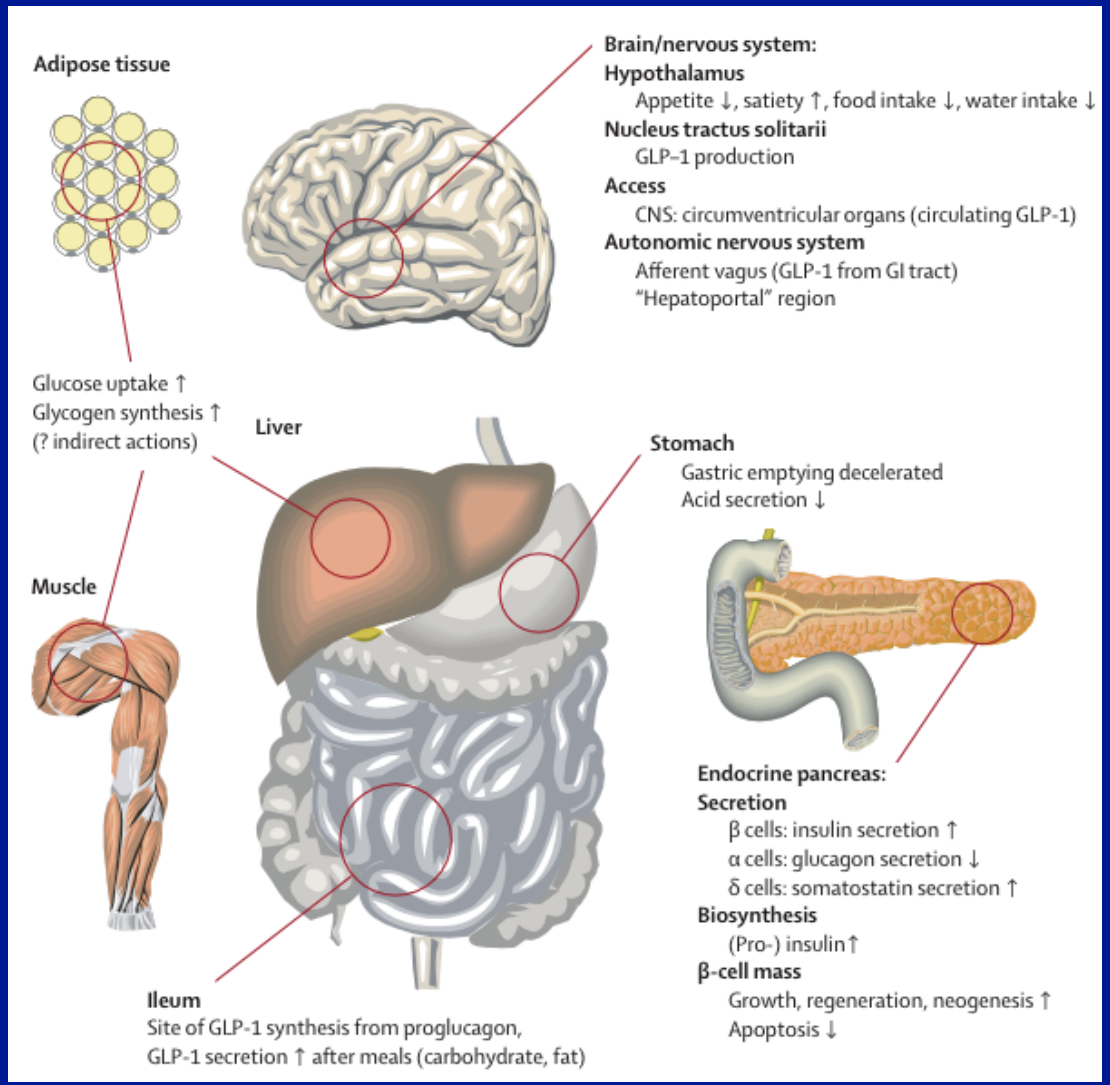
Basal/Bolus eg Insulatard/Actrapid



Twice Daily Mixed/Biphasic eg Mixtard 30



Glucagon-like peptide 1 (GLP-1)



- Stimulates Insulin secretion
- Inhibits Glucagon secretion
- Inhibits Gastric emptying
- Inhibits Appetite
- Stimulates Nausea

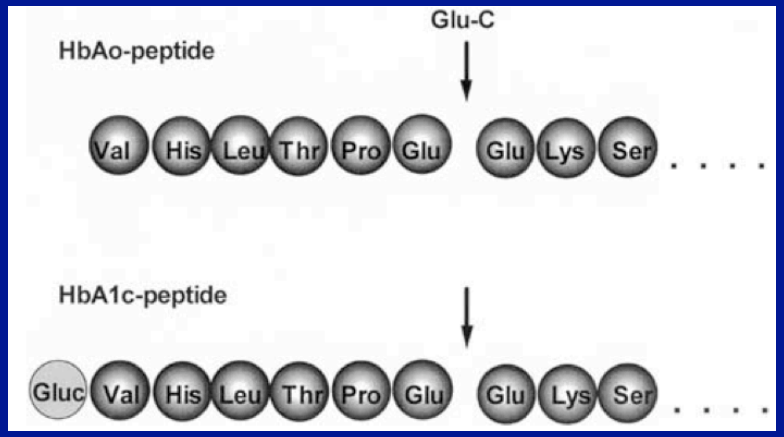
Why we treat diabetes

Aims of treatment

- Relieve symptoms of hyperglycaemia
  - Fatigue
  - Polyuria, polydipsia
  - Weight loss
- Prevent complications
  - Microvascular: retinal, renal, neural
  - Macrovascular: MI, stroke, peripheral vessels

What is HbA1c?

- Non-enzymatic glycosylated product of Hb (N-terminus of ß-chain HbA0)
- Mostly measures average glycaemia over 2-4 weeks
- HPLC, immunoassay, boronate affinity chromatography



- Rapidly available
- Point of care testing in 5 minutes

HbA1c FOR THE DIAGNOSIS OF DIABETES

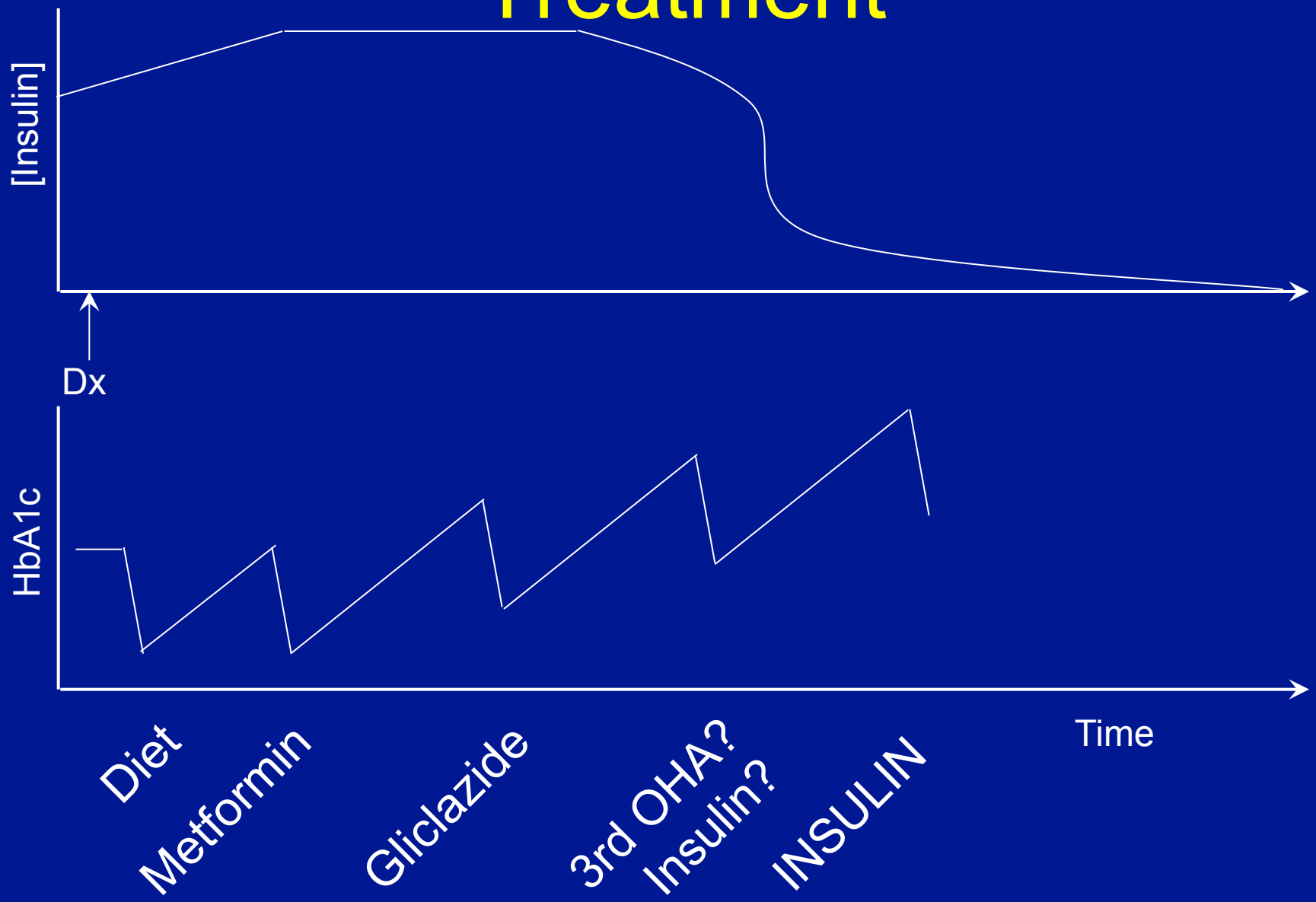
- Recommendations from the WHO 2011:
  - An HbA1c of 6.5% is recommended as the cut off point for diagnosing diabetes.
  - A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

HbA1c – Change in Units

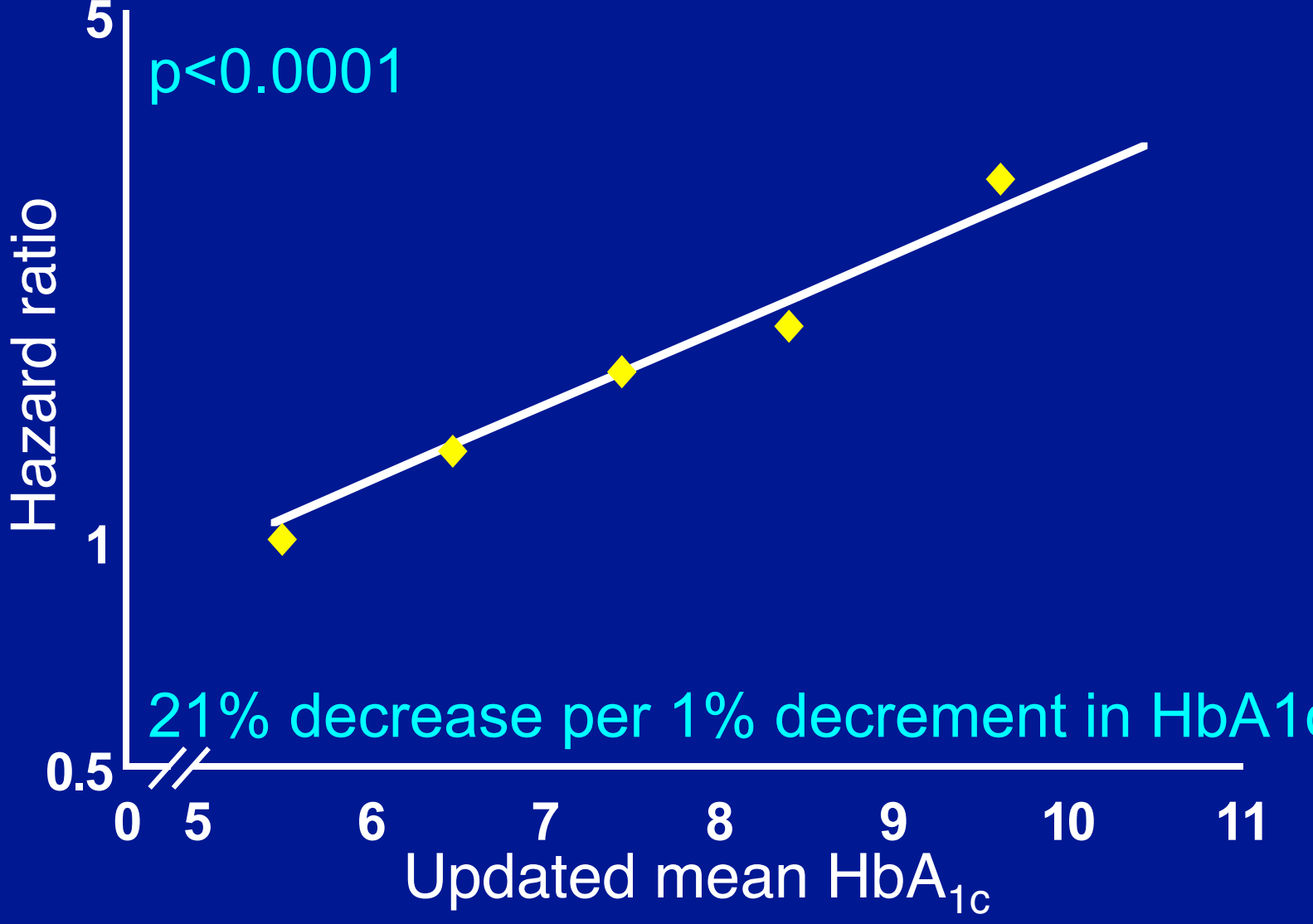
- Until 2009, it was traditional to express HbA1c as %
- HbA1c is now expressed as mmol/mol

DCCT- HbA1c %	IFCC-HbA1c mmol/mol
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
9.0	75
10.0	86

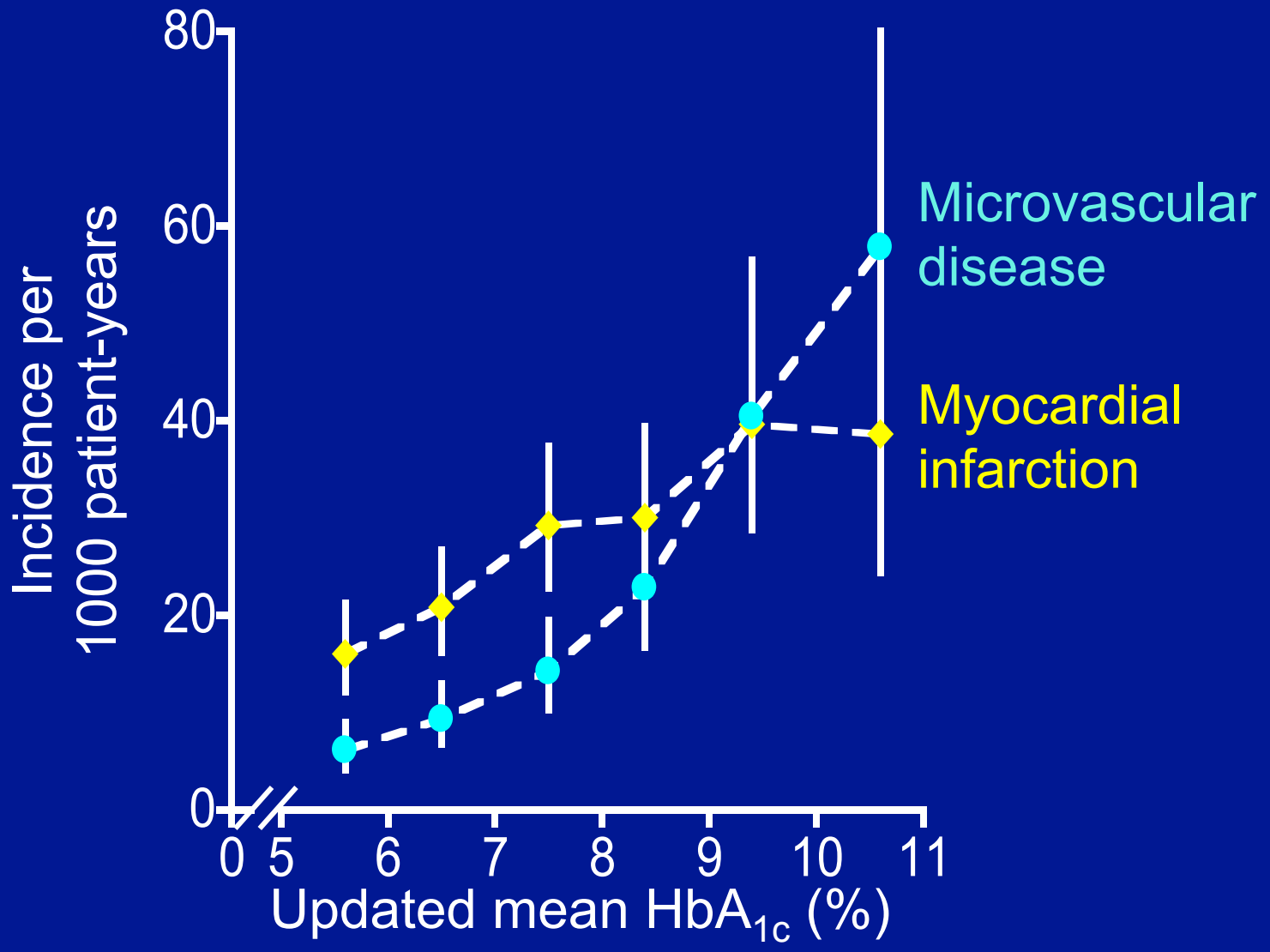
T2DM Pathophysiology and Treatment



Any Diabetes Related Endpoint



UKPDS 35. BMJ 2000; 321: 405-12



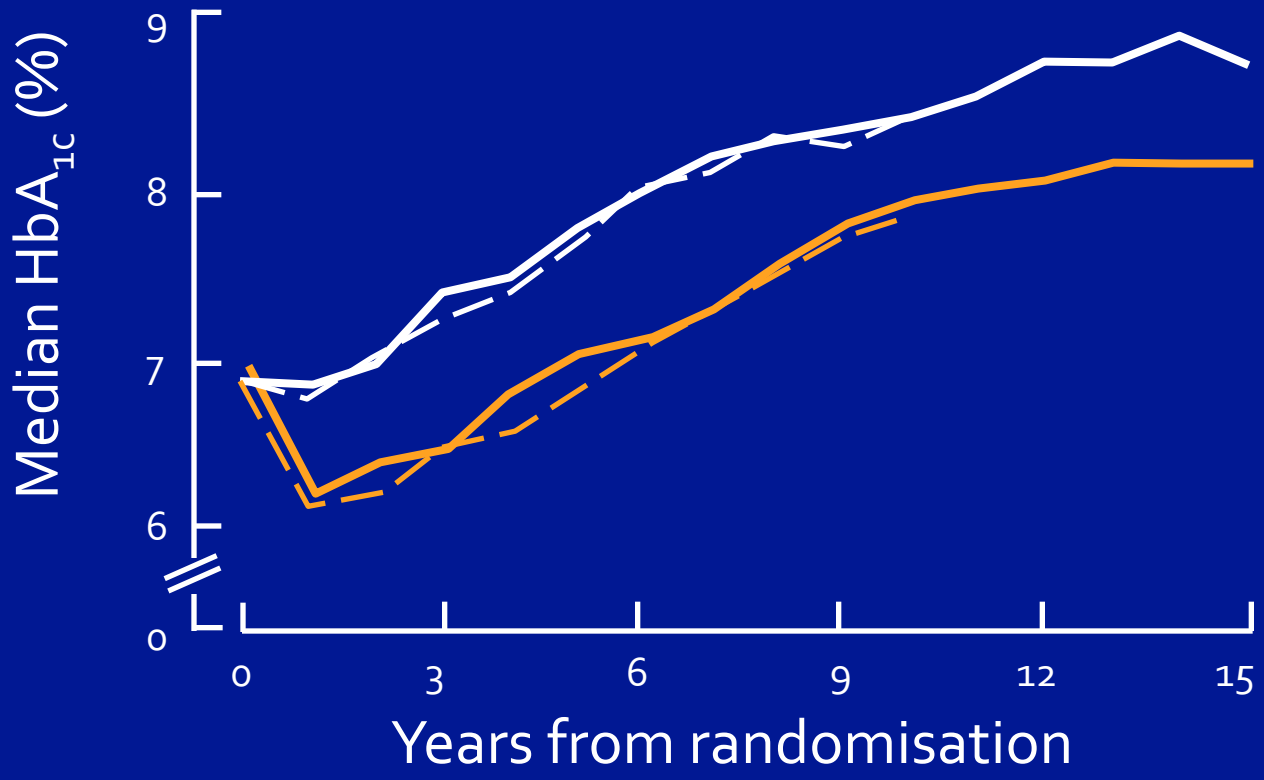
UKPDS 35. BMJ 2000; 321: 405-12

UKPDS 33: intensive therapy reduced HbA1c

Intensive policy, median HbA_{1c} 7.0%

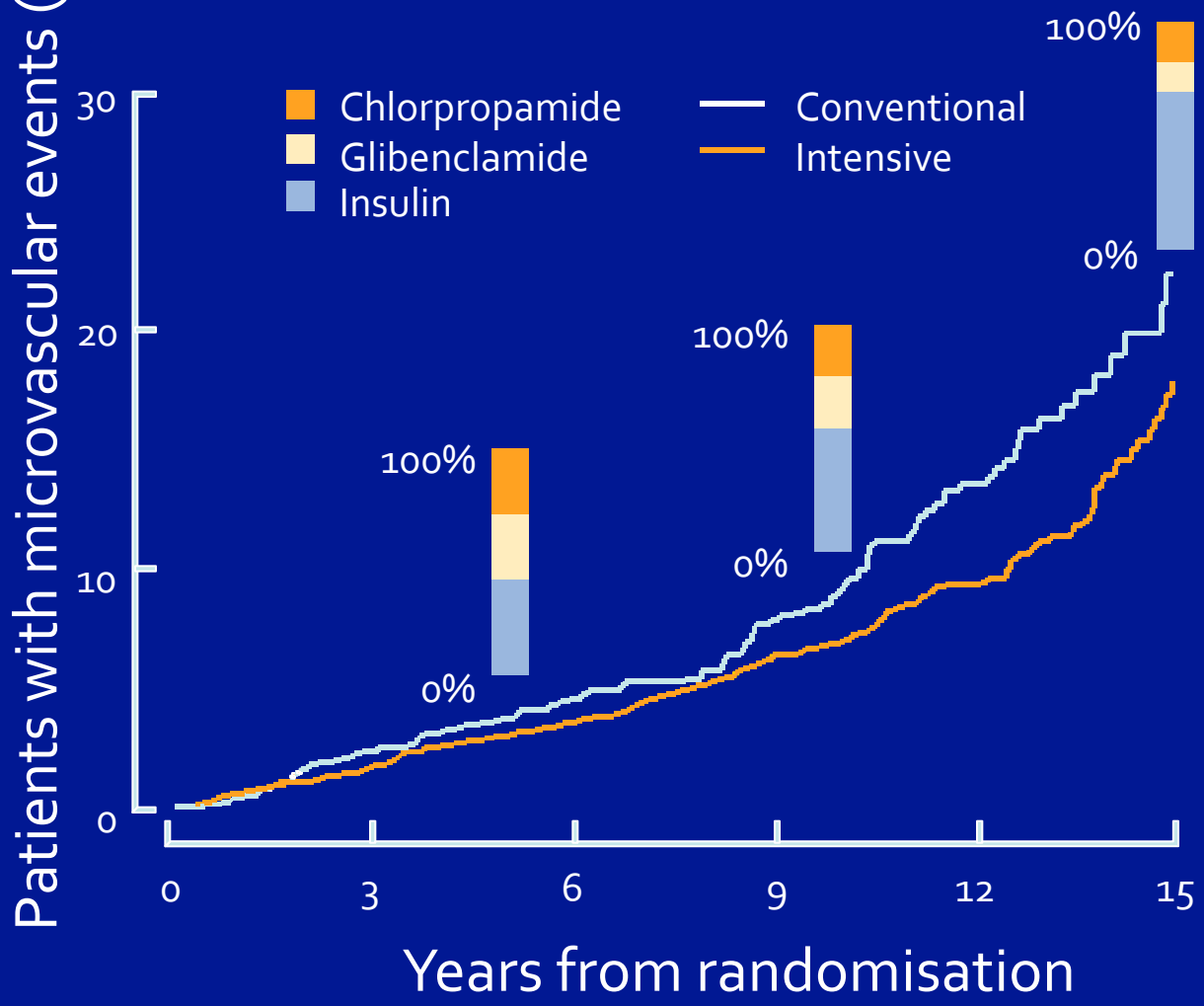
Conventional policy, median HbA_{1c} 7.9%

Dashed lines indicate patients followed for 10 years
Solid lines indicate all patients assigned to regimen



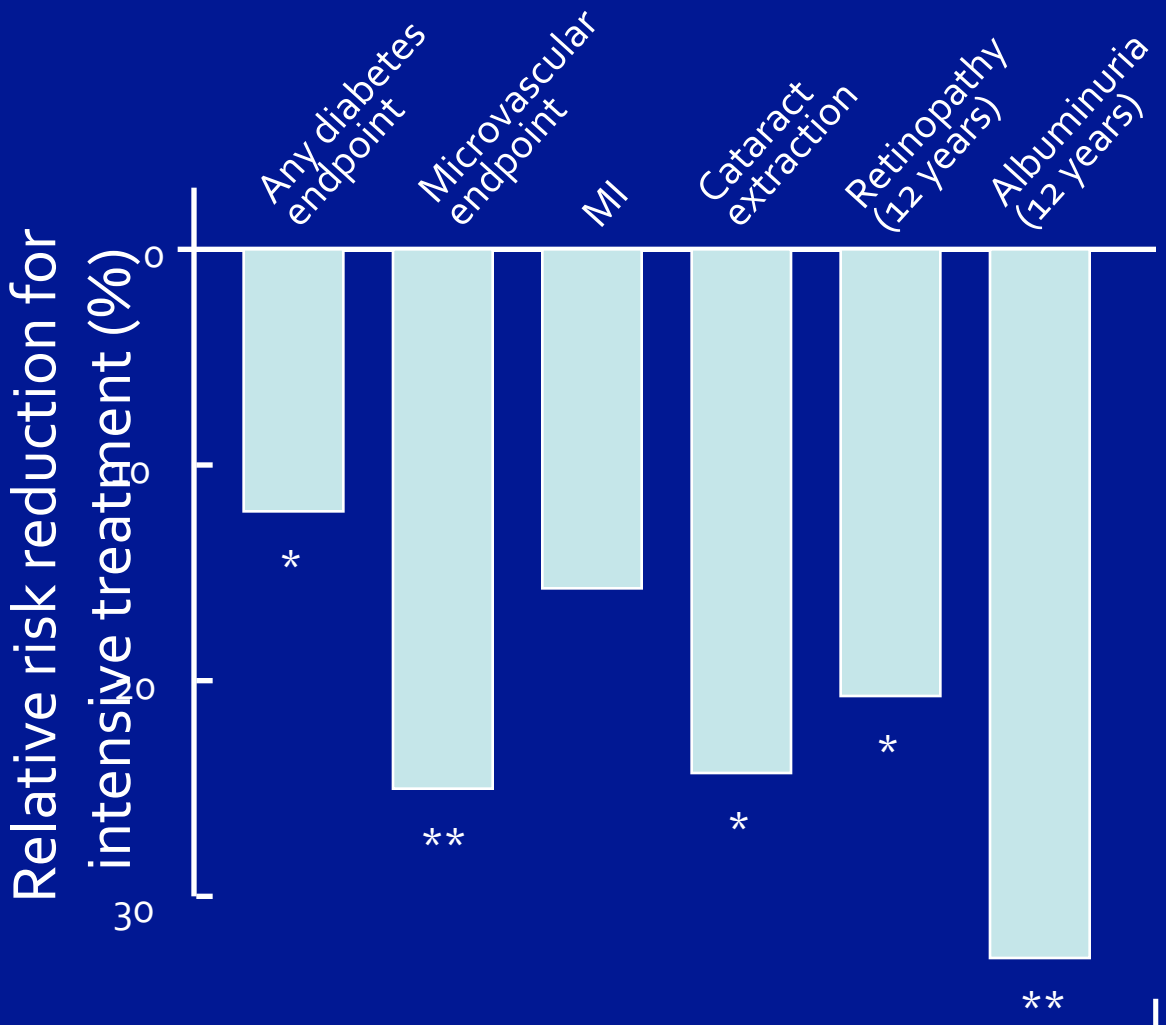
Lancet 1998;352:837–53

UKPDS 33: intensive therapy reduced microvascular events



Lancet 1998;352:837–53

UKPDS 33: relative risk reduction with intensive treatment



Intensive treatment reduced HbA_{1c} by 0.9% for a median of 10 years in 3,867 patients with type 2 diabetes

* $p < 0.05$ ** $p < 0.01$

Lancet 1998;352:837–53

Summary

- T1DM is
  - due to autoimmune islet destruction causing insulin deficiency
  - treated with insulin replacement therapy
- T2DM is
  - due to insulin resistance plus ß cell failure
  - treated with diet, OHAs and eventually insulin
- Complications of both types
  - broadly similar
  - can be classified as macro- and micro- vascular
- Treatment is aimed to
  - Relieve symptoms
  - Prevent complications