Update on the management of diabetes mellitus in chronic renal insufficiency

St George Hospital 2009

Assoc Prof Tony O'Sullivan
Consultant Endocrinologist

Introduction

- Oral hypoglycaemic agents
  - metformin
  - Sulphonylureas
  - glitazones
- Insulin therapy
  - Basal/bolus
  - Sliding scale
- Newer agents
  - Sitagliptin
  - exenatide
- Monitoring control – HbA1c
  - Accord & Advance studies

Approach to Diabetes Management

- Diabetes education
- Lifestyle changes - diet and exercise
- An effective insulin regimen or appropriate medication
- Monitor and document glycaemic control
- Dosage adjustment of insulin and medications
- Regular review of complications and management of risk factors
- Regular review of cardiovascular risk factors and their active management

What therapy should be used to keep your diabetes on target?

Metformin

- Initial drug of choice especially in overweight diabetics
- Safe in CKD stage 1 or 2
- Excreted in urine unchanged therefore c/I in stages 3-5
- Continue use with insulin – reduced CVS events
- Lowers HbA1c by 1-2 %
- Reduce B12 absorption

Sulphonylureas

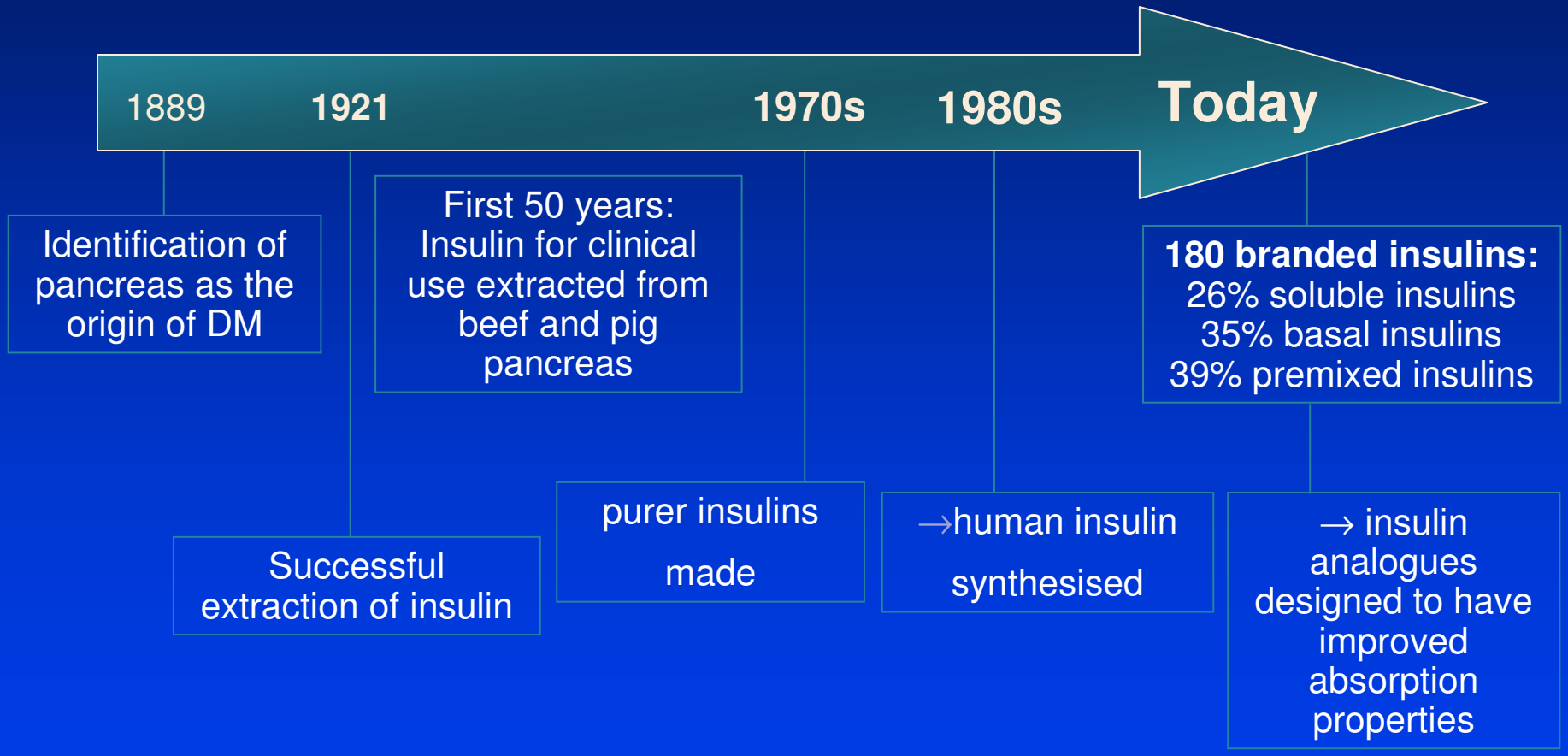
- Shorter acting
  - Glicazide (Diamicron) 30mg MR – no active metabolites
  - 80 mg being discontinued
  - Glipizide (minidiab) - no active metabolites
- Glibenclamide (daonil - longer acting) & glimepiride (Amaryl)
  - higher incidence of hypoglycaemia
  - Metabolites are active & some excreted by kidney

thiazolidinediones

- Rosiglitazone (4 & 8mg) and pioglitazone (15-45mg) don't need dose adjustment in CRI
- Decrease HbAic by 0.5-1.4 %
- Fluid retention and adipose tissue gain
- ?increased CV events with rosiglitazone
  - ADA recommended against use
  - Recent reports at ADA meeting suggest no increase risk
- c/I in heart failure or with history of acute coronary syndrome
- Pioglitazone – probably safe from a CVS point
  - C/I in NYHA class 3 & 4

Drs Banting & Best with Majorie the dog

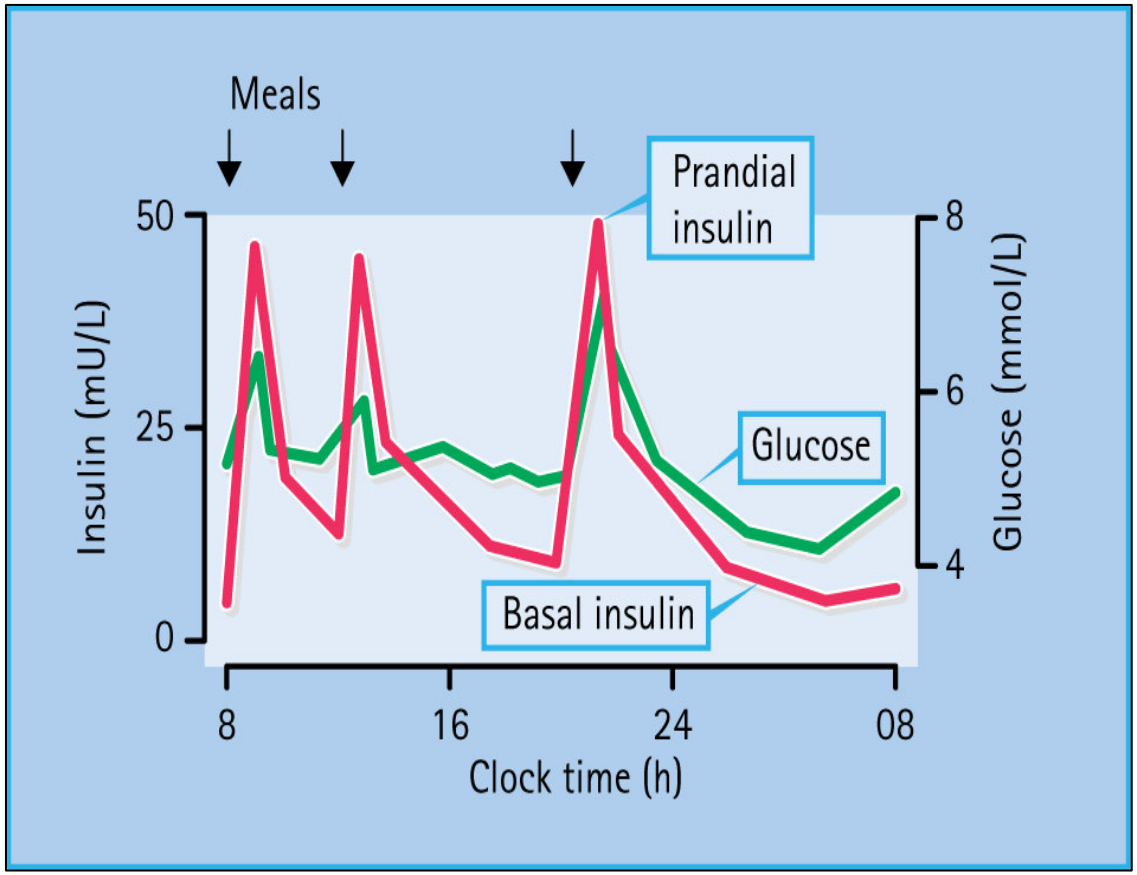
Insulin:
A revolution in the treatment of diabetes



Different insulin regimes to suit lifestyle

- Types of insulin
- Timing of insulin
- Delivery devices

Insulin treatment in Type 1 DM aims to replace insulin secretion



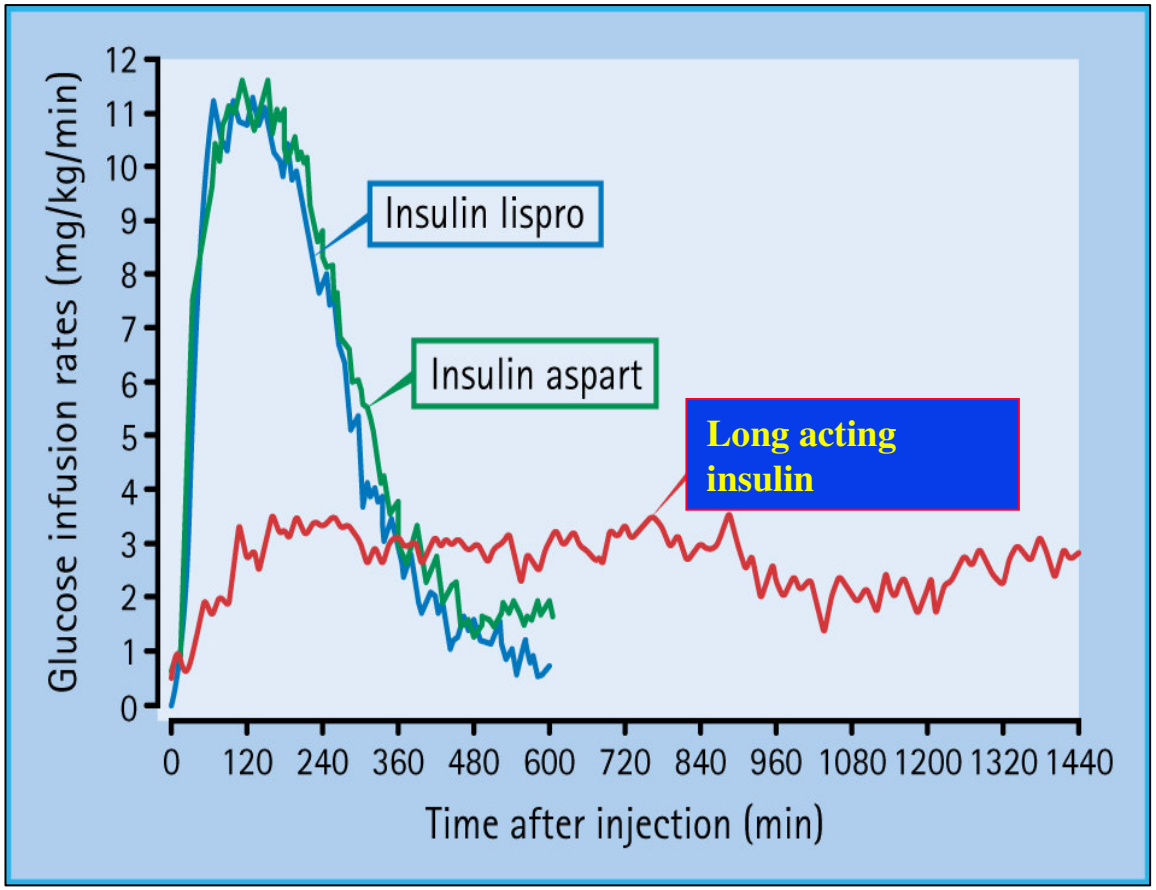
- Aims to mimic the physiological secretion of insulin
- Normal pattern of insulin secretion has a basal level with a peak after each meal
- Basal–bolus strategy aims to mimic this using short- and long-acting insulins

Watkins et al. Diabetes and its Management, Ed. 6. Blackwell Publishing, 2003;
Pickup & Williams. Slide Atlas of Diabetes. Blackwell Publishing, 2004

Currently available insulin preparations

- Rapid-acting: onset within 15 min; peak duration 1-2 h, duration up to 4-5 h
  - NovoRapid®
  - Humalog®
  - Apidra®
- Short-acting: onset within 30 min, peak effect 2–4 h, duration 6 hours
  - Regular insulin – actrapid or Humulin R
- Intermediate-acting: onset within 2 h, peak effect 4–8 h, duration 12-14 h
  - Humulin NPH or protophane
- Long-acting: onset within 2 h, duration 18–36 h
  - Levemir®
  - Lantus®
- Pre-mixed: contain both a fast- or rapid- and an intermediate-acting insulin
  - 30% insulin aspart / 70% protaminated insulin aspart (NovoMix® 30)
  - 30% short-acting / 70% NPH (biphasic human insulin - Mixtard® 30)
  - 25% insulin lispro / 75% protaminated insulin lispro (Humalog® Mix 25)

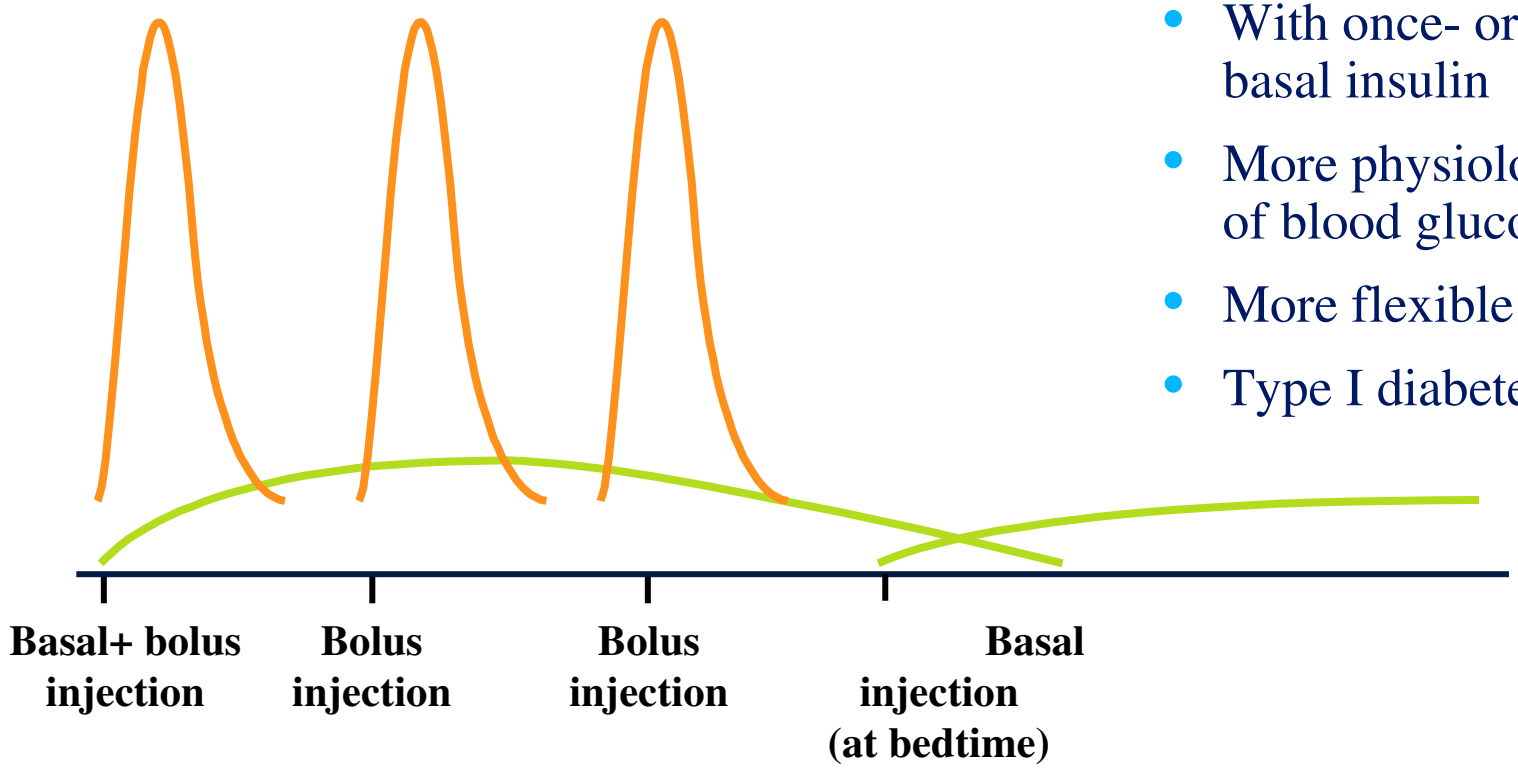
Rapid-acting insulin analogues



Heise et al. *Diabetes Care* 1998; 21:800–803; Heinemann et al. *Diabetes Care* 2000; 23:644–649; Heinemann et al. *Diabetes Care* 1998; 21:1910–1914

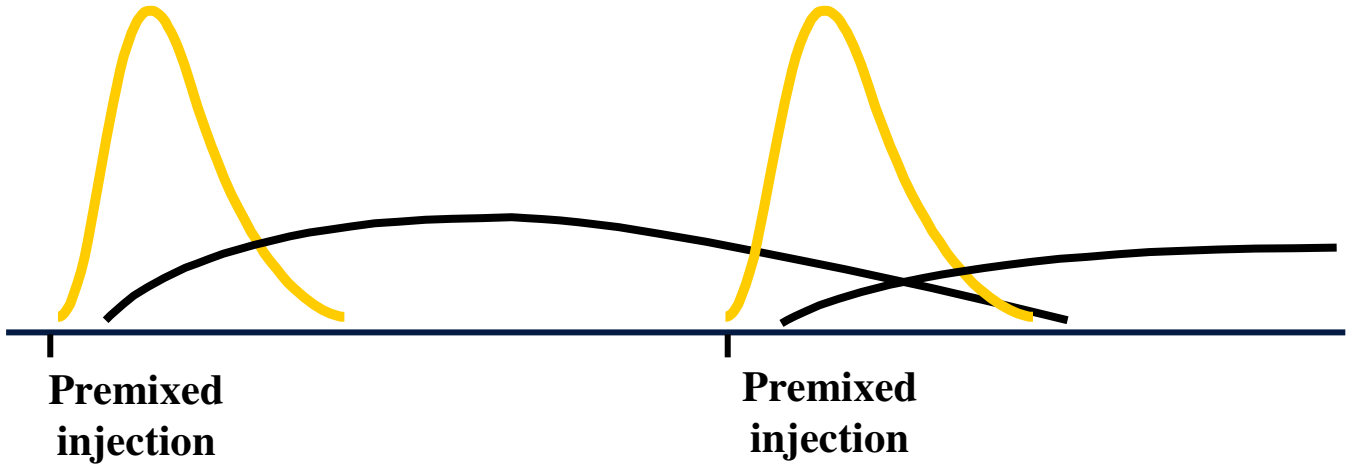
- Marketed products:
  - NovoRapid® (insulin aspart)
  - Humalog® (insulin lispro)

Multiple daily injection regimens (Basal–bolus)



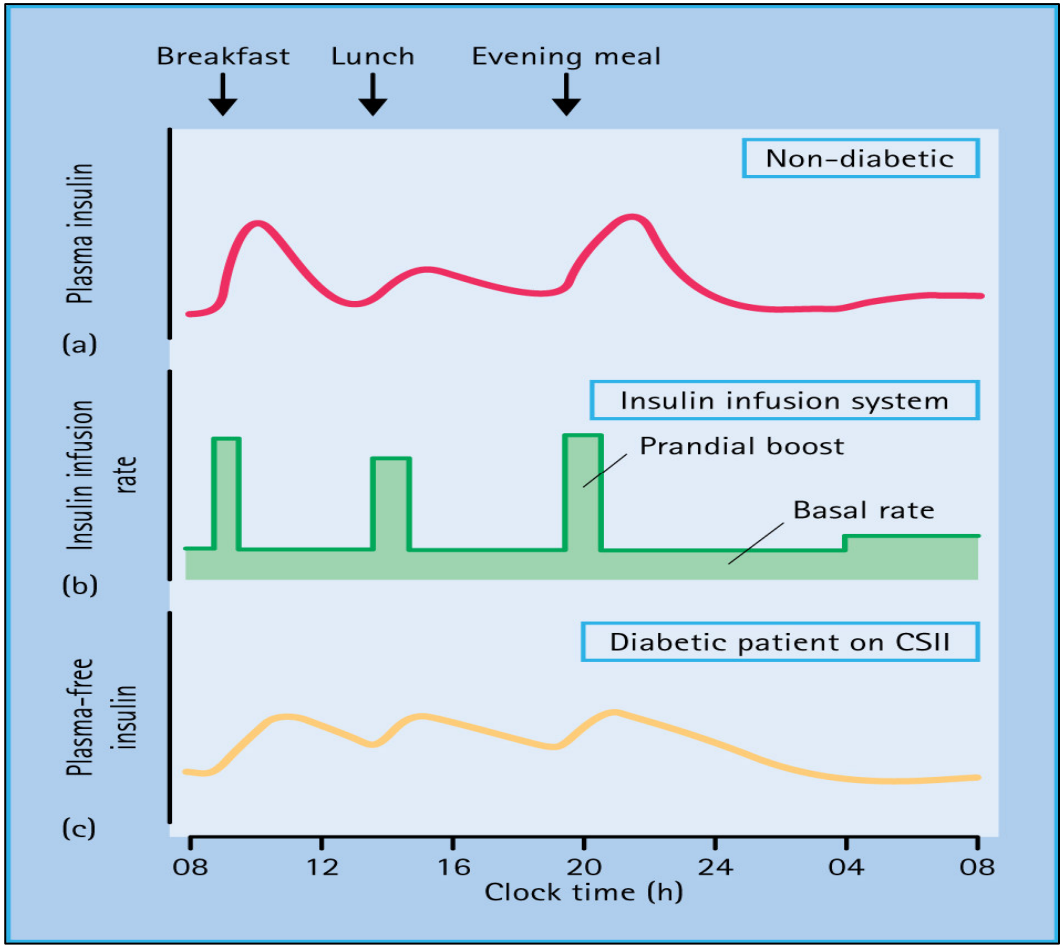
- Pre-meal rapid-acting insulin
- With once- or twice- daily basal insulin
- More physiological control of blood glucose levels
- More flexible regimens
- Type I diabetes mellitus

Twice-daily insulin regimens



- Twice-daily injections of short- and intermediate-acting mixed insulins
- Given before breakfast and the evening meal
- Not encouraged for most type 1 diabetes patients
- Used more for convenience in those patients unable to deal with the more complex physiological regime
- Used mostly with Type 2 DM

Subcutaneous insulin pump therapy



- Flexible insulin replacement therapy available
- Pump provides a constant rate of basal insulin
- Patient activates mealtime boluses of insulin when required
- Often used in children
- Cost an issue
- Need to monitor BGL very regularly

Watkins et al. Diabetes and its Management, Ed. 6. Blackwell Publishing, 2003;
Pickup & Williams. Slide Atlas of Diabetes. Blackwell Publishing, 2004

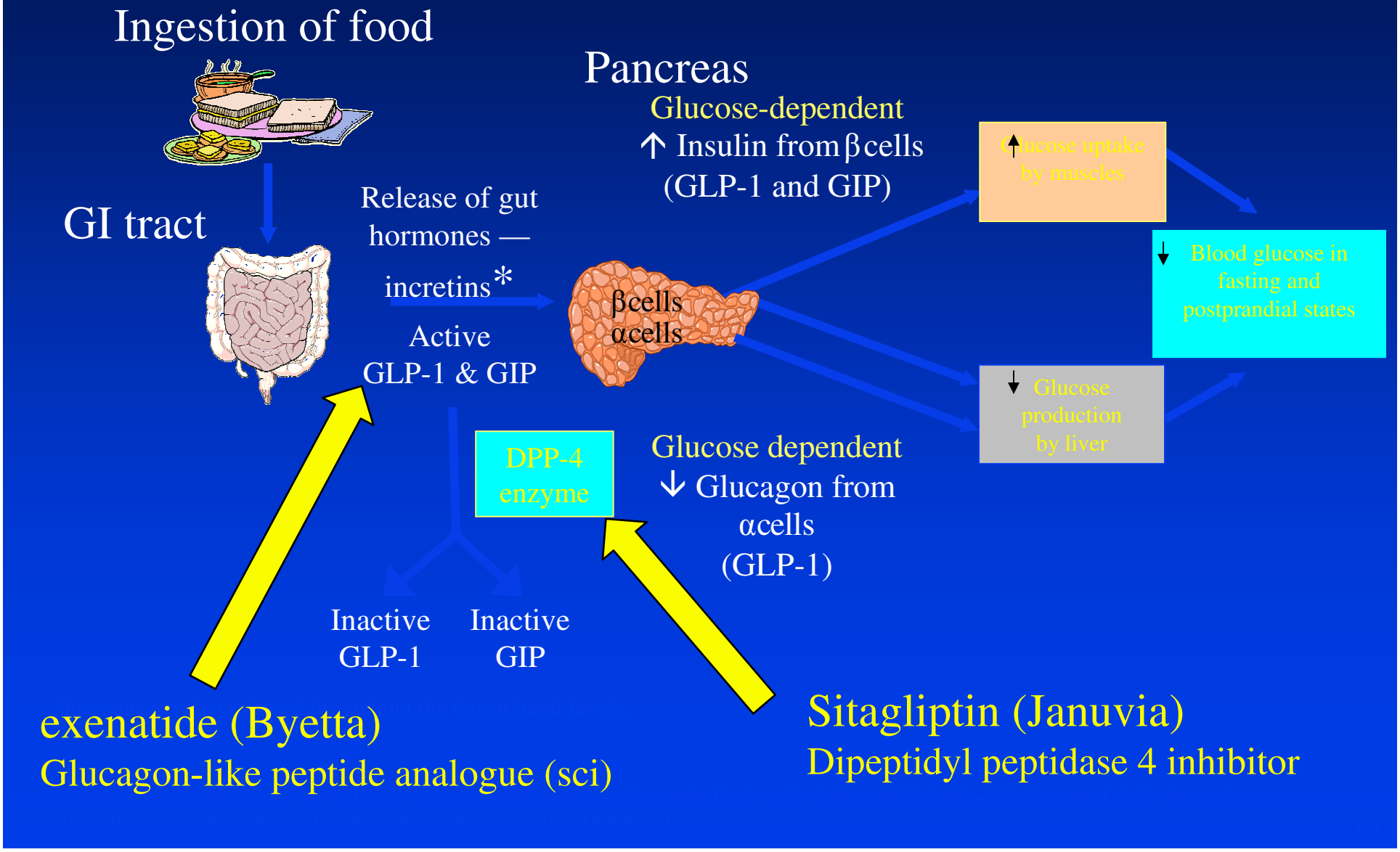
Insulin delivery devices

Innolet

Disposable flexipens

Lantus solostar

Role of Incretins in Glucose Homeostasis



Exenatide (Byetta)

- Glucagon-like peptide analogue
- 5 – 10 micrograms sci bd per meals
- Not on PBS
- $150 - 200 per month
- Longer acting analogues coming out
- Weight loss (upto 10 %) c/w insulin
- Adverse effects - nausea, pancreatitis

JANUVIA® (sitagliptin)
Indications and Usage

Indications in Type 2 diabetes

Combination therapy – PBS listing

For the treatment of diabetes mellitus type 2 in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

JANUVIA® (sitagliptin)
Dosage & Administration – authority required

Usual Dosing for JANUVIA

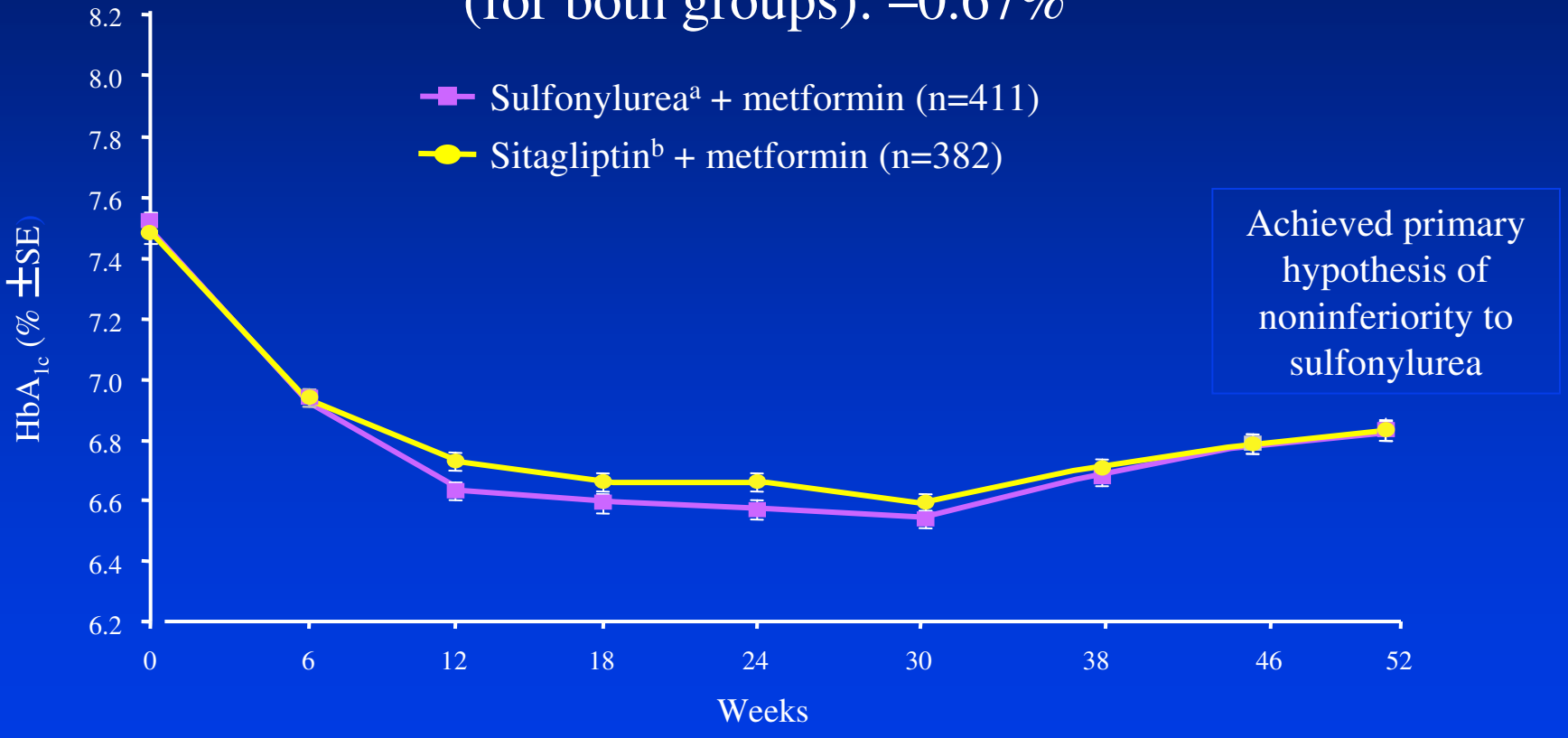
The recommended dose of JANUVIA is
100 mg once a day with or without food

Patients With Renal Insufficiency

100 mg daily	50 mg daily	25 mg daily
Mild renal insufficiency	**Moderate renal insufficiency**	**Severe or ESRD +/- Dialysis**
CrCl ≥ 50 mL/min	**CrCl ≥30 to <50 mL/min**	**CrCl <30 mL/min**

HbA_{1c} Over Time With Sitagliptin or Glipizide as Add-on Combination With Metformin: Comparable Efficacy

LS mean change from baseline (for both groups): –0.67%



Sitagliptin

- Insulin resistance, β-cell dysfunction, and elevated hepatic glucose production are the 3 core patho-physiologies of type 2 diabetes
- Incretins positively affect glucose homeostasis by physiologically helping to regulate
  - Insulin secretion from β cells in a glucose-dependent manner
  - Glucagon secretion in a glucose-dependent manner
- Sitagliptin, a once-daily 1st approved in class oral DPP-4 inhibitor, substantially improves HbA_{1c}, FPG, and PPG
- Sitagliptin is generally weight neutral, has a low risk of hypoglycaemia, and is generally well tolerated

Monitoring diabetes

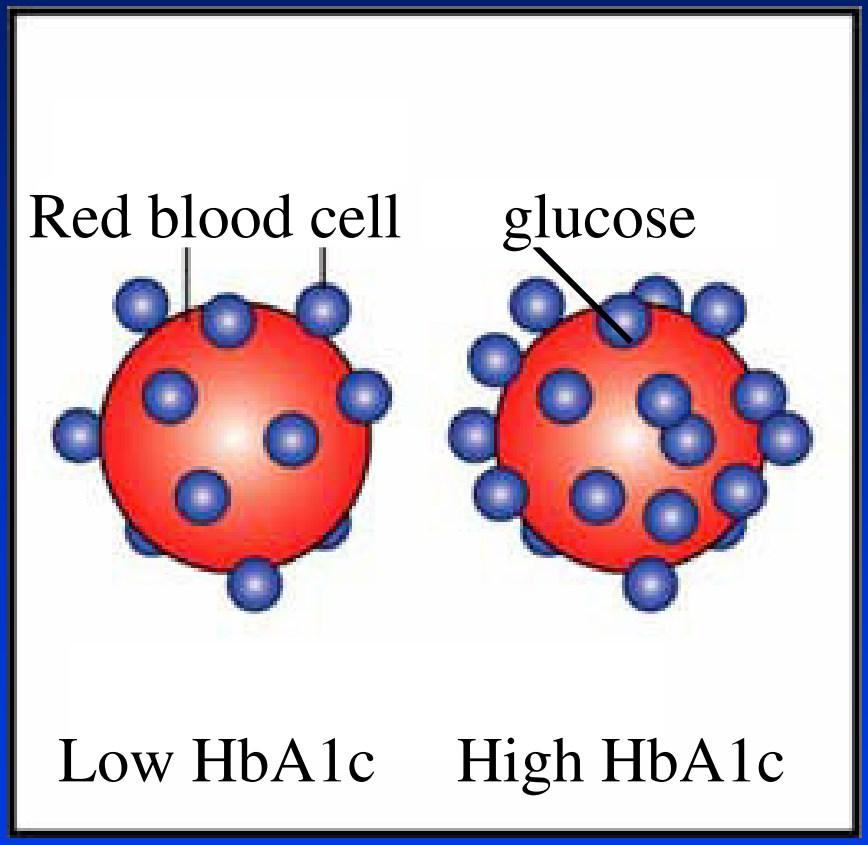
1. Fingerprick home blood glucose monitoring

2. Glycosylated haemoglobin

Both techniques are complimentary

Glycosylated haemoglobin (HbA1c)

- Best correlate with complications and death in DCCT & UKPDS
- ESRD – underestimate glucose control
  - Anaemia & EPO
  - 30 mmol/L of urea increase HbA1c by 1 %



Accord

- Any treatment to improve control – 90 % glitazone
- HbA1c: 8.1 to 6.4 %
- Most on aspirin & statins
- ?increased risk of death with intensive treatment
- Weight gain probably due to glitazones

Advance

- Required to receive glicazide – so less glitazones used
- HbA1c: 7.2 to 6.4 %
- Half on aspirin
- No difference in death between groups

Conclusions:

In DM risk factor control of lipids & BP, plus addition of aspirin
Has more effects on reducing CV events and death
Lowering HbA1c to less than 7 % is not beneficial

Going out with diabetes

Going out with diabetes

- Take insulin as arranged
- Plan meals/snacks
- Responsible with alcohol
  - Hypoglycaemia
    - missed meals & alcohol
    - Late effect after drinking
  - hyperglycaemia: soft drinks mixers
  - Hyoglycaemia my mimic intoxication
  - Watch hangovers: not eating, miss insulin

Going out with diabetes

- Be careful driving
  - Measure blood glucose before driving
- Recreational drugs - alter blood glucose
  - Stimulants
    - Decrease appetite
    - Increase metabolism
  - Increased physical activity
  - Altered sleep patterns
- Smoking