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
Successful extraction of insulin

First 50 years: Insulin for clinical use extracted from beef and pig pancreas

Purer insulins made

→ human insulin synthesised

180 branded insulins:
- 26% soluble insulins
- 35% basal insulins
- 39% premixed insulins

→ insulin analogues designed to have improved absorption properties

Identification of pancreas as the origin of DM

Successful extraction of insulin

1889 1921 1970s 1980s Today

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

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

- 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

Insulin delivery devices

Innolet

Disposable flexipens

Lantus solostar
Ingestion of food

GI tract

Release of gut hormones — incretins*

Active GLP-1 & GIP

Pancreas

Glucose-dependent

↑ Insulin from β cells

(GLP-1 and GIP)

β cells

α cells

Glucose dependent

↓ Glucagon from α cells

(GLP-1)

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

Blood glucose in fasting and postprandial states

↓ Glucose production by liver

↓ Blood glucose in fasting and postprandial states

Sitagliptin (Januvia)
Dipeptidyl peptidase 4 inhibitor

exenatide (Byetta)
Glucagon-like peptide analogue (sci)

Inactivation by DPP-4 enzyme

↑ Glucose uptake by muscles
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
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

<table>
<thead>
<tr>
<th>100 mg daily</th>
<th>50 mg daily</th>
<th>25 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild renal insufficiency</td>
<td>Moderate renal insufficiency</td>
<td>Severe or ESRD +/- Dialysis</td>
</tr>
<tr>
<td>CrCl $\geq$ 50 mL/min</td>
<td>CrCl $\geq$30 to &lt;50 mL/min</td>
<td>CrCl &lt;30 mL/min</td>
</tr>
</tbody>
</table>

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

Sulfonylurea<sup>a</sup> + metformin (n=411)
Sitagliptin<sup>b</sup> + metformin (n=382)

Achieved primary hypothesis of noninferiority to sulfonylurea

HbA<sub>1c</sub> Over Time With Sitagliptin or Glipizide as Add-on Combination With Metformin: Comparable Efficacy
Sitagliptin

- Insulin resistance, $\beta$-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 $\beta$ 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