How do you treat diabetes?

Polly Bingley
Outline

- Who is involved?
- Aims of treatment
- Treating the glucose
  - Principles and tools
  - Novel approaches
- Reducing risk of complications
  - Macrovascular
  - Microvascular
  - Other
- Managing established problems
Diabetes Care
The Team

The person with diabetes

The diabetes care team

10
20
30
Diabetes Care
principles of treatment

Education

• Complex life-long condition affecting personal life, family life and work.

• Need for information, advice, support, advocacy, empowerment
Treating diabetes aims

“As long and as healthy a life as possible”

• **Short term**
  • Relieve symptoms, avoid metabolic decompensation (hyper- and hypo-glycaemia) and infections

• **Long term**
  • Near normal life style
  • Near normal glucose control
  • Normal growth in children
  • Normal outcome of pregnancy
  • Reduction of cardiovascular risk
  • Regular screening for risk/complications and early treatment e.g. laser treatment for retinopathy
  • Support for late complications
Treating the glucose

Approaches

- Replace insulin
- Enhance endogenous insulin secretion
- Increase insulin sensitivity
- Reduce glucose absorption
- Increase glucose excretion
Replacing insulin
(covered in detail in e-tutorial and seminar)

- Aim: To mimic the insulin secretion pattern in a non-diabetic person using s.c. injections of different insulins used in combination

- Insulin action profile varies with:
  - Absorption from subcutaneous tissues alters with solubility → short, intermediate and long acting
  - Analogues
Insulin errors are common

NPSA figures Nov 2003 to Nov 2009
- 17,000+ insulin safety incidents
- 24% reported harm to the patient
- 18 incidents with fatal or severe outcomes

National Diabetes Inpatient Audit (NaDIA) 2010
- Overall 37% of inpatients experienced at least one medication error
- 26% of inpatients had at least one prescription error
- 20% experienced one or more medication management errors
- Patients with one or more medication errors more than 2x as likely to experience a severe hypoglycaemic episode (18% compared to 8%)
## Types of error

<table>
<thead>
<tr>
<th>Type of prescribing error</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin not written up</td>
<td>328</td>
<td>7.1%</td>
</tr>
<tr>
<td>Name of insulin incorrect</td>
<td>508</td>
<td>11.1%</td>
</tr>
<tr>
<td>Number (dose) unclear</td>
<td>349</td>
<td>7.6%</td>
</tr>
<tr>
<td>Unit abbreviated to u or written unclearly</td>
<td>613</td>
<td>13.4%</td>
</tr>
<tr>
<td>Insulin or prescription chart not signed</td>
<td>285</td>
<td>6.2%</td>
</tr>
<tr>
<td>Insulin not signed as given</td>
<td>580</td>
<td>12.7%</td>
</tr>
<tr>
<td>Insulin given/prescribed at wrong time</td>
<td>363</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

The consequences are serious

Nurse mistakenly gave 85 yr old woman a lethal dose of insulin

She was injected with 10x too much insulin using the wrong syringe and died six hours later

Coroner ruled that she was unlawfully killed
Replacing insulin more effectively

Other approaches

• Improved matching of insulin to carbohydrate intake
• Continuous subcutaneous insulin infusion pumps
• Continuous glucose monitoring systems
• Closed loop systems
• Whole pancreas transplant
• Islet transplantation
• Immunotherapy to preserve residual β cell mass
Enhancing endogenous insulin secretion (1)

sulphonyurea drugs (e.g. gliclazide)
(covered in detail in e-tutorial and seminar)

Sulphonylureas also activate Na/K+ ATPase

Activation of Enzymes

K^+

Ca^{2+}

G

Make Insulin

Glucose makes more ATP

2 3 4 5 6 7 8
Enhancing endogenous insulin secretion (2)
incretin mimetics
(GLP-1 agonists and DPP-4 inhibitors)

Incretin effect:
substantially more insulin is secreted in response to oral glucose than to i.v. glucose
Physiology

Glucose (and neural signals) trigger secretion of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). ↑ insulin

Type 2 diabetes,
- ↓ GLP-1 response
- GIP resistance
Problems

- GIP and GLP-1 rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) made in gut cells adjacent to secreting L cells
- half-life 1-2 minutes
Potential solutions

Incretin mimetics insensitive to DPP-4
- Exenatide
- Liraglutide

Incretin enhancers inhibit action of DPP-4
- vildagliptin
- sitagliptin

“If provoked, the shy and reclusive Gila Monster strikes back with a tenacious, venomous bite.”
Increasing insulin sensitivity (1)

Lifestyle changes

UKPDS 1983
The benefits of the trial of diet and exercise

- effective in lowering blood glucose and weight
- demonstrates to the patient
  - the importance of lifestyle changes in managing his/her diabetes
  - type 2 diabetes is more than just tablets
  - he/she is the key player
- all of these lessons will be important at every stage of the condition
Increasing insulin sensitivity (2)

Metformin

(covered in detail in e-tutorial and seminar)

- The **keystone** of management of type 2 diabetes
- Suppresses hepatic glucose production
- Activates AMP-activated protein kinase (AMPK) → effects on insulin signalling, energy balance, and glucose and fat metabolism
- enhances peripheral glucose uptake
- delays uptake of glucose from the intestinal tract
- ? GLP-1 agonist effect
Increasing insulin sensitivity (2)

Metformin

Other benefits

• ↓ appetite
• ↓ weight gain associated with insulin therapy
• ↓ risk of macrovascular complications
• Recent evidence suggest metformin reduces excess cancer risk in type 2 diabetes
• Price
Metformin
potential problems

Life threatening
• Lactic acidosis: Avoid metformin in
  • Renal failure
  • Heart failure
  • Liver failure

Common and unpleasant
• GI upset (diarrhoea, nausea, flatulence etc)
  • Introduce treatment gradually
  • Take tablets on a full stomach
Increasing insulin sensitivity (3)
Thiazolidiones (glitazones)

• Bind to PPAR \( \gamma \) (peroxisome proliferator-activated receptors) receptors in the cell nucleus
• Upregulate genes leading to multiple effects e.g.
  • ↓ insulin resistance
  • modification of adipocyte differentiation
  • ↓ VEGF-induced angiogenesis is inhibited
  • ↓ leptin levels and ↑ adiponectin etc.
• Two of three agents withdrawn (troglitazone and rosiglitazone, now only pioglitazone available)
Reducing glucose absorption

Acarbose

- inhibitor of intestinal alpha glucosidases
- delays the digestion and absorption of starch and sucrose
- Small but significant effect on hyperglycaemia
- Reduces HbA1c by about 0.5% in trials
- Use limited by flatulence
Increasing glucose excretion
sodium-glucose co-transporter inhibition
a novel strategy

• Mutations in kidney-specific SGLT2 isoform result in benign glycosuria
• Suppression of SGLT2 elevates renal glucose excretion
• SGLT2 inhibitors (e.g. Dapagliflozin) can reduce plasma glucose and decrease weight
• Side effects predictable from mechanism
• NICE approved for use with metformin and/or insulin
Treating the glucose

Approaches

Replace insulin

Enhance endogenous insulin secretion
- Sulphonylurea
- GLP-1 agonists
- DPP-4 inhibitors

Increase insulin sensitivity
- Weight loss
- Exercise
- Metformin
- Glitazone

Reduce glucose absorption
- Acarbose

Increase glucose excretion
- SGLT2 inhibition
Principles of treatment of type 2 diabetes

Lifestyle measures
  - diet & exercise

2-3/12

Thin?  
Sulphonylurea
  - Add metformin

Type 2 diabetes is a progressive disease (↓ insulin secretion)

Overweight?  
Metformin
  - Add sulphonylurea

Insulin ± metformin

Incretins?

Glitazones?
Reducing the risk of complications

1. Control risk factors

- BP < 140/80
- Glucose
  - HbA1c < 7.0%
- Lipids
  - Chol < 4.0 mmol/L

esp. microvascular

esp. macrovascular
Annual review

Exploration of any concerns

Metabolic management
- home blood glucose monitoring
- dietary assessment
- injection sites
  - HbA1c
  - hypoglycaemia

Identification of risk factors for CHD and other complications
- smoking
  - obesity, physical inactivity
- hypertension
  - dyslipidaemia

Surveillance for long term complications
- eyes: retinal photograph or dilated fundoscopy, visual acuity
- kidneys: creatinine, eGFR, proteinuria/microalbuminuria
- feet: standard foot assessment, including painful neuropathy
- erectile dysfunction

Other issues
1. psychological or coping problems:
   - depression
   - eating disorders etc.
2. pregnancy and contraception
   - pre-pregnancy counselling
3. lifestyle issues
   - work, leisure, travel
   - driving regulations
4. immunization
   - influenza
   - pneumococcus

Interim review
- concerns
- glycaemic control
- control of risk factors
- management options

Agree care plan

Consider need for referral for specialist advice and treatment
Managing diabetic emergencies
(covered in detail in e-tutorial and seminar)

• Diabetic ketoacidosis
• Hyperosmolar non-ketotic state
• Hypoglycaemia
Managing established problems

- Psychological support
- Neuropathy
  - Foot care
  - Drugs for neuropathic pain
  - Treatment of erectile dysfunction, gastroparesis etc
- Retinopathy
  - Laser
- Nephropathy
  - Renal replacement
- Macrovascular disease
  - revascularisation
Conclusion

Remember the person