Diabetes Mellitus: Diagnosis and Management

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Diabetes Mellitus

- Prevalence and incidence
- Screening and diagnostic criteria
- Review of medical therapies for type 2 DM
- Diagnosis and treatment of complications

Etiologic Classification

- **Type 1**
  - Immune-mediated, Idiopathic
  - β-cell destruction, leading to absolute insulin deficiency

- **Type 2**
  - From predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance

Etiologic Classification

- **Other Specific Types**
  - Genetic defects of β-cell function
  - Genetic defects in insulin action
  - Diseases of the exocrine pancreas
  - Endocrinopathies
  - Drug or chemical induced
  - Infections
  - Uncommon forms of immune-mediated
  - Other genetic syndromes

- **Gestational Diabetes**
Gestational Diabetes

- Any glucose intolerance first detected during pregnancy
- Affects ~ 5% of all pregnancies
- Increases risk of
  - Macrosomia
  - Cesarean section
  - Hypertension
  - Diabetes type 2

Prevalence of diabetes

- 6.2% of total population
- 20% of persons over 65
- Highest in certain ethnic groups
  - African American (up to 12%)
  - Asian American (up to 22%)
  - Latin American (up to 20%)
  - Native American (up to 60%)

Incidence of diabetes type 2

- 800,000 new cases every year
- 2,000 new cases every day

Prevalence of diabetes

- 1 million Type 1
- 11 million Type 2 diagnosed
- 6 million Type 2 undiagnosed
- 150,000 GDM
Screening and Diagnosis

- 45 years and older, every three years
- Younger age, more frequently if
  - BMI > 27 kg/m2
  - First degree relative with diabetes
  - Physical inactivity
  - African American, Latin American, Asian American, Pacific Islander, or Native American
  - History of GDM or baby weighing over 9 pounds
  - Hypertensive
  - HDL < 35 mg/dl or TG > 250 mg/dl
  - History of impaired glucose tolerance

Criteria for Diagnosis

- Fasting plasma glucose > 126 mg/dl, or
- Symptoms plus random plasma glucose > 200 mg/dl, or
- Two-hour plasma glucose > 200 mg/dl on OGTT of 75 gm glucose

Symptoms

- None
- Usual: polys, constipation, nocturia
- Change in vision
- Fatigue
- Numbness or tingling
- Infections: Yeast, UTI’s
- Periodontal disease
- Impotence

Criteria for Diagnosis

- Fasting plasma glucose > 126 mg/dl, or
- Symptoms plus random plasma glucose > 200 mg/dl, or
- Two-hour plasma glucose > 200 mg/dl on OGTT of 75 gm glucose
Criteria for Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Impaired</th>
<th>Diagnostic</th>
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</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>&lt; 100</td>
<td>100 – 125</td>
<td>≥ 126</td>
</tr>
<tr>
<td>OGTT</td>
<td>&lt; 140</td>
<td>140 – 199</td>
<td>≥ 200</td>
</tr>
</tbody>
</table>

Diabetes Control and Complications Trial (DCCT)

- 1400 patients with Type 1 DM
- Randomized to intensive vs. conventional therapy
- Followed for an average of 6.5 years
- 36 person-hours/patient/month
- Glycated hemoglobin levels of 7% vs. 9%

DCCT

- Intensive therapy provided significant 1º and 2º prevention of retinopathy (73% and 54%)
- Intensive therapy was associated with decreased incidence of microalbuminuria, albuminuria, and clinical neuropathy (40% to 70%)
- Benefits persisted four years after trial stopped
- Two to three times increased incidence of severe hypoglycemia, and increased costs with intensive treatment

Treatment of DM Type 1

- Insulin regimens
  - Multiple dosing
  - Continuous subcutaneous infusion
  - Aim for tight control except in younger children

- Individualized therapy

- Family education
Flexible Insulin Regimens

- Usual requirements 0.5 to 1.0 U/kg/d
- Absorption depends on site, conc., mixing
- Basal (background) therapy balanced with mealtime (bolus) insulin
- If pre-meal glucose above 250
  - urine ketones
  - ↑ basal and mealtime dose
  - hydration status

Physiologic Insulin Response

Basal insulin supplies about 50% of the body's needs. Insulin secreted in response to meals supplies the other 50%.

UKPDS (1998)

- 5,000 patients monitored over ten years
- Intensive treatment: insulin, sulfonylurea, metformin, or combination
- Conventional treatment: diet
- Initial differences in glycated hemoglobin: 7.0% vs. 7.9%
- Final overall differences: 7.9% vs. 8.5%

UKPDS -- results

10-40% risk reduction in microvascular complications (+ 25% reduction for each 1% drop in HbA1c)
UKPDS

- Overall risk of microvascular complications decreased with intensive therapy by 25%
- 80% of patients in conventional group eventually needed drug therapy
- No increase or decrease in cardiovascular complications

UKPDS: Hypertension

- 1000 patients
- Tight (144/82) vs. less tight (154/87) control
- Decreased risk of all complications by 24% - 56%
- ACEI and β-blocker equally effective
- Additive benefit of glucose and hypertension control

Oral Agents for DM Type 2

- Secretagogues
  - Sulfonylureas
  - Meglitinides - repaglinide
  - D-Phenylalanine derivative - nateglinide
- Insulin sensitizers
  - Metformin
  - Glitazones
- Others
  - α - Glucosidase inhibitors

Sulfonylureas

- Stimulate receptor-mediated insulin secretion
- Improve hepatic and peripheral insulin sensitivity
- Secondary treatment failure 5% to 10% per year
Sulfonylureas

- Increase dose every 7-14 days by 50% - 100%
- Side effects: hypoglycemia, weight gain, skin reactions, rare cholestatic hepatitis
- Maximum effective dose is half maximum recommended dose

<table>
<thead>
<tr>
<th>Name</th>
<th>Metabolism/excretion</th>
<th>Duration (hrs)</th>
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</thead>
<tbody>
<tr>
<td>acetohexamide</td>
<td>Liver/kidney</td>
<td>10-16</td>
</tr>
<tr>
<td>chlopropamide</td>
<td>Kidney</td>
<td>~ 60</td>
</tr>
<tr>
<td>tolazamide</td>
<td>Liver</td>
<td>12-20</td>
</tr>
<tr>
<td>tolbutamide</td>
<td>Liver</td>
<td>6-12</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Liver/kidney</td>
<td>24</td>
</tr>
<tr>
<td>glyburide</td>
<td>Liver/kidney</td>
<td>up to 36</td>
</tr>
<tr>
<td>glipizide</td>
<td>Liver/kidney</td>
<td>12-24</td>
</tr>
<tr>
<td>glipizide XL</td>
<td>Liver/kidney</td>
<td>24</td>
</tr>
</tbody>
</table>

Repaglinide and Nateglinide

- A meglitinide and a d-phenylalanine derivative
- Stimulate insulin secretion, different receptor than sulfonylureas; no effect on peripheral tissues
- Quickly absorbed; short half life (2 hours)
- OK to use in renal insufficiency
- Prescription guidelines
  - Take before meals
  - Skip dose if not able to eat within 30 minutes
  - Increase dose weekly
  - Side effects: hypoglycemia

Insulin Sensitizers

- Metformin and the glitazones
- Ongoing studies to determine if they prevent or delay onset of DM2
Metformin

- Suppresses hepatic glucose output
- Improves oxidative disposal of glucose and lactate
- Improves sensitivity of muscle to insulin
- Decreases total cholesterol and triglycerides
- Weight neutral or small weight loss

Absorbed in small intestine; maximal plasma concentration 1 to 2 hours after dose

Plasma half life 1.5 to 5 hours; not metabolized; 90% eliminated within 12 hours

Increases clearance of warfarin, decreases clearance of cimetidine, decreases B12 absorption

Accounts for majority of survival effect in UKPDS – specifically decreased MI incidence

Effect of Metformin on CVD

Metformin Treatment Guidelines

- Initial monotherapy or in combination (Metformin/glyburide)
- Start with 500 mg q.d.
- Take with meals; can increase dose quickly if tolerated
- Maximum dose up to 2550 mg/day (850 mg t.i.d.). Maximum response at 2000 mg/day.
- Limited by side effects: abdominal cramps, diarrhea, nausea, anorexia
**Metformin Precautions**

- Contraindicated in:
  - Renal insufficiency (SCreat >1.4 women, >1.5 men)
  - Liver disease or active alcohol abuse
  - Pregnancy and lactation

- Discontinue for:
  - IV contrast agents
  - Surgical procedures
  - Cardiac or respiratory failure, hypoxemia
  - Severe infection, sepsis

**Thiazolidinediones (Glitazones)**

- Bind to receptors that regulate transcription of insulin-responsive genes
- Insulin-sensitizing in muscle, liver, and adipose tissue
- Decrease hypertriglyceridemia, hyperinsulinemia, and hyperglycemia
- Increase both HDL and LDL cholesterol

**Troglitazone**

- Was first agent
- Associated with severe, idiosyncratic liver injury
- Off the market as of March, 2000
- Rosiglitazone and pioglitazone appear safe(r)
Thiazolidinediones (Glitazones)

- Troglitazone induces cytochrome p450 isoform 3A4; prone to multiple drug interactions
- In clinical trials, incidence of significant increases in ALT with rosiglitazone and pioglitazone was similar to placebo
- Few reports of liver injury with rosiglitazone and pioglitazone after millions of prescriptions

Thiazolidinediones (Glitazones)

- Begin with lowest daily dose, with or without food
- Maximal response to therapy takes up to 12 weeks
- Monitor liver enzymes: prior to therapy and every two months
- Side effects: transaminitis, weight gain, fluid retention, edema

Thiazolidinediones (Glitazones)

- TZD’s and heart disease

Thiazolidinediones (Glitazones)

- Contraindicated in heart failure
- Contraindicated in pregnancy
- OK to use in renal insufficiency
α-Glucosidase Inhibitors

- Act upon uptake at the intestinal brush border
- Slow absorption of carbohydrates and reduces rise in postprandial glucose levels
- Acarbose or miglitol, initial dose 25 mg t.i.d. with first bite of meal, increase sloooooowly
- Side effects: flatulence, diarrhea, abdominal cramps, decreased metformin absorption
- Contraindicated in significant liver or renal disease (SCreat >2.0)

Treatment Effectiveness

Average Reduction of Hb A₁c

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>1-2</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1-2</td>
</tr>
<tr>
<td>Metformin</td>
<td>1-2</td>
</tr>
<tr>
<td>Acarbose</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>0.5-1.5</td>
</tr>
</tbody>
</table>

Goals for Glycemic Control

<table>
<thead>
<tr>
<th>Whole Blood Values</th>
<th>Normal</th>
<th>Goal</th>
<th>Add’l Action Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average preprandial glucose</td>
<td>&lt;100</td>
<td>80-120</td>
<td>&lt;80/&gt;140</td>
</tr>
<tr>
<td>Average bedtime glucose</td>
<td>&lt;110</td>
<td>100-140</td>
<td>&lt;100/&gt;160</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma Values</th>
<th>Normal</th>
<th>Goal</th>
<th>Add’l Action Suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average preprandial glucose</td>
<td>&lt;110</td>
<td>90-130</td>
<td>&lt;90/&gt;150</td>
</tr>
<tr>
<td>Average bedtime glucose</td>
<td>&lt;120</td>
<td>110-150</td>
<td>&lt;110/&gt;180</td>
</tr>
</tbody>
</table>

HbA₁c (%) | <6 | <7 | >8

Approaching Glycemic Goals

- Targets must be individualized
- All measurements do not have to fall within the target range with self-monitoring
- If over half of the measurements within a given time fall within the range, glucose control is considered acceptable
- Risk of hypoglycemia should be factored into goals

- About 50 percent of people with type 2 diabetes require insulin to maintain a HbA1c level below 7%
Progressive decline in beta-cell function/insulin secretion in DM2

Patient, 2004

Ms. A is a 46 year old woman who was diagnosed with type 2 DM about 6 years ago. She has a history of GDM (her daughter is now 8 years old); both her sisters have DM2. She works as a home health aide. She is on metformin 1000 mg bid, and on glipizide 10 mg every morning. Her A1C, which was 7% in 2002, has been climbing steadily and is now 9.6%.

Patient, 2004, continued

- Adherence?
- Adequate doses of medications, taken at correct times?
- Changes in activity, weight, or diet? OR
- Natural progression of disease?

Patient, 2004, continued

Options
- Increase physical activity/Nutrition consult
- Glitazone
  - Expensive
  - MUST monitor ALT regularly
  - Weight gain/edema
- Increase Glipizide to 20 mg q AM
  - Not much extra benefit
- Add bedtime insulin (augmentation therapy, B.I.D.S.)
**Insulin resistance syndrome**

**Patient, 2004, continued**

- Her weight is 90 Kg
- She eats three meals/day
- She has the following record of her SMG

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Before dinner</th>
<th>Before bed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurs.</td>
<td>250</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>Fri.</td>
<td>240</td>
<td>160</td>
<td>175</td>
</tr>
<tr>
<td>Sat.</td>
<td>255</td>
<td>160</td>
<td>188</td>
</tr>
</tbody>
</table>

**Insulin Preparations**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Onset</th>
<th>Peak (hrs)</th>
<th>Duration (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro (rapid-acting)</td>
<td>10 - 30 mins</td>
<td>0.5 - 1</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Regular (short-acting)</td>
<td>30 - 60 mins</td>
<td>1.5 - 2</td>
<td>5 - 12</td>
</tr>
<tr>
<td>Premixed (70% NPH/30% R)</td>
<td>30 - 60 mins</td>
<td>3 (2-12)</td>
<td>13 - 18</td>
</tr>
<tr>
<td>NPH/Lente (intermediate-acting)</td>
<td>1-2 hrs</td>
<td>4 - 8</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Utralente (long-acting)</td>
<td>2 - 4 hrs</td>
<td>8 - 20</td>
<td>16 - 24</td>
</tr>
<tr>
<td>Glargine (long-acting)</td>
<td>1 - 2 hrs</td>
<td>No peak</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

**Physiologic Insulin Response**

Basal insulin supplies about 50% of the body’s needs. Insulin secreted in response to meals supplies the other 50%.
Bedtime insulin: augmentation

- Basal insulin
  - NPH
  - Ultralente
  - Glargine

Duration of Insulin

Bedtime insulin: augmentation

- Initial dose 10 – 20 U
- Approximate:
  - 0.15 – 0.2 U/Kg/d
  - 90 Kg * 0.15 = 13.5 U
  - FCG in mmol/L, (i.e.: if FCG = 250)
    - 250 / 18 = 14 U
  - Adjust to a FCG 90-130
    - Increase by 4U if FCG > 140 on three consecutive mornings

Glargine

- Long-acting insulin analogue - used once daily
- Structure is modified to a more acidic pH - delays its absorption over 24 hours, with no clear peak
- A clear insulin (most longer-acting insulins are cloudy)
- Cannot be mixed with other insulins
Glargine

- Mimics the action of basal or background insulin
- More consistent action because of lack of peak
- Risk of hypoglycemia is reduced because of its long duration of action
- Usually given once daily
- Most will require bolus coverage as well

Basal augmentation with NPH

Goals of Therapy

- Decrease morbidity and mortality
  - CHD, Stroke
- Maximize therapy of CV risk factors
- Identify and treat complications early
- Maintain function/quality of life
- Minimize side effects
Prevention of Complications

- Coronary heart disease
- Stroke
- Ischemic peripheral vascular disease
- Retinopathy
- Nephropathy
- Neuropathy

Coronary Heart Disease and Stroke

- Smoking cessation
- Daily aspirin therapy
- Hypertension control
  - ACE inhibitors, ß-blockers, Diuretics
  - Treatment of dyslipidemia

Treatment of Dyslipidemia

- Treatment based on LDL cholesterol level
  - Highest risk is LDL > 130
  - Statins are the best studied agents
  - Gemfibrozil helpful in isolated low HDL
    - Veterans’ Administration HDL Cholesterol Intervention Trial Study
    - Benefit in treating isolated decreased HDL in patients at risk for CHD

- Medical treatment recommended
  - If CVD or DM, and LDL > 100

Prevention of Microvascular Complications

- Control of blood pressure
- Glucose control
- Early identification and treatment of neuropathy, nephropathy, and retinopathy
Nephropathy

- Occurs in ~6% of patients with Type 2 DM (30% - 40% of patients with Type 1 DM)
- 40% of new ESRD diagnoses are patients with Type 2 DM
- Persistent microalbuminuria predicts progression to nephropathy.
- Risk for microalbuminuria rises with HgbA\textsubscript{1C} values above 8.1% in Type 1 DM

Nephropathy

- ACEI's slow progress to albuminuria and renal failure and reduce risk of death in Type 1 DM
- ACEI's decrease rate of progress and slow rate of loss of renal function in Type 2 DM
  - 24% in the HOPE study
- ARB's decrease progression to proteinuria in Type 2 DM

Nephropathy

- Non-dihydropyridine calcium channel blockers (i.e. diltiazem) have similar protective effects
- Control of systolic blood pressure to 130/80 mmHg offers similar protection
- Smoking cessation, glucose control, statin therapy,

Nephropathy

- Screen all patients at intake with urinalysis
- If proteinuria, quantify and begin treatment
- If normal, check for microalbuminuria
  - If abnormal, confirm and begin treatment
  - If normal, repeat every one to two years
Multifactorial Intervention of CVD (Steno 2 study, Denmark 1/2003)

- Open, parallel trial of 160 patients half each in conventional vs. multifactorial intervention treatment
- Target driven, intensified intervention
- Stepwise implementation of behavioral mod, pharmacologic therapy, treatment of HTN, dyslipidemia, microalbuminuria, and secondary prevention with aspirin
- Average age 55 years, mean FU 7.8 years

Interventions:

- Nutrition: <30% fats, <10% saturated fats
- Exercise: 30 min exercise 3-5x/week
- Protocol treatment
  - Stepwise treatment with metformin, a SU, and insulin
  - Followed guidelines for treating microalbuminuria, hypertension, and dyslipidemia

- Decreased risk CVD (HR 0.47)
- Decreased risk of nephropathy (HR 0.42)
- Decreased risk of neuropathy (HR 0.37)

Major differences between intervention and control groups?

- Lifestyle Modification: Exercise
- Treatments: ACEI and or ARB’s, Statins, Aspirin, multivitamin
Diabetes Prevention Program Research Group (2/02)

- 3200 patients with glucose intolerance
- Randomized: placebo vs. metformin vs. lifestyle modification (goals 7% weight loss and 150 min exercise/week)
- Average age 51, BMI 34, 68% women, 35% ethnic minorities
- Mean FU 2.8 years

Diabetes Prevention Program Research Group

- Incidence of DM2
  - 11% in placebo
  - 7.8% metformin
    - most effective in <45 y.o. or BMI>35
  - 4.8% lifestyle mod
    - most effective in >60 y.o, regardless of BMI

- Metformin decreased incidence by 31% (NNT 14 for 3 years)
- Lifestyle mod decreased incidence by 58% (NNT 7 for 3 years)

The End

Good luck on your exam!

Insulin: the advanced seminar

- Individualized; flexible; plans for sick days
- Accounting for and counting carbs
  - 1U for every 5 – 15 gms of CHO
- Accounting for activity level
  - Decrease dose by 30 – 50% depending on timing and length of exercise
- Team care
  - Weekly adjustments with acute changes
  - Chronic management
Patient, 2008

Ms. Alegria developed nephropathy, despite being on benazepril for the last 3 years. Since her CrCl is approximately 52, she had to discontinue her metformin. Her BP is 120/80, her LDL is 95, and she is on daily aspirin. You start her on NPH/Reg premixed 70/30 insulin at 20 U b.i.d. At follow-up 2 months later, her A1C is now 10.2, and she tells you that she often feels sweaty and anxious mid morning and at bedtime, and that she has gained 4 Kg.

Patient, 2008, continued

- Her weight is now 98 Kg
- She eats three meals and two snacks/day
- She has the following record of her SMG

<table>
<thead>
<tr>
<th></th>
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<th>Before bed</th>
</tr>
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<tbody>
<tr>
<td>Thurs.</td>
<td>100</td>
<td>180</td>
<td>65</td>
</tr>
<tr>
<td>Fri.</td>
<td>95</td>
<td>199</td>
<td>88</td>
</tr>
<tr>
<td>Sat.</td>
<td>106</td>
<td>102</td>
<td>59</td>
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</table>

Goals for Glycemic Control (ADA)

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>GOAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ave pre-prandial</td>
<td>100</td>
<td>80 – 120</td>
</tr>
<tr>
<td>Ave bedtime</td>
<td>110</td>
<td>100 - 140</td>
</tr>
<tr>
<td>Plasma values</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>110</td>
<td>90 – 130</td>
</tr>
<tr>
<td>Ave bedtime</td>
<td>120</td>
<td>110 - 150</td>
</tr>
</tbody>
</table>

Patient, 2008, what is going on?

- Not enough insulin?
- Too much insulin?
- Not at the right times?
- Increased caloric intake (carbohydrate snacks)?
- All of the above?
Pre-mixed 70/30 b.i.d.: NPH effect

Pre-mixed 70/30 b.i.d.: total insulin effect

Total insulin effect & stacking

Patient, 2004, continued

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<td>Sat.</td>
<td>106</td>
<td>102</td>
<td>59</td>
</tr>
<tr>
<td>Sun.</td>
<td>234</td>
<td>211</td>
<td>80</td>
</tr>
</tbody>
</table>
Physiologic Insulin Response

Basal insulin supplies about 50% of the body's needs. Insulin secreted in response to meals supplies the other 50%.

Bolus therapy/prandial therapy

Advantages:
- Less weight gain
- Fewer hypoglycemic episodes
- Flexible meal times

Regular insulin
- Needs to be given 30 mins. before meals

Lispro (Humalog®)
- Can be given at mealtime

Basal-bolus therapy

Figure 6. Split-mixed regimen. (Neutral protamine Hagedorn = NPH)
Replacement therapy

- Average insulin needs (patients w/DM2):
  - 0.5 U/Kg/day – 2.0 U/Kg/day

- About 50% should be given as prandial therapy

Replacement therapy

- Supplement:
  - About 1 U will change BG by 50 mg/dL (less in the face of increased resistance)

- Correct (in order)
  - Hypoglycemia
  - Fasting glucose (by increasing basal insulin)
  - Pre-prandial levels (by increasing bolus insulin or changing to rapid acting)

Replacement therapy: NPH & lispro

Replacement therapy: glargine and lispro

Figure 7. Basal plus meal-related regimen using glargine plus aspart or lispro.
Insulin: the advanced seminar
Is there a downside?

- Hypoglycemia episodes (about one severe episode/year in the UKDPS)
- Weight gain: from insulin effect and from over treatment/hunger response
  - About 2 Kg in UKDPS
- Worsening of retinopathy
  - Reported with rapid correction of initial A1C>10
  - **However**, early worsening rarely progresses to neovascularization