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
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

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- 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 1° and 2° 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**

- 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>chlorpropamide</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>
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**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

Metformin

- 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

- 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

**Thiazolidinediones (Glitazones)**
- Troglitazone was first agent
- Associated with severe, idiosyncratic liver injury
- Off the market as of March, 2000
- Rosiglitazone and pioglitazone appear safe
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: CV Risk

- Nissen, NEJM 2007: “data suggest a cv risk associated with the use of rosiglitazone.”
- Home, NEJM 2007: “interim findings …were inconclusive … no evidence of any increase in death from either cv causes or all causes. Rosiglitazone associated with an increased risk of heart failure. data were insufficient to determine whether the drug was associated with an increase in the risk of m.i.”
- Erdmann, AJCC 2007: “In high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS.”

Thiazolidinediones: CHN

Endocrine/Clinical Pharmacy recommendations until further information is available (FDA hearing July 30, 2007):
- The data on cardiovascular outcomes effects of rosiglitazone are far from conclusive but raise cause for concern.
- The data on cardiovascular outcomes effects of pioglitazone are also not conclusive but there are no data to suggest it has adverse cardiovascular outcomes and it may be beneficial.

Contraindicated in heart failure
Contraindicated in pregnancy
OK to use in renal insufficiency
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

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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reduction (%)</th>
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<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 - 1.5</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>0.5 - 1.5</td>
</tr>
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Goals for Glycemic Control

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<tr>
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<th>Normal</th>
<th>Goal</th>
<th>Additional 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>
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<table>
<thead>
<tr>
<th>Plasma Values</th>
<th>Normal</th>
<th>Goal</th>
<th>Additional Action Suggested</th>
</tr>
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<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 (%)<br />
- Normal: <6<br />- Goal: <7<br />- Additional Action Suggested: >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%

**Patient A**

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 A continued**

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

Patient, 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 resistance syndrome

Insulin Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Onset</th>
<th>Peak (hrs)</th>
<th>Duration (hrs)</th>
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<td>30 – 60 mins</td>
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<td>NPH/Lente (intermediate-acting)</td>
<td>1-2 hrs</td>
<td>4 - 8</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Ultralente (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

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 theoretically reduced because of long duration of action
- Usually given once daily
- Most will require bolus coverage as well

Basal augmentation with NPH

Basal augmentation with glargine
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, β-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

Multifactorial Intervention of CVD

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

Multifactorial Intervention of CVD

- 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

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<td>180</td>
<td>65</td>
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<td>Fri.</td>
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<td>88</td>
</tr>
<tr>
<td>Sat.</td>
<td>106</td>
<td>102</td>
<td>59</td>
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Goals for Glycemic Control (ADA)

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<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>
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<td>Plasma values</td>
<td></td>
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<td>120</td>
<td>110 - 150</td>
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</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?

Insulin and its analogues

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NPH dosed b.i.d.

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Total insulin effect

Total insulin effects & stacking

Patient, 2004, continued

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>Before dinner</th>
<th>Before bed</th>
</tr>
</thead>
<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>
</tr>
<tr>
<td>Sun.</td>
<td>234</td>
<td>211</td>
<td>80</td>
</tr>
</tbody>
</table>

Physiologic Insulin Response

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

- 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

- 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

Replacement therapy: glargine and lispro

Insulin: the advanced seminar

Is there a downside?

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  - Reported with rapid correction of initial A1C>10
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