Distinguishing between Diabetes Mellitus Type 1 and Type 2, (with Overview of Treatment Strategies)

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Glucose Tolerance Categories

Adapted from The Expert Committee on the Diagnosis and Classification of DM. *Diabetes Care*. 1997;20:1183-1197.

**FPG**
- Diabetes Mellitus: 126 mg/dL
- Impaired Fasting Glucose: 100 mg/dL
- Normal: 7.0 mmol/L
- Prediabetes: 6.1 mmol/L

**2-Hour PG on OGTT**
- Diabetes Mellitus: 200 mg/dL
- Impaired Glucose Tolerance: 11.1 mmol/L
- Normal: 7.8 mmol/L

Categories of Increased Risk for Diabetes (Prediabetes)

- FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l) [IFG]
- 2-h PG in the 75-g OGTT 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l) [IGT]
- A1C 5.7-6.4%

*Diabetes Care* 2010;33:S62-S69
Classification of Diabetes

- Type 1 DM
  - Due to Beta Cell destruction whether immune or non-immune.
  - Requires Insulin as replacement Therapy

- Type 2 DM
  - Primarily due to resistance to the action of Insulin.
  - Therapy should be directed toward reducing insulin requirements.
  - Has secondary Beta cell loss that may require stimulation of insulin release or Insulin therapy late in the disease process
Classification of Diabetes

• Based on epidemiologic grounds
• Based on ethic background
• Associated conditions
• Laboratory

At Diagnosis Type 2 Diabetes

• More common in Latinos, African Americans and Native Americans
• Older
• Heavier (Centrally Obese = Increased Waist to Hip)
• Family history of diabetes
• More likely to have
  – Hypertension
  – Hypertriglyceridemia
  – Low HDL
• More cardiovascular disease
Multiple Risk Factors: Implications for CHD Risk

- Hypertension
  - SBP 150 mm Hg
    - x1.5
- Dyslipidemia
  - TC 260 mg/dL
    - x2.3
- Glucose Intolerance
  - x1.8


At Diagnosis Type 1 Diabetes

- More commonly Caucasian
- Tend to be younger
- More likely normal weight or to present with significant weight loss
- Unlikely to have family members with diabetes
- Likely to have other auto-immune endocrine problems such as hypo or hyperthyroidism
Caveats

- Childhood obesity has lead to increase in Type 2 DM in children and young adults.
- LADA (Latent Autoimmune Diabetes in Adults)
- African Americans, Latinos and even Native Americans most often are admixed with Caucasian
- African Americans often have hypertension
- Latinos often have normal BP at diagnosis

Diabetes Types and Stages

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<th>Stages</th>
<th>Normoglycemia</th>
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<td>Normal glucose regulation</td>
<td>Impaired Glucose Tolerance or Impaired Fasting Glucose (Pre-Diabetes)</td>
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<td>Types</td>
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Diabetes Care 2010;33:962-969
Laboratory

- C-Peptide
- Islet antibodies
  - Most likely positive GAD

Natural History of Type 2 Diabetes

R. Bergenstal and D. Kendall, International Diabetes Center
Natural History of Type 1 Diabetes

What Do the Diabetes Share?

- Hyperglycemia
- Hyperglycemia related complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
Cumulative Incidence of a Sustained Change in Retinopathy in Patients with IDDM Receiving Intensive or Conventional Therapy

The Diabetes Control and Complications Trial Research Group.

Implications for Therapy

- Type 1 Diabetes will need insulin for survival
- Multi Dose Insulin (MDI) is preferred
  OR
- Insulin pump
Example of Connaught insulin produced in Toronto, 1923

Human Insulin

A-chain  21 amino acids
B-chain  30 amino acids

Monomers  Dimers  Self-aggregation in solution  Hexamers
Action Profiles of Insulins

Aspart, glulisine, lispro 4–5 hours
- Regular 6–8 hours
- NPH 12–16 hours
- Ultralente 18–20 hours
- Glargine ~24 hours

Insulin Injection Devices

Insulin pens
- Faster and easier than syringes
  - Improve patient attitude and adherence
  - Have accurate dosing mechanisms, but inadequate resuspension of NPH may be a problem

Insulin Pumps

Continuous Subcutaneous Insulin Infusion (CSII)

- For motivated patients
- Expensive
- External, programmable pump connected to an indwelling subcutaneous catheter
  - Only rapid-acting insulin
  - Programmable basal rates
  - Bolus dose without extra injection
  - New pumps with dose calculator function
  - Bolus history
- Requires support system of qualified providers
Pramlitide

- Injected before meals to:
  - Slow gastric emptying
  - Suppress glucagon
  - Decrease appetite (limit weight gain)

Type 2 Medications

- Metformin uniformly recommended as initial therapy for type 2 diabetes unless contraindicated
  - Renal insufficiency
  - Severe liver disease
  - Significant alcohol intake
- GI intolerance
Benefits of Metformin

- Inexpensive
- Reduces insulin resistance at the liver level
- Weight neutral or some weight loss
- Improvement in lipids
- CV benefits
- Reduced cancer incidence
- Decrease in dementia

Other Insulin Sensitizers

- Thiazoladinedione (TZD)
  - Pioglitazone
  - Rosiglitazone

Improve insulin resistance at the muscle, adipose tissue and liver

Lipid benefit (HDL↑ TG↓ ApoB ↓)
CV benefit
**TZD Benefits**

- Improved Insulin Resistance
- Reduced Cancers (other than bladder)
- Increase in HDL cholesterol
- Reduce Triglycerides
- Reduced ApoB (reduced LDL particle number)

*[Pioglitazone only]*

- Reduced MI or Stroke (especially 2nd event)
- Decrease peripheral resistance

**TZD Baggage**

- Weight gain
- Edema
- Fractures (Women)
- ? Bladder cancer?
Other Type 2 Agents

• GLP-1 agonists
• DPP-4 inhibitors
• SGLT-2 inhibitors
• Colesevelam
• QR bromocriptine
• Alpha Glycosidase inhibitors

QR Bromocriptine

• Improves insulin resistance by actions on CNS
• May have some weight loss
• Reduced CV events by 50% in clinical trials

• May cause nausea
• Not to be used in shift workers or rotating schedules
GLP-1 Agonist

- Improve insulin production by Beta-cells
- Induce Weight loss
- Reduction in BP
- Improvement in lipids

DPP-4 Inhibitors

- Extend the action of endogenous GLP-1 and GIP
- Oral medications
- Weight neutral
- No risk of increased CV events
- Question of increase in CHF
SGLT-2 Inhibitors

- Cause modest weight loss (about 5 lb)
- Lower BP
- Diuretic effect

Colesevelam

- Bile sequestering resin
- Lower LDL cholesterol as well
- Can be constipating
Alpha Glycosidase Inhibitors

- Weight neutral of mild weight loss
- Safe – action within the lumen of the intestine
- CV safety
- GI side effects
- Modest effect on glucose lowering

Combinations That Make Sense (Metformin with Almost Anything)

- Metformin/ Pioglitazone
  - Weight neutral or almost
  - Less edema
  - Complimentary lipid effects
  - Reduced Cancer and CV risk

- Metformin with colesvelam balancing GI side-effects
Other Combinations

• Pioglitazone/ SGLT-2 inhibitor
  – Diuretic effect of SGLT-2 balancing Na+ retention of TZD

• DPP-4 inhibitor/ SGLT-2 inhibitor
  – Diuretic effect of SGLT-2 reducing risk for CHF of DPP-4 inhibitor

Pathophysiological Contributions to Hyperglycemia in Type 2 Diabetes:

1. Pancreatic insulin secretion
2. Pancreatic glucagon secretion

5. Gut carbohydrate absorption
8. Kidney- Increased glucose reabsorption
4. Liver

6. Fat- Increased lipolysis, inc FFA

3. Muscle

7. Brain- Inc. Appetite Insulin Resistance, Decrease , GLP-1

HYPERGLYCEMIA

Peripheral glucose uptake
Summary

• Type 1 Diabetic patients require insulin and our task is to provide it in as physiologic manor as possible matching insulin to intake

• Type 2 Diabetic patients have many options which should include 1 or more agents that reduce insulin resistance if possible even if they have reached a state where they require insulin as part of their therapy.

References


• http://www.drugs.com/condition/diabetes-mellitus-type-ii.html