The “Sugar Fix”: Practical Approaches to Blood Glucose Management in Diabetes

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Outline

- Overview and goals
- Pharmacologic therapies
  - Oral medications
  - Insulin
  - Incretins
  - Insulin Delivery System Technologies
- Case discussions

2008 Age-Adjusted Estimates of Adults with Diagnosed Diabetes in Pennsylvania


The State of Diabetes 2011

Positives
- Scientific advances
- Better understanding of disease state
- New therapies
- Improved monitoring devices/technology
- Evidence that Diabetes Education is effective

2008 Age-Adjusted Estimates of the % Obese Adults in PA

BMI=30 kg/m²

### State of Diabetes 2011

**Negatives**
- Increased prevalence/mortality
- Increased costs
- Sub-optimal quality of care
- Insufficient diabetes education/nutrition programs
- Poor access to specialists
- Lack of attention to psychological needs
- Limited time with providers

### Goals
- **Prevention of Diabetes**
  - Lifestyle and nutrition counseling
  - Weight control
  - Identification of new cases through screening
- **Prevention of Complications**
  - Blood glucose control
  - Blood pressure control
  - Lipid control
  - Preconception Counseling and peri-natal screening

### Priorities of Care for Adults with Diabetes

#### Classifications of Diabetes Mellitus

- **Type 1 diabetes**: 5% to 10% of cases
  - Immune-mediated beta-cell destruction leading to absolute insulin deficiency
  - Emphasis on hypoglycemia prevention
  - Prevention of DKA
  - Endocrinologist Care
- **Type 2 diabetes**: 90% to 95% of cases
  - Insulin resistance
  - Insulin deficiency
  - Hallmark is central obesity

#### Other Classifications

- Gestational diabetes mellitus (GDM)
  - ~4% of pregnant women
- Impaired glucose homeostasis
  - Impaired fasting glucose (IFG):
    - FPG >100 and <126 mg/dL
  - Impaired glucose tolerance (IGT):
    - 2 hr OGT PG >140 and <200 mg/dL
    - 79 million people in US > age 20yrs

#### Principles of Metabolic Control

- Defined target goals
- Medical nutrition therapy/physical activity
- Blood glucose monitoring
- Diabetes education
- Physiologic basal bolus insulin replacement (Type 1)
- Stepwise and combined pharmacologic therapies (Type 2)
  - Oral medications and other
  - Insulin

### Other Essentials

- History and Physical Exam
- Prevention
- Medical Nutrition Therapy/Physical Activity
- Patient Education
- Emotional assessment
- Behavioral Health
- Family, peers, medical
- Distress, depression, complications
- Prevention of complications
- Prevention of Diabetes
- Hallmark is central obesity
- Insulin deficiency
- Insulin resistance
- Endocrinologist Care
- Diabetes education
- Defined target goals
- Blood glucose monitoring
- Medical nutrition therapy/physical activity
- Physiologic basal bolus insulin replacement (Type 1)
- Stepwise and combined pharmacologic therapies (Type 2)
  - Oral medications and other
  - Insulin
Diagnostic Criteria for Diabetes

<table>
<thead>
<tr>
<th>Glycemia</th>
<th>FPG (mg/dL)</th>
<th>OGTT (mg/dL)</th>
<th>Casual PG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;100</td>
<td>&lt;140</td>
<td></td>
</tr>
</tbody>
</table>

Diagnostic Criteria for Diabetes

IFG or IGT >100 and <126 >140 and <200

Diabetes >126 >200 >200 plus symptoms

Diabetes Care

Guidelines for Glycemic Control

<table>
<thead>
<tr>
<th>Goal</th>
<th>Non-pregnant adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt;7</td>
</tr>
<tr>
<td>Preprandial plasma glucose (mg/dL)</td>
<td>90–130</td>
</tr>
<tr>
<td>Peak postprandial plasma glucose (mg/dL)</td>
<td>&lt;180</td>
</tr>
</tbody>
</table>

GOALS SHOULD BE INDIVIDUALIZED

DCCT: Diabetic Complication Event Rates

<table>
<thead>
<tr>
<th>Complication</th>
<th>Conventional</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy Progression</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>Laser Rx</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>39%</td>
<td>30%</td>
</tr>
<tr>
<td>Clinical Neuropathy</td>
<td>47%</td>
<td>38%</td>
</tr>
</tbody>
</table>


UKPDS Results of Intensive Therapy: Sulfonylureas/Insulin

Risk Reduction vs Conventional Therapy


Microvascular Complications: Risk Reduction per 1% Decrease in A1C

<table>
<thead>
<tr>
<th>Study</th>
<th>Retinopathy</th>
<th>Nephropathy</th>
<th>Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>27-38%</td>
<td>22-28%</td>
<td>29-35%</td>
</tr>
<tr>
<td>Kumamoto</td>
<td>28%</td>
<td>50%</td>
<td>↑NCV</td>
</tr>
<tr>
<td>UKPDS</td>
<td>19%</td>
<td>26%</td>
<td>18%</td>
</tr>
</tbody>
</table>

NCV = Nerve Conduction Velocity

Stages of Type 2 Diabetes

Why Are Patients Not Meeting Targets?

- Type 2 diabetes has a progressive decline in β-cell function
- Most patients will need insulin to reach glucose targets
- Long lapse between treatment failure and therapy advancement
  - True for both specialists and primary care physicians
  - Reluctance on the part of patients and healthcare providers to advance to injectable medications


Post-prandial Glucose Contributes to Nearly 50% of Overall A1C When A1C Is 8.4 or Below


Correcting Fasting Hyperglycemia...

...is Usually the First Task when A1C is > 8.5%

...then, Tackle Postprandial Hyperglycemia if A1C still > 7%!
Combination Therapy

Combination therapies for the treatment of T2DM have been proven in many instances to be more effective than treatment with a single agent

- The combination of insulin plus metformin and insulin plus a TZD are particularly effective means of lowering glycemia.¹
- Dipeptidyl peptidase IV inhibitors and sulfonylurea is more beneficial than sulfonylureas alone²


Causes of Hyperglycemia in Type 2 Diabetes

Established Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Site of Action</th>
<th>Major Mode of Action</th>
<th>Primary Glucose Lowering Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Peripheral tissue</td>
<td>Allow uptake and utilization of glucose</td>
<td>Fasting or postprandial</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Peripheral tissue</td>
<td>Improve insulin sensitivity</td>
<td>Fasting</td>
</tr>
<tr>
<td>Metformin</td>
<td>Liver</td>
<td>Decrease hepatic glucose output</td>
<td>Fasting</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Pancreas</td>
<td>Stimulate insulin release from β-cells</td>
<td>Fasting</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Pancreas</td>
<td>Stimulate insulin release from β-cells</td>
<td>Postprandial</td>
</tr>
<tr>
<td>Glucosidase inhibitors</td>
<td>GI tract</td>
<td>Delay absorption of carbohydrates</td>
<td>Postprandial</td>
</tr>
</tbody>
</table>

A word about metformin

- Food and Drug Administration prescribing guidelines for metformin contraindicate its use in men and women with serum creatinine concentrations >1.5 and >1.4 mg/dL, respectively.
- Most healthcare providers in the USA do not use metformin if eGFR < 60 mL/min.
**Recommendations for use of metformin based on eGFR**

<table>
<thead>
<tr>
<th>eGFR level (ml/min per 1.73 m²)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤60</td>
<td>No renal comorbidity or on metformin</td>
</tr>
<tr>
<td>&gt;60 and ≤90</td>
<td>Monitor renal function annually, contraceptive use</td>
</tr>
<tr>
<td>&lt;60 and &gt;90</td>
<td>Increase monitoring of renal function (every 3-6 months)</td>
</tr>
<tr>
<td>&lt;60 and &gt;30</td>
<td>* Пауза антидиабетической терапии</td>
</tr>
<tr>
<td>≤30</td>
<td>Continuation of therapy with caution</td>
</tr>
</tbody>
</table>

Additional care is required in patients at risk for acute kidney injury or with anticipated significant fluctuations in renal status, based on previous history, other comorbidities, or potentially renally excreted medications.

Based on recommendations from National Institute for Health and Clinical Excellence Guidelines United Kingdom, Canadian Diabetes Association and Australian Diabetes Society.


**Efficacy of Oral Antihyperglycemics Declines With Time**

- A1C rises at -0.2% to 0.3% yearly on stable therapy
- This rate is the same as for diet alone, sulfonylureas, and metformin
- β-Cell function declines at the same rate with all these treatments
- Combination treatments are routinely needed
- Future direction: β-Cell preservation therapies


**GLP-1 Modes of Action in Humans**

- Upon ingestion of food...
  - GLP-1 is secreted from the L-cells in the intestine
  - This in turn...
    - Stimulates glucose-dependent insulin secretion
    - Suppresses glucagon secretion
    - Slows gastric emptying
    - Reduces food intake

- Long term effects observed in animals...
  - Improves β-cell efficiency and increases β-cell mass


**The Potential for GLP-1 Agonists and Other Gut Hormones**

- Limitations of native or mimetic GLP-1 as therapy
  - Rapidly degraded by DPP-IV in minutes
  - Requires continuous subcutaneous injection

**Alternative approaches**

- Modification of molecule to prolong time of action- GLP-1 Agonists
  - Agents to limit DPP-IV activity-DPP IV Inhibitors

**For Whom?**

- A patient whose diabetes is not controlled by oral therapy with metformin, a sulfonylurea, or combination of the two
- Initial therapy when weight loss is desired and use of metformin is not appropriate
**Difference in GLP-1 Activation vs DPP-IV Inhibition**

<table>
<thead>
<tr>
<th></th>
<th>GLP-1</th>
<th>DPP-IV/Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhance insulin secretion</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Reduce glucagons</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>+++</td>
<td>No</td>
</tr>
<tr>
<td>Weight loss</td>
<td>++</td>
<td>No</td>
</tr>
<tr>
<td>Administration</td>
<td>Injectable</td>
<td>Oral</td>
</tr>
<tr>
<td>Inflammation, allergic reactions</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>

GLP-1: glucagon-like peptide-1

**Summary of Incretin Therapies**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Administration</th>
<th>A1C Reduction</th>
<th>Weight Change</th>
<th>Main Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incretin Mimetics: GLP-1 Agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Twice daily injection</td>
<td>Up to ~0.8%</td>
<td>↑</td>
<td>Nausea</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Once daily injection</td>
<td>Up to ~0.75%</td>
<td>↓</td>
<td>Nausea</td>
</tr>
<tr>
<td>Incretin Enhancers: DPP-IV Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Oral</td>
<td>Up to 0.8%</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Oral</td>
<td>Up to 0.8%</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Oral</td>
<td>Up to 0.8%</td>
<td>++</td>
<td>—</td>
</tr>
</tbody>
</table>

**Amylin the Hormone: Deficient in Diabetes**

Co-located and co-secreted with insulin from pancreatic β-cells

**Pramlintide**

- Is a synthetic analogue of human amylin
- Use in Type 1 and Type 2
- Improves glucose control in postprandial period
- Is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia (particularly in patients with type 1 diabetes)
- Reduces weight independently of nausea (increased satiety)
- 50% reduction of mealtime insulin
- Frequent blood glucose monitoring

**Pramlintide Doses/Vial**

- **Type 2**
  - 1 vial = 25 doses of 120 µg
  - 500 units/vial = 20 units = 25
  - 120 µg 2 times/day = 3 vials/month
  - 120 µg 3 times/day = 4 vials/month
- **Type 1**
  - 1 vial = 50 doses of 60 µg
  - 500 units/vial = 10 units = 50
  - 60 µg 3 times/day = 2 vials/month
  - 30 µg 3 times/day = 1 vial/month

**Physiologic Insulin Profile**
Indications for Insulin

- Type 1 diabetes
- Type 2 - disease progression
  - May use insulin as initial treatment any time; especially if symptomatic or FPG > 200 mg/dl and HbA1c > 10%
  - May use insulin alone or in combination if OAD’s do not achieve target
- Gestational diabetes
- Acute illness, surgery, hospitalization, DKA, hyperosmolar state


Insulin Preparations

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human insulins</td>
<td>Regular, NPH, U-500 Regular</td>
</tr>
<tr>
<td>Insulin analogues</td>
<td>Aspart, lispro, apidra, glargine, detemir</td>
</tr>
<tr>
<td>Premixed insulins</td>
<td>Human 70/30, 50/50</td>
</tr>
<tr>
<td></td>
<td>Humalog mix 75/25</td>
</tr>
<tr>
<td></td>
<td>Novolog mix 70/30</td>
</tr>
</tbody>
</table>

Insulin Action Profiles

- Aspart, lispro 4–6 hours
- Regular 6–8 hours
- NPH 12–20 hours
- Detemir 18–24 hours
- Glargine 24 hours

Human Insulins and Analogues

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
<th>Onset of Action</th>
<th>Peak</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro/aspart/rapidra</td>
<td>~15 minutes</td>
<td>1–2 hours</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Human regular</td>
<td>30–60 minutes</td>
<td>2–4 hours</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Human NPH</td>
<td>2–4 hours</td>
<td>4–10 hours</td>
<td>12–20 hours</td>
</tr>
<tr>
<td>Detemir</td>
<td>2–4 hours</td>
<td>nearly flat dose-dependent</td>
<td>18–24 hours</td>
</tr>
<tr>
<td>Glargine</td>
<td>2–4 hours</td>
<td>flat</td>
<td>~24 hours</td>
</tr>
</tbody>
</table>

Insulin Therapy Regimens

- No typical dose!
- Dosing schedules vary from once daily to Multiple Daily Injections (MDI)
- Insulin Pen or Insulin Pump

**Intensive Insulin Therapy**

**Education should include**
- Assessment of management skills and level of knowledge
- Intensive training on hypoglycemia awareness, prevention and treatment
- SMBG testing and pattern management
- Advanced insulin dosage adjustment training
- Professional help for emotional and motivational counseling

**Insulin Adjustment Considerations**

- Insulin variables
  - Type, dose
  - Insulin action peak, duration
  - Timing
  - Delivery method
- Food intake
  - Type, composition, quantity, timing
- Physical activity
  - Proactive insulin or food adjustment

**Typical Multiple-Injection Regimens**

- Three SMBG-adjusted pre-meal injections of a rapid acting insulin analog (aspart, humalog or apidra) insulin plus glargine taken at bedtime
- Three injection regimen: pre-breakfast N and R, pre-supper R and bedtime N
- 70/30 insulin with meals bid and bedtime N
- Timing of insulin with meals is crucial!

**Starting Insulin: Calculating total daily dose (TDD)**

To Calculate:
- TDD = 0.2 to 0.5 units per pound of body weight
  - 0.4 units/kg/day with poorly controlled or new T2D
  - 0.2 units/kg/day for T1D
- ½ TDD given as basal; ½ TDD divided between 3 meals for basal-bolus regime
- 2/3 TDD given in AM and ½ TDD in PM for pre-mixed insulin (if using N and R- 2/3 of AM and PM dose is given as N and ½ as R)

David M. Nathan, M.D.

**Start-up Insulin Dosing Examples in T2D**

<table>
<thead>
<tr>
<th>Body weight</th>
<th>TDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 lbs (90 kg)</td>
<td>45 units</td>
</tr>
</tbody>
</table>

Examples:
- Glargine 23 units at HS and 7 unit aspart TID AC
  - OR
- 70/30 30 units q AM and 15 units q PM AC Bk and Supper
  - OR
- NPH 20 units plus 10 units R in AM and 10 units N plus 5 units R AC supper

**Treat to Target with basal insulin analogue plus OAD**

- Add 10 units at HS
- Increase by 2-3 units every 3 days until FBS is at goal
- May need to add pre-meal insulin at largest meal

**Correctional insulin: When sliding scale isn’t really sliding scale**

<table>
<thead>
<tr>
<th>SMBG</th>
<th>Short acting Insulin Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>decrease 2-3 units after treating with 15gm CHO</td>
</tr>
<tr>
<td>50-70</td>
<td>decrease 1-2 Units</td>
</tr>
<tr>
<td>70-130</td>
<td>base dose</td>
</tr>
<tr>
<td>150-200</td>
<td>increase 1 Units</td>
</tr>
<tr>
<td>200-250</td>
<td>Increase 2 Units</td>
</tr>
<tr>
<td>250-300</td>
<td>Increase 3 Units</td>
</tr>
</tbody>
</table>

**Insulin Storage and Disposal**

- Avoid heat, light and freezing
- Store unopened products in the refrigerator
- Insulin in use can be kept at room temperature; store back-up in refrigerator
- Discard vial after 28 days
- Check product for expiration date and appearance
- Follow local EPA guidelines

**Drugs That Alter Diabetes Control**

- Drug-Induced Hypoglycemia:
  - Alcohol inhibits gluconeogenesis
  - Beta-adrenergic receptor antagonists (Beta-blockers) inhibit the effects of catecholamines on gluconeogenesis and glycogenolysis
  - Quinolone antibiotics
- Drug Induced Hyperglycemia:
  - Epinephrine
  - Glucocorticoids
  - Oral contraceptives
  - Phenytoin and clonidine
  - Thiazides

**Insulin Injection Devices**

- **Insulin pens**
  - Faster and easier than syringes
  - Improve patient attitude and adherence
  - Have accurate dosing mechanisms
    - Visual impairments
    - Tremor
  - Cost effective in lower doses: contains 300 units
  - Education and pen needles

**Insulin Pumps**

Continuous subcutaneous insulin infusion (CSII)
- External, programmable pump connected to an indwelling subcutaneous catheter to deliver rapid-acting insulin
- Smart pump features
- Appropriate patient selection

**Continuous Subcutaneous Insulin Infusion (CSII) Therapy**

- Initiated and monitored by specialist trained in pump therapy on an outpatient basis
- SMBG > 4 times a day
- Catheter change infusion set q 2-3 days
- Pre-programmed Continuous flow of rapid acting insulin provides basal insulin
- Sample dosage: TDD based on weight
  - basal 50%
  - premeal 16% 12% 16%
  - prebedtime snack bolus 6%
Continuous Glucose Monitoring Systems (CGMS)

- Alerts uncontrolled hyper or hypoglycemia (hypoglycemia unawareness)
- Improves BG control even for people with A1c below 7%
- Used to "tweak" insulin pump settings
- Future implications...

Conference Evaluation

Online evaluations at: www.pacnp.org/conference