Pathogenesis of Type 2 Diabetes and Corresponding Staged Therapy

Elliot Sternthal, MD, FACP
Clinical Director of Diabetes Services
Boston Medical Center
Boston, MA

Type 2 Diabetes: Expanded Key Concepts

- Pathophysiology
  - β-cell function: decreased insulin & amylin secretion
  - Insulin action: increased insulin resistance in liver, muscle, & fat
  - α-cell function: increased glucagon secretion (reduced intraintra-islet insulin suppression)
  - Gut: deficiency of incretin GLP-1 (exacerbates insulin deficiency & glucagon excess and reduces CNS control of satiety & gastric emptying)

- "Glucotoxicity" aggravates ALL impairments
- Multiple mechanisms required to correct multiple dysfunctions resulting in hyperglycemia
- Most patients require combination therapy

New ADA/EASD Consensus Algorithm

At Diagnosis: Lifestyle + Metformin

Lifestyle + Metformin + Sulfonylurea
Lifestyle + Metformin + Basal Insulin
Lifestyle + Metformin + Intensive Insulin
Lifestyle + Metformin + Pioglitazone
Lifestyle + Metformin + GLP-1 agonist
Lifestyle + Metformin + Basal Insulin

Tier 1: Well-validated therapies
Tier 2: Less well-validated therapies

Points to Ponder

- Is this consensus statement realistic?
- Will insulin be started early in the treatment algorithm given the established “track record” of delayed and inadequate insulin use in T2DM?
- Can use of “tried and true” agents provide disease-modifying therapy?
- What is the role of early use of combined sensitizer or incretin-restoring therapy?
- Is limiting associated weight gain important?

Is There Another Option?

Staged Therapy

Consideration of the corresponding pathophysiologic profile (metabolic staging) associated with A1C intervals can provide guidance in initiating and advancing therapy for type 2 diabetes
Mild Hyperglycemia: 
(A1C 6%-7%) Key Concepts

- β-cell function and mass, although reduced, may be adequate
- Reducing demand on β-cell function may be sufficient to restore near-normal glycemia via:
  - Increasing insulin sensitivity in liver (metformin) and muscle & fat (thiazolidinediones, TZDs)
  - Delaying and prolonging glucose entry into the circulation (alpha-glucosidase inhibitors, AGIs)
  - Enhancing glucose-dependent, 1st-phase insulin secretion and glucagon suppression (incretin mimetic or enhancer)

Mild Hyperglycemia 
(A1C 6%-7%) Key Concepts (cont’d)

- Targeting postprandial hyperglycemia has greater influence on A1C <7.3% than reducing fasting glycemia
- Correction of glucotoxicity further improves β-cell performance and insulin action
- No risk of hypoglycemia
- Monotherapy may be adequate

Moderate Hyperglycemia: 
(A1C 7%-8%) Key Concepts

- Greater β-cell deficiency exists
- Need for combination therapy may be necessary when A1C remains >7.5%
- Insulin secretagogue (meglitinide or sulfonylurea) may be needed for A1C 7.5%-8%
**Moderately Severe Hyperglycemia (A1C 8%-9%) Key Concepts**

- Moderately severe reduction in β-cell function and mass
- Usually will need to initiate treatment with combination therapy if only sensitizers are used
- A more potent secretagogue such as a sulfonylurea is often necessary at initiation and always necessary with advancing therapy
- Adding insulin +/- amylinomimetic (pramlintide) is an option when advancing therapy

---

**Severe Hyperglycemia (A1C >9%) Key Concepts**

- Severe reduction in β-cell function and mass with insulinopenia and expansion of α-cell mass with hyperglucagonemia
- Combination therapy, almost always with a sulfonylurea, is necessary from the start
- Insulin +/- oral agents is an option for initiation of therapy and a necessity if other combination therapy is inadequate or there is a catabolic state

---

**Suggested Treatment Schema for Type 2 DM**

- **Mild hyperglycemia: A1C 6%-7%**
  - Initiating therapy
    - AGI
    - Metformin
    - TZD
    - Sitagliptin
  - Advancing therapy
    - Metformin + TZD
    - Metformin +/- TZD + exenatide
    - AGI + TZD
    - Sitagliptin + metformin or TZD

Choice of agent will be influenced by body mass index (BMI), fasting blood sugar, 2-hr post-prandial blood glucose, age, renal and hepatic status.
<table>
<thead>
<tr>
<th>Suggested Treatment Schema for Type 2 DM (cont’d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Moderate hyperglycemia: A1C 7%-8%</td>
</tr>
<tr>
<td>- Initiating therapy</td>
</tr>
<tr>
<td>• AGI</td>
</tr>
<tr>
<td>• Metformin</td>
</tr>
<tr>
<td>• Thiazolidinedione (TZD + metformin combination)</td>
</tr>
<tr>
<td>• Sitagliptin (sitagliptin + metformin combination)</td>
</tr>
<tr>
<td>• Meglitinide</td>
</tr>
<tr>
<td>• Sulfonylurea (low dose)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggested Treatment Schema for Type 2 DM (cont’d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Advancing therapy</td>
</tr>
<tr>
<td>• Metformin + TZD</td>
</tr>
<tr>
<td>• Metformin +/- TZD + exenatide</td>
</tr>
<tr>
<td>• AGI + TZD</td>
</tr>
<tr>
<td>• Sitagliptin + metformin or TZD</td>
</tr>
<tr>
<td>• Meglitinide + metformin +/- TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin +/- TZD</td>
</tr>
<tr>
<td>• Sulfonylurea +/- metformin + sitagliptin</td>
</tr>
<tr>
<td>• Sulfonylurea +/- metformin + exenatide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggested Treatment Schema for Type 2 DM (cont’d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Insulin added (use with exenatide or sitagliptin not yet established)</td>
</tr>
<tr>
<td>• HS NPH or glargine or detemir</td>
</tr>
<tr>
<td>• Bid 70/30 or analog 75/25 or 70/30 (d/c SU)</td>
</tr>
<tr>
<td>• Mealtime analog lispro or aspart or glulisine (d/c SU)</td>
</tr>
<tr>
<td>• Basal-bolus insulin (d/c SU)</td>
</tr>
<tr>
<td>• Pramlintide added to mealtime insulin</td>
</tr>
</tbody>
</table>
# Suggested Treatment Schema for Type 2 DM (cont’d)

<table>
<thead>
<tr>
<th>Severe Hyperglycemia: A1C &gt;9%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderately Severe Hyperglycemia: A1C 8%-9%</strong></td>
</tr>
<tr>
<td><strong>Initiating therapy</strong></td>
</tr>
<tr>
<td>• Sulfonylurea (high dose)</td>
</tr>
<tr>
<td>• Metformin</td>
</tr>
<tr>
<td>• Metformin + TZD combination</td>
</tr>
<tr>
<td>• Metformin +/- TZD + exenatide</td>
</tr>
<tr>
<td>• Metformin or TZD + sitagliptin (sitagliptin + metformin combination)</td>
</tr>
<tr>
<td>• Meglitinide + metformin +/- TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin or TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + exenatide</td>
</tr>
<tr>
<td>• Sulfonylurea + sitagliptin</td>
</tr>
<tr>
<td><strong>Advancing therapy</strong></td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + exenatide</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + sitagliptin</td>
</tr>
<tr>
<td>• Insulin (use with exenatide or sitagliptin not yet established)</td>
</tr>
<tr>
<td>- HS NPH or glargine or detemir</td>
</tr>
<tr>
<td>- Bid 70/30 or analog 75/25 or 70/30 (d/c meglitinide or SU)</td>
</tr>
<tr>
<td>- Mealtime analog lispro or aspart or glulisine (d/c secretagogue)</td>
</tr>
<tr>
<td>- Basal-bolus insulin (d/c secretagogue)</td>
</tr>
<tr>
<td>• Pramlintide added to mealtime insulin</td>
</tr>
</tbody>
</table>

---

## Suggested Treatment Schema for Type 2 DM (cont’d)

<table>
<thead>
<tr>
<th>Severe Hyperglycemia: A1C &gt;9%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderately Severe Hyperglycemia: A1C 8%-9%</strong></td>
</tr>
<tr>
<td><strong>Initiating therapy</strong></td>
</tr>
<tr>
<td>• Sulfonylurea (high dose)</td>
</tr>
<tr>
<td>• Metformin</td>
</tr>
<tr>
<td>• Metformin + TZD combination</td>
</tr>
<tr>
<td>• Metformin +/- TZD + exenatide</td>
</tr>
<tr>
<td>• Metformin or TZD + sitagliptin (sitagliptin + metformin combination)</td>
</tr>
<tr>
<td>• Meglitinide + metformin +/- TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin or TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + exenatide</td>
</tr>
<tr>
<td>• Sulfonylurea + sitagliptin</td>
</tr>
<tr>
<td><strong>Advancing therapy</strong></td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + exenatide</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + sitagliptin</td>
</tr>
<tr>
<td>• Insulin initiated as below +/- metformin +/- TZD</td>
</tr>
</tbody>
</table>

---

## Suggested Treatment Schema for Type 2 DM (cont’d)

<table>
<thead>
<tr>
<th>Severe Hyperglycemia: A1C &gt;9%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderately Severe Hyperglycemia: A1C 8%-9%</strong></td>
</tr>
<tr>
<td><strong>Initiating therapy</strong></td>
</tr>
<tr>
<td>• Sulfonylurea (high dose)</td>
</tr>
<tr>
<td>• Metformin</td>
</tr>
<tr>
<td>• Metformin + TZD combination</td>
</tr>
<tr>
<td>• Metformin +/- TZD + exenatide</td>
</tr>
<tr>
<td>• Metformin or TZD + sitagliptin (sitagliptin + metformin combination)</td>
</tr>
<tr>
<td>• Meglitinide + metformin +/- TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin or TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + exenatide</td>
</tr>
<tr>
<td>• Sulfonylurea + sitagliptin</td>
</tr>
<tr>
<td><strong>Advancing therapy</strong></td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + TZD</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + exenatide</td>
</tr>
<tr>
<td>• Sulfonylurea + metformin + sitagliptin</td>
</tr>
<tr>
<td>• Insulin initiated as below +/- metformin +/- TZD</td>
</tr>
</tbody>
</table>
Advancing Insulin In Patients With Type 2 Diabetes

John White, PA-C, PharmD
Professor of Pharmacotherapy
Washington State University
Spokane, WA

Reasons for Inadequate Diabetes Care

- Lots of diabetes drugs; all generally lower A1C 1%–1.5%
- Progressive nature of disease:
  - Most patients eventually require insulin for blood glucose management
- Treatment inertia of health care providers
  - “Insulin resistance”
- Patient resistance
  - Cost, complexity, side effects
  - “I don’t want insulin”

Clinical Inertia: Failure to Advance Therapy When Required

Percentage of subjects advancing when A1C >8%

At insulin initiation, the average patient had:
- 5 years with A1C >8%
- 10 years with A1C >7%

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>66.6%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>35.3%</td>
</tr>
<tr>
<td>Metformin</td>
<td>44.6%</td>
</tr>
<tr>
<td>Combination</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

Key Decision Points for Insulin Therapy in Type 2 Diabetes

- When to start insulin versus adding more oral agents
  - Exenatide and sitagliptin
- What insulin program to start with
  - Once-daily long-acting analog
- How to start insulin and optimize dosing
- Whether to discontinue oral agents when insulin is started
- When to proceed to mealtime insulin

Progression of Type 2 Diabetes

Insulin Therapy in Type 2 Diabetes

- More than half of patients with type 2 diabetes require insulin to reach A1C goal <7%
- Insulin doses are usually higher in type 2 diabetes patients (~1.2 U/kg) than in type 1 patients
- Increasing use of insulin earlier in course of therapy for type 2 patients
- Individualize insulin therapy for each patient
  - Oral medications(s) + qd insulin or
  - Intensive insulin +/- other anti-hyperglycemic medications
Advancing Therapy–Considerations

- A1C delta needed?
- Patient acceptance
- Complexity of regimen
- Cost
- Side effects and secondary effects

Advantages of Insulin + Oral Agent vs Switching to Insulin Alone

- Combination therapy reduces dose of insulin required
  - SU: 21%-38% decrease
  - Metformin: 19%-32% decrease
  - Metformin + SU: 62% reduction
- Glucose control will not deteriorate during the transition to insulin
- Patient learns practical skills needed before switching to insulin-only regimen
- Simple insulin regimens improve patient compliance

The Basal/Bolus Insulin Concept

- Basal insulin
  - Suppresses glucose production between meals and overnight
  - 40%-50% of daily needs
- Bolus insulin (mealtime)
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1 hr
  - 10%-20% of total daily insulin requirement at each meal
Physiologic Serum Insulin Secretion Profile

<table>
<thead>
<tr>
<th>Time</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>50</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Tactics for Type 2 Diabetes: Starting Basal Insulin

- Add single, evening insulin dose
  - NPH or detemir (bedtime)
  - 70/30 (evening meal)
  - Glargine (bedtime or anytime?)
- Dose: 10 units or 10% patient weight in lb (200 lb = 20 units) or 0.15 units per kg
- Adjust dose by FBG
- Increase insulin dose weekly as needed
  - Increase by 2 units or 10%-20% if FBG > 140 mg/dL
- Treat to target (usually <120 mg/dL)

Advancing Basal/Bolus Insulin

- Indicated when FBG is acceptable but
  - A1C >7% or >6.5%
  - SMBG before dinner >140 mg/dL
- Insulin options
  - To glargine, detemir, or NPH, add mealtime aspart/lispro
  - To dinner-time 70/30, add morning 70/30
- Oral agent options
  - Usually discontinue SU or glinides if bolus insulin is added
  - Continue TZD or metformin?
Summary

- Be aggressive
  - Follow standards of care
  - Making frequent adjustments in therapy is the norm—this is a progressive disease
- Use insulin in patients who need it
- Start basal insulin (once daily) along with the patient’s OHAs
  - Use enough insulin—FPG <110-120 mg/dL
  - Be enthusiastic and positive when discussing with patient
- Add mealtime analog insulin if A1C is not to goal
  - Start with largest meal—try starting with 4 units

Performance Improvement Strategies

Elaine Fleck, MD
Associate Clinical Professor
Columbia University
Director, Internal Medicine
Ambulatory Care Practice
New York-Presbyterian Hospital
New York, NY
Improving Care

- Recognize that there is a gap between care as it is and care as it could and should be for patients
- Identify an action plan that you would like to accomplish to improve this care
- Understand and implement an intervention that can change the nature of care delivery in your practice

---

Fundamental Questions for Improvement

- What are we trying to accomplish?
- How will we know that a change is an improvement?
- What changes can we make that will result in improvement?

---

Performance Improvement: First Steps

- Define areas that need improvement
- Identify champions
- Assign responsibilities
- Develop a patient registry
The PDSA Cycle for Learning and Improvement

Act
- What changes are to be made?
- Next cycle?

Plan
- Objective
- Questions and predictions (why)
- Plan to carry out the cycle (who, what, where, when)

Study
- Complete the analysis of the data
- Compare data to predictions
- Summarize what was learned

Do
- Carry out the plan
- Document problems and unexpected observations
- Begin analysis of the data

Repeated Use of the PDSA Cycle

Tips for Success

- Improvement occurs in small steps
- Repeated attempts needed to implement new ideas
- Assess regularly, measure results to improve plan
- Failed changes = learning opportunities
- Plan communication
- Engage leadership support
- Communicate: Involve your medical team
- Collect data before and after making change
- Share and borrow ideas
Tour of Suggested Interventions

- **Go to:**
  - [http://www.mentorqi.com/Apps/System/Logon.aspx](http://www.mentorqi.com/Apps/System/Logon.aspx)
  - User name: test  Password: test
  - Click on MENTOR MODULE in the grey bar at the top
  - Click on Launch Program under the Diabetes Module
  - View: Build Action Plan

Interventions

- **Six selected interventions for Action Plan**
  - A1C testing - Goal setting
  - Exercise - Nutrition
  - Glucose self-monitoring - Proper therapy
Additional Resources for Practice Improvement

- Group classes
- Conversation mapping
- Nurse case management in underinsured
- POC testing
- Self-management education
- Nurse-directed diabetes care
  - Davidson MB. *Diabetes Care*. 2003;26:2281-2287

Promoting Self-care in Type 2 Diabetes

Jane Jeffrie Selye
MPH, MSN, GNP, CDE, BC-ADM
Diabetes Nurse Practitioner
Division of Endocrinology
New York Presbyterian-Weill Cornell Medical Center
New York, NY
Diabetes Is a Self-care Disease

- Requires multiple daily self-care activities that change over time...
- Decisions need to be made on an ongoing basis regarding meals, physical activity, medications, and monitoring
- This requires education, motivation, and support


AADE 7 Self-care Behaviors

Healthy eating
Being active
Monitoring
Taking medications
Problem solving
Healthy coping
Reducing risks

Diabetes Self-care Assessment

Meal Planning
- Is patient spacing meals and snacks throughout the day?
- Does patient know how to identify carbohydrates?
- Does patient know how to measure portion sizes of carbs?
- Does patient know how to read a Nutrition Facts label?
- Have you discussed specific weight-loss strategies?
- Has the patient ever received individualized counseling on how to plan meals from an RD or CDE?
Diabetes Self-care Assessment (cont’d)

Physical Activity
♦ Does patient have a physical activity plan?
♦ Which activities? Aerobic vs anaerobic?
♦ How often and for how long?
♦ Time of day?
♦ Need to adjust meals/meds?
♦ Where does he/she exercise? Is an alternative plan needed for bad weather?
♦ Does patient carry medical ID, hypoglycemia tx?
♦ Comfortable clothes and footwear?

Diabetes Self-care Assessment (cont’d)

Medication
♦ Does patient know mechanism of action of each medication?
♦ When does patient take each diabetes medication in relation to meals?
♦ Have you observed his or her injection technique?
♦ Does patient know how to store medications?
♦ Does patient know about open expiration dates?
♦ Does patient know what to do with syringes, pen needles once used?

Diabetes Self-care Assessment (cont’d)

Blood Glucose (BG) Monitoring
♦ Does patient have working meter?
♦ Have you observed his/her technique?
♦ When is BG being checked?
♦ Is patient aware of his/her targets? What does patient do when the target is too high or too low?
♦ Does the patient log results?
♦ Have you reviewed the results and made treatment changes based upon them?
Compliance vs Concordance

- Patient & Provider are equal partners in self-care
- Provider assists patient in making informed decisions
- Relationships are built over time
- Behavioral goals are set and mutually agreed upon


Common Barriers to Self-care

- Depression: up to 2x more common in patients with diabetes
- Denial/despair around diagnosis
- Myths/poor understanding/culture
- “I’ve got a little sugar”
- Lack of social support
- High cost of meds/supplies
- Lack of physical & cognitive ability to perform self-care


Tools to Encourage Self-care

- Knowledge is power
- Back to basics: Re-assess prior knowledge & skills
- Look at all diabetes meds and supplies: Ask patients to tell you & show you exactly what they do, how they do it, and when they do it . . .
### Tools to Encourage Self-care (cont’d)

- Focus on comfort: examine & modify all blood glucose and injection supplies
- Evaluate feasibility of treatment regimen in relation to patient’s cognitive and physical ability, reimbursement, motivation, and quality of life

### Tools to Encourage Self-care (cont’d)

**Blood Glucose Monitoring (BGM)** can be a motivating tool
- Set short-term BGM “experiments” based on current meds and potential treatment changes
- Review and discuss log book at each visit
- Consider periodic review of log by fax or phone between visits

### Tools to Encourage Self-care (cont’d)

- Create library of resources to reinforce teaching
- More is NOT better: Choose 1 or 2 simple handouts on each main topic
- Ask preferences for learning: written, audio, video
Tools to Encourage Self-care (cont’d)

- Read all handouts first to determine accuracy, reading level, cultural appropriateness, etc

Strategies for Success: Clear Health Communication

- “Teach back”
  - Have patient repeat instructions in his or her own words
- Ask Me 3
  - What is my main problem?
  - What do I need to do?
  - Why is it important for me to do this?


Strategies for Success: Clear Health Communication (cont’d)

- Use simple & same language (eg, sugar OR glucose)
- Limit to no more than 3 health messages per visit
- Be specific: Delineate steps to successful behavioral change
- Practice skills, difficult situations
- Provide written instructions, toll-free #s
Summary

- Provide education AND support
- Encourage patient empowerment by facilitating self-care behaviors
- Set realistic, achievable, short-term goals
- Monitor outcomes and adjust treatment plan as needed
- Plan for difficult situations
- Motivate, motivate, motivate!

Q&A