Multiple, Complex Pathophysiological Abnormalities in T2DM

Pathogenesis of Type 2 Diabetes

UKPDS: Progressive Hyperglycemia Secondary to Beta-Cell Failure

Incretins and Insulin: Management of T2DM
The Holy Grail is to mimic Physiologic Serum Insulin Secretion Profile


Plasma Insulin (µU/mL)

Time

4:00 8:00 12:00 16:00 20:00 24:00 28:00 32:00

Breakfast Lunch Dinner

Doesn't seem that hard....

Insulin Therapy in Type 2 DM

Take home points:
- Insulin controls blood glucose
- Insulin is not a penalty
- Using basal insulin is simple and safe
- Complex regimens are demanding for the patient and the provider

Ideal Basal/Bolus Insulin Absorption Pattern:
Multiple daily injections or insulin pump

Plasma Insulin (µU/mL)

Time

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00

Breakfast Lunch Dinner

SMBG is based on regimen

Many insulin regimens are effective

SMBG is based on regimen
Is there another way?

Glucagon Like Peptide receptor agonists
GLP1 RA

Pancreatic Islet Morphology: Normal Glucose Tolerance and T2DM

T2DM = type 2 diabetes mellitus

Insufficient Insulin and Elevated Glucagon in T2DM (↓ Insulin/Glucagon Ratio)

T2DM = type 2 diabetes mellitus, NGT = normal glucose tolerance; CHO=carbohydrate
GLP-1 and DPP4
The Incretin Effect in Healthy Subjects

GLP-1 Modulates Numerous Functions in Humans

Complementary:

This is overwhelming
Mrs Jones is here for a 30 minute visit
Lifestyle: Always first line

Relationship of walking to mortality among US adults with diabetes

- DESIGN: Prospective cohort study
- SUBJECTS: 2896 adults from 1990 and 1991 National Health Interview Survey
- RESULTS:
- CONCLUSIONS: Walking was associated with lower mortality across a diverse spectrum of adults with diabetes. One death per year may be preventable for every 61 people who could be persuaded to walk at least 2 h/wk.

Arch Intern Med. 2003 Jun 23;163(12):1440-7

<table>
<thead>
<tr>
<th></th>
<th>Inactive</th>
<th>2 hours/wk</th>
<th>3-4 hours/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause</td>
<td>Ref 1.0</td>
<td>39%</td>
<td>54%</td>
</tr>
<tr>
<td>CV</td>
<td>Ref 1.0</td>
<td>34%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Patient Centered:

Approach to the management of hyperglycemia

Risks potentially associated with hypoglycemia and other drug adverse effects

Disease duration

Life expectancy

Important comorbidities

Established vascular complications

Patient attitude and expected treatment efforts

Resources and support system

HbA1c 7%

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Courtesy of S Inzucchi

Diabetes Care 2012;35:1364–1379

Diabetologia 2012;55:1577–1596
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM.
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Approach to the management of hyperglycemia

PATIENT / DISEASE FEATURES
- More stringent HbA1c 7%
- Less stringent

HIGHLY MODIFIABLE

Resources and support systems
- Readily available
- Limited

PATIENT ATTITUDE & EXPECTED TREATMENT EFFORTS
- Highly motivated, adherent, excellent self-care capacities
- Less motivated, non-adherent, poor self-care capacities

RISKS POTENTIALLY ASSOCIATED WITH HYPOGLYCEMIA AND OTHER DRUG ADVERSE EFFECTS
- Low
- High

DISEASE DURATION
- Newly diagnosed
- Long-standing

LIFE EXPECTANCY
- Long
- Short

IMPORTANT COMORBIDITIES
- Absent
- Severe
- Few / Mild

ESTABLISHED VASCULAR COMPLICATIONS
- Absent
- Severe
- Few / Mild

PERHAPS MODIFIABLE
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)


Diabetes Care 2015;38:140–149
Diabetologia 2015;58:1077–1087.011-014-3460-0

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Figure 2. Ang-hyperglycemic therapy
In T2DM: General recommendations
Figure 2: Target-hyperglycemic therapy
in T2DM: General recommendations

Common themes:
- Diet and physical activity
- Patient goals and resources
- Start with metformin
- If A1c>9% start insulin

The 5 P's: Consideration in the Design of a Personalized T2DM Treatment Regimen
- PATHOPHYS
- POTENCY
- PRECAUTIONS
- PERKS
- PRACTICALITIES
The 6 P’s: Consideration in the Design of a Personalized T2DM Treatment Regimen

Pathophysiology informs treatment
Percentage of Patients Who Reached the Intensive-Treatment Goals at a Mean of 7.8 Years

Glycosylated Hemoglobin <6.5%
Patients (%)

0
20
30
40
50
60
70
80

Intensive Therapy
Conventional Therapy

Cholesterol <170 mg/dl
Triglycerides <150 mg/dl
Systolic BP <130 mm Hg
Diastolic BP <80 mm Hg

P<0.001
P=0.06
P=0.21
P=0.19

Steno-2 Study

Composite End Point of Death from CV Causes, Nonfatal MI, CABG, PCI, Nonfatal Stroke, Amputation, or Surgery for Peripheral Atherosclerotic Artery Disease

Primary Composite End Point (%)

Hazard ratio = 0.47 (95 percent c.i., 0.24 to 0.73; P=0.008)


Steno-2 Study