• Presented on ESIM CME, February 2017.

• “Contents do not necessarily reflect positions of the Ethiopian Society of Internal Medicine (ESIM)”
UPDATE ON DIABETES CASE-BASED DISCUSSIONS

By
Ahmed Reja

Organised by
Ethiopian Society of Internal Medicine & Novartis

Intercontinental Hotel, Addis Ababa, February 12, 2017
What is the shortest word among study of sciences?
(_____ logy)
Oology
The study of eggs
By 2040 1 in 10 adults will have Diabetes (642 million)

In 2015 1 in 11 adults has Diabetes (415 million)

Every 6 seconds a person dies from diabetes (5 million deaths)

1 in 2 adults with diabetes is undiagnosed

12% of global health expenditure is spent on diabetes ($673 billion)

1 in 3 people with diabetes will develop retinopathy

Every 30 seconds a person living with diabetes loses a leg (1 million cases)

World burden of diabetes

IDF Atlas 7th edition 2015

Year

Year 1985
Year 2000
Year 2015
Year 2040

No of people with diabetes in millions

30
177
415
642

No of people with diabetes
Adult Mortality from Diabetes, HIV/AIDS, TB, & Malaria

- 5 million Diabetes (2015 IDF)
- 1.5 million HIV/AIDS (WHO 2013)
- 1.5 million TB (WHO 2013)
- 0.6 million Malaria (WHO 2013)
Burden of diabetes in Africa

IDF Atlas 7th edition 2015

No of people with diabetes in millions

Year 2000 | Year 2010 | Year 2015 | Year 2040
---|---|---|---
7 | 12 | 14 | 34

No of people with diabetes in millions
Prevalence of diabetes in Ethiopia

5-6%
Type 2 diabetes is a progressive disease

Goal of antihyperglycemic therapy

- Macrovascular complications
- Microvascular complications

β-cell function
Insulin resistance
Blood Glucose

Prevention
Diagnosis
Treatment

Type 2 diabetes

IFG / IGT
IFG: impaired fasting glucose
IGT: impaired glucose tolerance

Adapted from DeFronzo RA. Med Clin N Am 2004;88:787–835.
Pathogenetic mechanisms leading to progressive nature of T2D

- Genes
- Aging
- Obesity

Muscle Insulin Resistance

Increased lipolysis in visceral fat

Increased fatty acids

Hyperinsulinemia

Increased gluconeogenesis in liver

Impaired Glucose Tolerance

Decreased insulin secretion

Diabetes

β Cell compensation

β Cell decompensation

Gluco-toxicity
Early and effective treatment of hyperglycemia

- limits glucotoxicity on Beta cells
- key to future outcomes
- has long term benefits
Decline in $\beta$-Cell Function with Diabetes Progression: UKPDS

Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS.


Contribution of Fasting & Post-Prandial Glycemia to A1C in T2DM

Pathophysiology Based Therapy of Typ2 DM

- **Glucose Production**
- **Insulin Resistance**
- **Glucose Absorption**
- **CNS Effect**
- **Insulin Secretion**

Therapies:
- Metformin
- Thiazolidinedione
- Sulfonylurea
- Meglitinide
- DPP4 Inhibitor
- GLP-1 Analog
- SGLT2 Inhibitor
- Bile Acid Resin
- Glucosidase Inhibitor
- Bromocriptine

Target States:
- Euglycemia
- Glycosuria
- Incretin Effect
- Glucose Absorption
- Insulin Secretion
- CNS Effect
Case Presentation.... 1

• A 50-yr old man is consulting you because of erectile dysfunction
• BP = 130/80 mmHg
• Urine = alb +1
• Normal lipid profile
• FBS = 150 mg/dl & 160 mg/dl

• What are the issues to consider and what would you do?
Discussion

• Must be long standing diabetes
• Other microvascular complications screening
• Complete cardiovascular evaluation
  • Diabetes by itself
  • Proteinuria
  • Erectile dysfunction
• Immediate treatment with metformin and intensify treatment
Case Presentation 3

- 48-year-old lady
- Type 2 DM – 3 years duration
- No HPN or Dyslipidemia
- Metformin 1000 mg BID
- HbA1C = 7.4%

Do we need to improve glycemia?

What is the next best option?

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**Type 2 Diabetes and CHD: 7-year Incidence of Fatal/Nonfatal MI (East West Study)**

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1373</td>
<td>1059</td>
</tr>
<tr>
<td>7-year incidence rate of MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior MI*</td>
<td>4%</td>
<td>45%</td>
</tr>
<tr>
<td>MI</td>
<td>19%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>No prior MI*</td>
<td>20%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>45%</td>
</tr>
</tbody>
</table>

* These patients had no prior MI at baseline.

# Hyperglycemia Management: Multiple Combinations of Antihyperglycemic Therapy Can Work

## Initial drug monotherapy
Proceed to next step if HbA1c not achieved after 3 months

## Dual Therapy
Proceed to next step if HbA1c not achieved after 3 months

## Triple Therapy
Proceed to next step if HbA1c not achieved after 3 months

## Combination Injectable Therapy

---

<table>
<thead>
<tr>
<th>Healthy eating, weight control, increased physical activity, and diabetes education</th>
<th>Metformin</th>
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<tbody>
<tr>
<td>Efficacy (↓HbA1c)</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>high</td>
<td>low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Efficacy (↓HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side effect(s)</th>
<th>Costs</th>
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</thead>
<tbody>
<tr>
<td>SU</td>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
<tr>
<td>TZD</td>
<td>high</td>
<td>low risk</td>
<td>gain</td>
<td>edema, HF, Fxs</td>
<td>high</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>intermediate</td>
<td>low risk</td>
<td>neutral</td>
<td>rare</td>
<td>high</td>
</tr>
<tr>
<td>SGLT2i</td>
<td>intermediate</td>
<td>low risk</td>
<td>loss</td>
<td>GU, dehydration</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>high</td>
<td>low risk</td>
<td>loss</td>
<td>GI</td>
<td>high</td>
</tr>
<tr>
<td>Insulin (basal)</td>
<td>highest</td>
<td>high risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
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<tbody>
<tr>
<td>SU +</td>
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<tr>
<td>DPP-4i +</td>
</tr>
<tr>
<td>SGLT2i +</td>
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<tr>
<td>GLP-1 RA +</td>
</tr>
<tr>
<td>Insulin (basal) +</td>
</tr>
</tbody>
</table>

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Metformin + Basal insulin + Mealtime insulin or GLP-1 RA

Case Presentations ...2

• 60-yr old male, has HPN & Dyslipidemia for 10 yrs. He underwent coronary artery stenting 5 yrs ago. Type 2 DM was diagnosed 2 yrs ago and is on Metformin 1000 mg twice daily. Gives Hx of BPH

• BP = 130/85 mmHg, BMI = 28 kg/m² FBG = 166 mg/dL, ECG = old MI

• Rx: - Lisinopril 20 mg daily
  - HCTZ 12.5 mg daily
  - Atorvastatin 40 mg daily
  - Metoprolol 50 mg daily
What is the target A1C?

A. < 6.5%
B. < 7.0 %
C. < 7.5 %
D. < 8.0 %
What is the appropriate next step to improve glycemic control?

A. Basal insulin  
B. DPP-4 Inhibitor  
C. GLP-1 RA  
D. SGLT 2 Inhibitor  
E. Sulphonylurea  
F. Any of the above
T2D management considerations for individualized treatment: ADA/EASD Position Statement 2015

- **Hypoglycaemia and AE risks**: Low to High
- **Disease duration**: Newly diagnosed to Long-standing
- **Life expectancy**: Long to Short
- **Important comorbidities**: Absent to Severe
- **Established vascular complications**: Absent to Severe
- **Patient attitude and expectations**: Highly motivated to Less motivated
- **Resources and support system**: Readily available to Limited

- **HbA₁c**: 7%

Adapted from Inzucchi SE et al. Diabetes Care 2015;38:140−149

T2D, type 2 diabetes; AE, adverse event; CV, cardiovascular
What comes after metformin?

• Factors to consider
  1. Efficacy of lowering HbA1C
  2. Hypoglycaemia risk
  3. Effect on weight
  4. Side effects
  5. Cost
## Comparison of Glucose Lowering Agents

<table>
<thead>
<tr>
<th>Class of agents</th>
<th>HbA1C reduction (%)</th>
<th>SBP mmHg</th>
<th>Body weight (Kg)</th>
<th>Hypoglycaemia risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>+7 to -5</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.15-1.1</td>
<td>0 to -3</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>0.8 to 1.4</td>
<td>-1 to -3</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>TZDs</td>
<td>0.5-1.4</td>
<td>-5</td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>SUs</td>
<td>1.5</td>
<td>-5 to +7</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5-3.5</td>
<td>0 to +2</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>SGLT 2 Inhibitors</td>
<td>0.5-1.0</td>
<td>-3 to -5</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>
Case Presentation ...3

- 48-yr old lady has type 2 diabetes for 3 yrs. She is now on metformin 1 g BID
- BP = 110/70 mmHg, BMI = 27 kg/m²  A1C = 7.3%, FBG = 128 mg/dL

- What is the target A1C?
  A. < 6.5%
  B. < 7.0%
  C. < 7.5%
  D. < 8.0%
What is the next best option to reach target glycemia?

A. Basal insulin
B. DPP-4 Inhibitor
C. GLP -1 RA
D. SGLT2 Inhibitor
E. Sulphonylurea
F. Pioglitazone
Definition of Incretins

Gut derived factors that increase glucose-stimulated insulin secretion

INtestine + seCRETion of +INsulin

INCRETIN
The Incretin Effect in Healthy Subjects

- Oral Glucose
- Intravenous (IV) Glucose

N = 6; Mean (SE); *P ≤ 0.05
The Incretin Effect Is Diminished in Subjects with Type 2 Diabetes

Control Subjects (n = 8)

Normal Incretin Effect

Subjects with Type 2 Diabetes (n = 14)

Diminished Incretin Effect

Adapted with permission from Nauck M et al. *Diabetologia* 1986;29:46-52.
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Role of incretins in glucose homeostasis

Ingestion of food

GI tract

Active GLP-1

DPP-4 Enzyme

Inactive GLP-1

↑Insulin

β Cells

↑ Glucose uptake

Blood Glucose

↓Glucagon

Hepatic Glucose Production

α Cells

↓ Hepatic Glucose Production
GLP-1 Receptor Agonists (GLP-1 RAs)

• Designed to fulfill the role of native GLP-1
• Exhibit resistance to degradation by DPP-4
• Present for therapeutic use at supraphysiologic levels (equivalent to 6–10-fold normal GLP-1 levels)

• Drugs include
  • Exenatide (Byetta) - BID
  • Liraglutide (Victoza) - OD
  • Exenatide long-acting release (LAR) (Bydureon) - QW
  • Albiglutide - QW
  • Dulaglutide - QW
  • Lixisenatide - OD
LEADER: Primary Outcome*

HR: 0.87
95% CI: 0.78, 0.97
P < .001 for noninferiority
P = .01 for superiority

*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

GLP-1 receptor agonists

• Have a glucose-dependent MOA
• Slow gastric emptying
• Increase satiety
• Induce Weight loss
• Not associated with hypoglycaemia
• Effective with lowering postprandial glucose levels
DPP-4 Inhibitors (DPP-4 Is)

- Impair the activity of the DPP-4 enzyme
- Increase the half-life of endogenous GLP-1
- Produce modestly elevated levels of GLP-1

Available drugs

- **Sitagliptin (Januvia)**  Janumet
- **Saxagliptin (Onglyza)**  Kombiglyze
- **Vildagliptin (Galvus)**  Galvusmet
- **Alogliptin (Nesina)**  Kazano
- **Linagliptin (Tradjenta)**  Jentadueto

Available drugs with metformin:
- **Sitagliptin (Januvia)**  Janumet
- **Saxagliptin (Onglyza)**  Kombiglyze
- **Vildagliptin (Galvus)**  Galvusmet
- **Alogliptin (Nesina)**  Kazano
- **Linagliptin (Tradjenta)**  Jentadueto
Case Presentation ...4

- 41-yr old lady has HPN, Dyslipidemia and Type 2 DM for 3 yrs. She is on metformin 1 g BID
- BP = 150/90 mmHg, BMI = 30 kg/m², A1C = 7.8%,

- Target A1C?
  A. < 6.0%
  B. < 6.5%
  C. < 7.0%
  D. < 7.5%
• Next Best Option?

A. Sulphonylurea
B. Pioglitazone
C. DPP-4 Inhibitor
D. SGLT2 Inhibitor
What one important aspect would you look for in the history when you select therapy?
Case Presentation..... 5

• A 48 year old gentleman known to have HPN, dyslipidemia since 6 years, and who underwent PCI for AMI 2 years ago is referred from cardiac clinic because of elevated blood glucose levels. At the time of AMI, his FBS was 108 mg/dL and was advised on diet & exercise.

• BP = 150/90 mmHg, PR = 80 /min, regular, Waist = 112 cm, BMI = 32.4 kg/m²; Bibasilar crackles, flat JVP, S3 heart sound, Liver palpable 2 cm BRCM with smooth surface, trace pedal edema

• Lab data: FBS = 216 mg/dL, HbA1C = 8.4%
  TC = 178 mg/dL, TG = 230 mg/dL, HDL-C = 38 mg/dL,
  LDL-C = 94 mg/dL, SGOT = 47 (5-40), SGPT = 60 (5-56)
  eGFR = 72 ml/min/1.73m²
Identified Problems

• Uncontrolled
  • Diabetes
  • Hypertension
  • Dyslipidemia
• Obesity
• Fatty Liver
• He needs
  • Comprehensive Management

• For now let us concentrate on glucose control
What is the target HbA1C?

• A. 6%
• B. 7%
• C. 7.5%
• D. 8%
What is the best strategy to improve glycaemic control?

• A. Metformin

• B. GLP-1 Receptor Agonist

• C. Metformin + SGLT2 Inhibitor

• D. Metformin + Basal Insulin
Role of the kidney in glucose homeostasis

3 major mechanisms:

1. Release of glucose into the circulation via gluconeogenesis (25%)

2. Uptake of glucose from the circulation to satisfy its energy needs

3. Reabsorption of glucose at the level of the proximal tubule (100%)
180 g glucose filtered daily

90%

180 g glucose reabsorbed daily

10%

S1

S2/S3

SGLT 2

SGLT 1

NO GLUCOSE

RENAL HANDLING OF GLUCOSE
## Sodium-GLucose CoTransporters (SGLT)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT 1</td>
<td>GIT, Kidneys</td>
<td>Low Capacity, High Affinity</td>
</tr>
<tr>
<td>SGLT 2</td>
<td>Kidneys</td>
<td>High Capacity, Low Affinity</td>
</tr>
<tr>
<td>SGLT 3</td>
<td>Skeletal Muscle, Enteric Nervous System</td>
<td>? Glucose Sensor (not transporter)</td>
</tr>
</tbody>
</table>
Inhibiting SGLT2 Promotes Urinary Glucose Excretion

- SGLT2 inhibitors lower the threshold at which glucose is excreted, leading to
  - Increased urinary glucose excretion
  - Decreased return of glucose to circulation
  - Decreased blood glucose levels

---

RT = renal threshold.
Renal SGLT2 Levels Are Increased in Type 2 Diabetes

Normalized Glucose Transporter Protein Levels

* \( P < .05 \) between groups.
Rationale for inhibiting SGLT 2 to manage type 2 DM

- Novel, insulin independent mechanism of action
- Glycaemic efficacy maintained even with worsening beta cell function and insulin resistance
- Potential to complement other oral & injectable antidiabetic agents
- Low risk of hypoglycaemia
- Potential to reduce BP
- Negative energy balance due to glucosuria (200-300 kcal/day) = weight loss
Mechanism of Action

Increase the removal of glucose via SGLT2 inhibitors

Mechanism of Action (cont)

Increase the removal of glucose via SGLT2 inhibitors

Glomerulus

Proximal Convoluted Tubule

Early

Distal

Decreased glucose reabsorption into systemic circulation

Glucose  SGLT-2  SGLT-2 inhibitor  SGLT-1

Mechanism of Action (cont)

Increase the removal of glucose via SGLT2 inhibitors

Benefits of SGLT 2 Inhibition

- Corrects novel pathophysiologic defect
- Promotes weight loss
- Reduces BP
- No hypoglycaemia
- Insulin sparing effect
- Compliments action of other antidiabetic agents
- Reduces HbA1C
- Reversal of glucotoxicity
Available SGLT 2 Inhibitors once daily doses

• Canagliflozin (Invokanna) 100, 300 mg
• Dapagliflozin (Farxiga) 5, 10 mg
• Empagliflozin (Jardiance) 10, 25 mg
• Ipragliflozin (Suglat) 25, 50 mg
Fixed Drug Combinations

• Metformin & SGLT2 Inhibitors
  • Invokamet
  • Xigduo
  • Synjardy

• Metformin and DPP-4 inhibitors
  • Janumet
  • Galvusmet
  • Kombiglyze

• SGLT2 inhibitor and a DPP-4 inhibitor
  • empagliflozin/linagliptin
  • dapagliflozin/saxagliptin
# SGLT2 Inhibitors Need Adequate Renal Function to Be Efficacious

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Administration</th>
</tr>
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<tbody>
<tr>
<td>Canagliflozin</td>
<td>Not recommended if eGFR &lt; 45</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Not recommended if eGFR &lt; 60</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Not recommended if eGFR &lt; 45</td>
</tr>
</tbody>
</table>

Assess renal function before initiating SGLT2 inhibitor and periodically monitor thereafter.

Invokana® PI 2016; Farxiga® PI 2016; Jardiance® PI 2016.
EXTRAGLYCEMIC EFFECTS OF SGLT2 INHIBITORS

• Weight loss of 2 kg to 5 kg
• Lower blood pressure
  • 3 – 5 mm Hg for systolic blood pressure & 2 mm Hg for diastolic blood pressure
  • Weight loss, diuresis, Na depletion, & reduced arterial stiffness contribute to the blood pressure improvement
• Cholesterol improvement
  • Lower triglyceride levels
  • Increase HDL-C
  • Modestly raise LDL-C
  • No change in the ratio of HDL-C to LDL-C
• Beneficial in patients with Type 2 Diabetes & CHF
• Cardiovascular benefits
Which SGLT2 inhibitor may be most appropriate for the patient discussed?

A. Canagliflozin

B. Dapagliflozin

C. Empagliflozin

D. Specific SGLT2 inhibitor doesn't matter
EMPA-REG OUTCOME: Effect of Empagliflozin vs Placebo on Individual CV Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RRR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-point MACE</td>
<td>14%</td>
<td>.0382</td>
</tr>
<tr>
<td>CV death</td>
<td>38%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>13%</td>
<td>.2189</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>↑24%</td>
<td>.1638</td>
</tr>
</tbody>
</table>

EMPA-REG OUTCOME: Effect of Empagliflozin vs Placebo on All-Cause Mortality and HF Hospitalization

All-Cause Mortality

- Empagliflozin: 10 patients
- Placebo: 15 patients
- P < .0001
- 32% RRR

HF Hospitalization

- Empagliflozin: 5 patients
- Placebo: 8 patients
- P = .0017
- 35% RRR

EMPA-REG OUTCOME: Effect of Empagliflozin vs Placebo on CV Death

CV Death

- Patients With Event (%)
- Months

- Empagliflozin
- Placebo

HR, 0.62
95% CI: 0.49-0.77
P < .0001
38% RRR

CV benefit

• Attained at HbA1C 7.81% (Baseline was 8.07%)
• Mortality benefit is not only due to improvements in glycemia
• Cardiorenal effects
  • Reduced hospitalization for CHF
  • Reduction in arterial stiffness
  • Reduction in cardiac oxygen demand
  • Weight loss
  • Reduction in waist circumference and visceral fat
• Blood pressure improvement
• Cholesterol Improvement
EMPA-REG Microvascular Outcomes: Renal Protection

Incident or Worsening Nephropathy

Doubling of Serum Creatinine

SGLT2 inhibitors: Benefits and potential concerns

**Potential advantages**
- Novel, insulin-independent mechanism
- Durable glucose lowering at all stages of disease
- Can be used with wide range of oral glucose-lowering drugs and insulin
- Weight loss
- Blood pressure lowering
- Low risk of hypoglycaemia
- Potential long-term cardiovascular benefits

**Concerns**
- Increase in urinary tract infections
- Increase in genital infections
- Potential for volume depletion
- Ketoacidosis
- Renal safety
- Effects on bone health
- Risk of CV disease (LDL increase; diuretic effect / volume depletion; BP lowering)
- Polyuria/Nocturia
- Increased BUN and haematocrit
- Possible increased risk of bladder and breast cancer
Case 5 (Cont’d)
3-month follow-up visit

• HbA1C has decreased from 8.4% to 7.5%
• Fasting plasma glucose - 123 mg/dL
• Blood pressure = improved to 140/80 mm Hg
• Lost 3 kg
• Cholesterol is 90 mg/dL
What is the appropriate next step?

A. Reinforce diet, exercise, and drug compliance
B. Bariatric surgery
C. Intensify pharmacotherapy
   • Add Basal Insulin?
   • Add GLP-1 Receptor Agonist?
D. Increase Atorvastatin to 40-80 mg
Case Presentation ...

- 48-yr old man is recently diagnosed to have type 2 diabetes.
- A1C = 8.6%  BMI = 31 kg/m²

- Best way of achieving glycemic control is

A. Intensify therapy with lifestyle, metformin and sequential addition of other therapies
B. Educate & empower patient to make more changes to lifestyle
C. Combination oral therapy
D. Intensify therapy with insulin
Case Presentation ...7

• 63-yr old lady with CAD, HPN & Dyslipidemia is referred from cardiac clinic because of hyperglycemic symptoms & newly diagnosed type 2 diabetes. HbA1C = 9.3%

• What is the recommended therapy at this stage?
• Patient refuses insulin.
• So initial therapy is best with

A. Metformin + Sulphonylurea
B. DPP-4 Inhibitor + SGLT2 Inhibitor
C. Metformin + Sulphonylurea + DPP-4 Inhibitor
D. Metformin + DPP-4 Inhibitor + SGLT2 Inhibitor
Barriers to insulin

• Misconceptions/perceptions
  • Last resort
  • Negative family or relative experience,
  • “End of the road” perception
  • Causes complications (renal, eye, etc)
# Available Insulin Formulations

**Human**

<table>
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<th>Insulin</th>
<th>Onset of action</th>
<th>Peak</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
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</tr>
<tr>
<td>Regular</td>
<td>30-60 min</td>
<td>1-5 hrs</td>
<td>6-10 hrs</td>
</tr>
<tr>
<td><strong>Intermediate acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-2 hr</td>
<td>6-14</td>
<td>16-24 hrs</td>
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NPH – Neutral Protamine Hagedorn
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<th>Insulin</th>
<th>Onset of action</th>
<th>Peak</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Rapid acting</td>
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<tr>
<td>Aspart</td>
<td>10-20 min</td>
<td>1-3 hrs</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Lispro</td>
<td>15-30 min</td>
<td>0.5-2.5 hrs</td>
<td>3-6.5 hrs</td>
</tr>
<tr>
<td>Glulisine</td>
<td>10-15 min</td>
<td>1-1.5 hrs</td>
<td>3-5 hrs</td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>1.1 hr</td>
<td>No</td>
<td>Up to 24 hrs</td>
</tr>
<tr>
<td>Detemir</td>
<td>0.8-2 hrs</td>
<td>No</td>
<td>Up to 24 hrs</td>
</tr>
<tr>
<td>Ultra long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec</td>
<td>30-90 min</td>
<td>No</td>
<td>Up to 42 hrs</td>
</tr>
</tbody>
</table>
## Available Insulin Formulations ...3

### Premixed human

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset of action</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH/Regular 70/30</td>
<td>30-60 min</td>
<td>1.5-6 hrs</td>
<td>18-24 hrs</td>
</tr>
<tr>
<td>NPH/Regular 50/50</td>
<td>30-60 min</td>
<td>2-5.5 hrs</td>
<td>18-24 hrs</td>
</tr>
</tbody>
</table>
New longer-acting basal insulins

- **Insulin glargine U300**
  - New formulation of the same insulin glargine U100 molecule
  - Delivered in higher concentration
  - Smaller volume
  - Slower release of the insulin
  - Prolonged duration of action over 24 hrs

- **Insulin degludec (U100 and U200)**
  - New insulin analogue with a modified B chain
  - Forms hexamers and dihexamers after subcutaneous injection
  - Longer duration of action upto 42 hrs
  - Half-life is ~ 25 hours
  - Flatter action profile with less patient-to-patient variability
## Available Insulin Formulations ...4

### Premixed Analogs

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset of action</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS/Aspart 70/30</td>
<td>10-20 min</td>
<td>1-4 hrs</td>
<td>Up to 24 hrs</td>
</tr>
<tr>
<td>NPL/Lispro 75/25</td>
<td>10-30 min</td>
<td>1-6.5 hrs</td>
<td>Up to 24 hrs</td>
</tr>
<tr>
<td>NPL/Lispro 50/50</td>
<td>10-30 min</td>
<td>0.8-4.8 hrs</td>
<td>Up to 24 hrs</td>
</tr>
</tbody>
</table>

APS – aspart protamine suspension
NPL – neutral protamine lispro
Available Insulins

Adapted from McMahon GT. And Dluhy RG *N Engl J Med* 2007; 357:1759-1761
Time-action profiles for NPH and insulin glargine

NPH human insulin

Insulin glargine

Detemir

Serum insulin, pmol/L

0 8 16 24

Time, hours
Regular human insulin controls PPG

Benefits

✓ Structurally identical to endogenous insulin
✓ Less immunogenic
✓ Unlimited production/manufacturing

Limitations

✗ Unphysiological time course for acceptable PPG control
✗ Safety concerns (hypoglycaemia) if the meal is not eaten when scheduled
✗ High intraindividual and interindividual variability in insulin absorption
✗ Risk of hyperinsulinemia
✗ Risk of late postprandial hypoglycaemia (before next meal or nocturnal)
✗ Patient inconvenience/compliance

Rapid-acting insulin analogs

- Less variability in absorption at injection sites
- More rapid onset and shorter duration of action
- Greater peak effect
- Better control over PPG
- Decreased risk for hypoglycemia
- Flexibility with meal timing
- Option of postprandial administration
NPH Insulin

• Provides basal insulin level

• Limitations
  • Variable absorption both within and across patients
  • A distinct peak and decline
Insulin Analogs: Detemir & Glargine

• Improved pharmacokinetic and pharmacodynamic characteristics
• Longer duration of action that permits once-daily dosing
• Lower risk for hypoglycemia
• Reduced incidence of weight gain
Case Presentation …8

• 49-yr old lady has type 2 DM for 6 years. She works in a garment factory with 3 shifts in 24 hrs
• Rx: Glimepiride 6 mg daily, Metformin 1.5 g daily
• Urinalysis shows trace protein; Fundoscopy – few microaneurysms left eye
• A1C = 8.6%, FBG = 180-220 mg/dL, PPG = 170-200 mg/dL

• What is next step to optimize glycaemic control?
  A. Increase Glimepiride to 8 mg/day & Metformin to 2 g/day
  B. Add DPP4 Inhibitor
  C. Add SGLT2 Inhibitor
  D. Add Pioglitazone
  E. Add Insulin
• Which insulin regimen would you choose?

A. Basal
B. Basal Plus
C. Basal – Bolus
D. Premixed insulin
• 43-yr old male has type 2 DM for 8 years.
• Rx: Glimepiride 8 mg daily, Metformin 2 g daily
• A1C = 7.3%, FBG = 140-170 mg/dL, PPG = 220-280 mg/dL

• What is next step to optimize glycaemic control?

A. Add DPP4 Inhibitor
B. Add SGLT2 Inhibitor
C. Add Pioglitazone
D. Add Insulin
• Which insulin regimen would you choose?

A. Basal
B. Basal Plus
C. Basal – Bolus
D. Premixed insulin
Which Regimen?

• **Premixed Insulin**
  - Postprandial increment > 54 mg/dL
  - Large CHO intake at 1 or 2 meals
  - Predictable eating pattern, working hours
  - Unlikely to manage Basal-Bolus regimen

• **Basal Insulin**
  - Postprandial increment < 18 mg/dL
  - No large CHO intake at meals
  - Unpredictable eating pattern, working hours
  - Likely to manage Basal-Bolus regimen

• **Basal Bolus**
  - Comfortable with more frequent injections
  - Comfortable with more frequent monitoring
  - Good dexterity, motivated patient
**Basal Insulin** (Continue Metformin)

**Start:** 10 u once daily

**Adjust:** 2-4 u 1-2 times/week to reach target FBS

**Hypo:** reduce by 4 u

If FBS in target but A1C is high or TDD > 0.5 u/kg/day

**Treat PPG**

Add 1 **Prandial Insulin** before largest meal. Start 4 u & adjust by 2-4 u Q3-5 d

Then add 2\(^{nd}\) and 3\(^{rd}\) **Prandial Insulin**

**Not Controlled**

**BASAL-BOLUS**

Add > 2 prandial insulins before meals

Start: 4 u/d & adjust by 2-4 u until FBS & PPG targets

Change to **Premixed Insulin**

Start: current basal dose 2/3 am & 1/3 pm

Adjust: 2-4 u Q 3-5 d
A 54 year old male with history of AMI 3 year ago was diagnosed with type 2 diabetes a year ago, but had no follow up. He is being seen today because of RBS of 302 mg/dL.

His physical exam today is normal. He has a BMI of 28. He admits to feeling a little tired, recently, and has been getting up at night to urinate at least two to three times per week.

Treatment:
  • HCTZ, 25 mg qd
  • Metoprolol  50 mg qd
  • Aspirin 81 mg qd
  • Simvastin 20 mg  at bed time
Findings

- BP: 130/90 mmHg
- BMI: 28 kg/m²
- RBS = 302 mg/dL, A1C: 10.2%
- Total Cholesterol: 153 mg/dL
- LDL: 70 mg/dL
- HDL: 41 mg/dL
- Triglycerides: 225 mg/dL
- Creatinine: 0.8 mg/dL
- LFTs = Normal
How would you initially treat this patient?

A. Diet & Exercise
B. Diet & Exercise plus Metformin
C. Diet & Exercise plus Sulphonylurea
D. Diet & Exercise plus Insulin
Follow up visit 2

- HbA1C = 9.5%
- No hypoglycaemia symptoms or episodes
- Weight has increased by 2 kg
- Taking 20 units of Basal Insulin

HBGM (mg/dL):

- Fasting – 185
- Pre lunch – 236
- Predinner – 224
- Bedtime - 196
What is the next best adjustment of therapy?

A. Increase the dose of basal insulin
B. Start mealtime regular insulin
C. Change to premixed insulin (30/70)
D. Switch to Metformin
Follow up Visit 3

• HbA1C = 8.6%
• Basal Insulin Dose = 30 units once daily

• HBGM (mg/dL):
  • Fasting = 124
  • Pre-Lunch = 196
  • Pre-Dinner = 168
  • Bedtime = 154
What is the next best adjustment of therapy?

A. Increase the dose of basal insulin
B. Start mealtime regular insulin
C. Change to premixed insulin (30/70)
D. Switch to Metformin
Visit 4

• Patient is feeling more energetic and gained weight.
• His A1C has dropped to 7.5%
• He is currently taking 30 U of Basal Insulin in the morning, and 6 U of prandial insulin before breakfast.
• His HBGM values are:
  • HBGM (mg/dL):
    • Fasting = 123
    • Pre-Lunch = 126
    • Pre-Dinner = 130
    • Bedtime = 175
What is the next best adjustment of therapy?

A. Increase the dose of basal insulin
B. Add a second dose of mealtime regular insulin
C. Add a Sulphonylurea
D. Switch to Metformin
Visit 5

- Patient is happy of his condition
- Takes Basal Insulin 30 u once daily and prandial insulin 6 u with breakfast and 4 u with dinner
- A1C = 7%
- HBGM: mg/dL
  - Fasting = 110
  - Pre lunch = 120
  - Pre dinner = 123
  - Bedtime = 130
What is the next best adjustment of therapy?

A. Add a third dose of mealtime regular insulin
B. Switch to Sulphonylurea
C. Stop insulin and switch to Metformin
D. Switch to Metformin and down titrate insulin
Case Presentation 11

- 52-year old man, smoker, on metformin 1 g BID
- Type 2 DM – 3 years
- AMI – a year ago
- No symptoms of CVS
- BP = 145/90
- Wt = 92kg, Ht = 170 cm
- Liver 4 cm
- Retina = hemorrhages, exudates

- HbA1C = 9%
- SGOT = 72
- SGPT = 68
- LDL = 128
- HDL = 28
- TG = 250

How would you manage?
Answer

• Multiple & Comprehensive Approach
• Diet – low fat, high fiber
• Exercise – 30 min or more 5 days per week
• Weight reduction
• Smoking cessation
• BP control
• Lipid control
• Glycemic control
• ASA
Steno-2: Multifactorial Intervention and CVD in Type 2 DM

HR = 0.47 (95% CI, 0.24 - 0.73; P=.008)

Composite end point of death from CV causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation, or surgery for peripheral arterial disease

Steno-2: 13+ Year Follow-Up

Cumulative Incidence of Death (%)

- Conventional therapy
- Intensive therapy

P = 0.02

6.3%

50%

30%

2.5%

Years of Follow-Up

Comprehensive Care

- **Lifestyle Modifications**
  - Healthy Diet
  - Regular Exercise
  - Ideal Weight
  - No Smoking
  - Avoidance of Alcohol Abuse

- **Statins**
  - DM + CVD
  - Age > 40 yrs + 1 CVD risk factor
  - Age < 40 yrs if LDL > 100 mg/dL
<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS and LDL cholesterol $\geq$50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins</td>
<td>Moderate plus ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS and LDL cholesterol $\geq$50 mg/dL (1.3 mmol/L) or in patients with a history of ASCVD who cannot tolerate high-dose statins</td>
<td>Moderate plus ezetimibe</td>
</tr>
<tr>
<td>High-intensity statin therapy (lowers LDL cholesterol by ≥50%)</td>
<td>Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to &lt;50%)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10–20 mg</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 20–40 mg</td>
<td>Rosuvastatin 5–10 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40–80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>
Comprehensive Care (Cont’d)

• Blood Pressure Management
  • 120/80 - <140/90 mmHg – Lifestyle modification
  • > 140/90 mmHg
    • ACEIs or ARBs
  • 2 or more drugs needed
    • > 160/100 mmHg
      • Administer one of the drugs at bed time

• ASA for Primary prevention
  • Males > 50 yrs, Females > 60 yrs + 1 CV risk factor
## ABCDEFS of Diabetes Management

<table>
<thead>
<tr>
<th></th>
<th>FBS</th>
<th>PPG</th>
<th>HbA1C</th>
<th>90-130 mg/dl</th>
<th>90-130 mg/dl</th>
<th>&lt; 180, &lt; 160, &lt; 140</th>
<th>&lt; 7%</th>
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<tbody>
<tr>
<td><strong>Hyperglycemia</strong></td>
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<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt; 140/90 mmHg</td>
<td></td>
<td></td>
<td>No Nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 125/75</td>
<td></td>
<td></td>
<td>With Nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td>Total Cholesterol</td>
<td></td>
<td></td>
<td>&lt; 200 mg/dl</td>
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<tr>
<td></td>
<td>LDL-C</td>
<td></td>
<td></td>
<td>&lt; 100 mg/dl (only DM)</td>
<td></td>
<td>&lt; 70 mg/dl (DM+CVD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL-C</td>
<td></td>
<td></td>
<td>&gt; 40 mg/dl (men)</td>
<td></td>
<td>&gt; 50 mg/dl (women)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td></td>
<td></td>
<td>&lt; 150 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D – damage to kidneys  E – eye exam  F – foot exam  S – stop smoking
Glycemic Targets (HbA1C) *(Patient-centered)*

- General Target < 7%

- More Stringent 6.0 % – 6.5 %
  - Younger patients
  - Newly diagnosed
  - Long-standing disease, no significant complications

- Less Stringent 7.5% - 8.0%
  - Older patients
  - Long-standing disease and significant complications
  - CV risk factors
  - History of CVD
Treatment Algorithm

Lifestyle Therapy + Entry A1C

- **A1C < 7.5%**
  - Monotherapy
    - Metformin
    - SGLT 2 Is
    - DPP-4 Is
    - SUs
    - TZDs
    - GLP-1 RAs
  - 3mos

- **A1C > 7.5%**
  - Dual Therapy
  - 3mos
  - 3mos

- **A1C > 9%**
  - Insulin
  - Dual or Triple Therapy if NO Symptoms
  - 3mos
  - 3mos
Case Presentation…..12

• 26-year old, male, type 1 DM 4 years, routine follow up
• Headaches in the mornings upon awakening
• NPH Insulin 36 u am and 24 u pm
• Regular insulin 8 u and 6 u pm
• BP = 120/70 mmHg,
• Weight = 65 kg 3 months ago, today = 68 kg
• FBS mostly > 240 mg/dl
• Pre-dinner Blood Sugar = 140-170 mg/dl

• What is the most helpful single test?
• How would you manage?
Answer

• Measure blood glucose level around 2-3 a.m.
• Nocturnal Hypoglycemia leading to rebound hyperglycemia
• Shift evening NPH to bedtime or reduce the evening dose
Time-action profiles for NPH and insulin glargine

![Graph showing serum insulin levels for NPH human insulin and insulin glargine over time.](image-url)
Case Presentation…..13

- A 30 year old man is diagnosed to have diabetes based on FBS of 256 mg/dl and HbA1c of 8%. Urine Ketone is negative.

- You suggested insulin, but patient and family adamantly refuse but you insisted.

- He reluctantly accepts and goes to the nurse and asks her for an alternative place to go to as he does not want to start insulin.
• He goes to another place and finally finds a doctor who put him on combined metformin and glimepiride.
Follow up

- After 4 weeks
  - FBS = 160 mg/dl, A1c = 7.5%
- Patient has no symptoms and is happy that blood sugar is decreasing on tablets.
- After 3 months
  - FBS 128 mg/dl, HA1c = 6.9%
Cont’d

• He returns 6 months later with
  • FBS = 180 mg/dl, A1c 8.8%

• Oral agents are escalated and after another 3 months, he comes with
  • Poly symptoms & weakness
  • FBS = 260 mg/dl, trace ketones in urine, A1C 10%
Cont’d

• Discuss the case and explain the reason for glycemic deterioration?
• What is the diagnosis?
• What would help in the diagnosis?
Answer

• Diagnosis:
  • LADA

• Lab
  • Insulin/C peptide
  • Markers of autoimmunity
Case Presentation.....14

• A 48-year old lady known to have HPN for 6 years and with BMI of 36 kg/m$^2$ presents for the first time with SOB and weakness

• BP = 140/80 mmHg, PR = 112 beats/min

• RBS = 525 mg/dL, Urine glucose = 4+, Urine Ketones = 2+

• Lipids: TC = 212 mg/dL, TG = 256 mg/dL, HDL-C = 34 mg/dL

• What is the diagnosis, management & follow up?
Principles of Comprehensive Management of Type 2 Diabetes

1. Lifestyle modification
2. Individualized approach
3. Address both FPG & PPG
4. Minimize risk of hypo & weight gain
5. Combination therapy usually required
6. Comprehensive BP and Lipid Management
7. Initial regimen should be simple
Summary & Conclusions

1. Hyperglycaemia is a major modifiable factor driving development and progression of macro- and microvascular complications

2. Early and intensive treatment is key in reducing risk of complications (Hit Early, Hit Hard but Safely)

3. Multiple classes of anti-hyperglycaemic agents are available & treatment decisions must be individualized & comprehensive

4. Delayed insulin initiation increases the risk of long term complications & current algorithms recommend use of insulin if not at goal within the first year of treatment
Thank you