Pathophysiology of Type 2 DM

Disharmonious concert

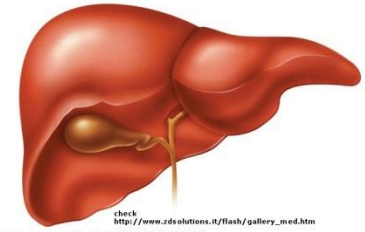
Professor ZAFAR A. LATIF

Eight players

- Tune harmoniously in Non-DM.

But in Type 2 DM

Hyperglycemia



Liver

↑ HGP

Insulin resistance

Liver:

- Non DM- HGP 2mg/kg/min,
- Incase of DM HGP 2.5 mg/kg/min

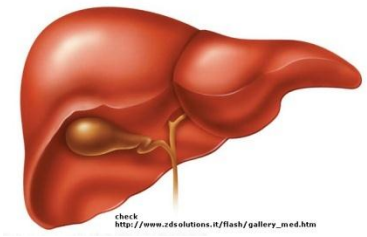
↓

occurs despite of 2-3 fold increase in insulin secretion

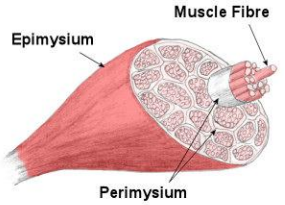
↓

insulin resistance.

Hyperglycemia



↑ **Liver**
HGP



↓ **Muscle**
Glucose uptake

Muscle:

- Lean Type 2 DM- severe insulin resistant.
- Intramyo cellular defect :-
  - Impaired glucose transport & phosphorylation.
  - ↑Glycogen synthesis.
  - ↓Glucose oxidation.

β cell failure

- **Liver:**

insulin resistance → ↑HGP

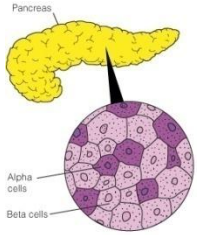
Despite fasting hyperinsulinemia.

- **Muscle:**

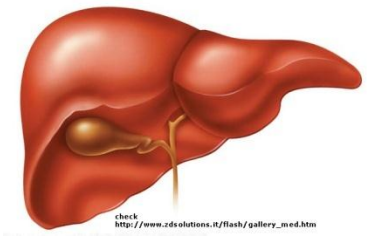
insulin resistance → impaired glucose uptake following carbohydrate meal.

B - Cell

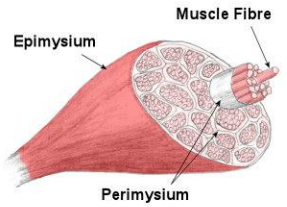
↓ Insulin secretion



Hyperglycemia



↑ **Liver**
HGP



↓ **Muscle**
Glucose uptake

- **ß-cell:** insulin resistance

  ↓

  major stress to ß-cell. Initial augmentation of insulin secretion

  ↓

  ß-cell failure

  ↓

  initial rise in PPG then FBG

β-cell: Bihormonal deficiency

↓

↓ Amylin action contribute abnormal glucose metabolism

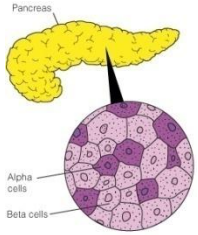
- Amylin: Complement action of Insulin by suppressing glucagon and also by vagus mediated gastric emptying regulation.

- **Obesity & physical inactivity are insulin resistant**
- **Age**
- **Genetic: Susceptible locus in chromosome 12**

  (Finnish study).

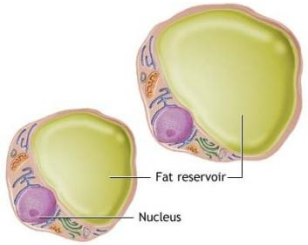
B - Cell

↓ Insulin secretion



Fat cell

↑ Lipolysis



Hyperglycemia

Fat cell:

- Lipotoxicity - increased FFA in ß-cell

↓

impaired insulin secretion`

↓

ß-cell failure

•Hypersecretion of islet amyloid polypeptide (IAPP) & deposition in pancreas

↓

progressive B- cell failure

Fat cell:

a) ↑ FFA (Free fatty acid) - resistant to anti-lypolytic effect

b) ↑ FFA (Free fatty acid) - Stimulate gluconeogenesis

↓

induce hepatic/ muscle insulin resistance

c) Dysfunctional fat -

induces inflammatory and atherosclerotic provoking adipocytokines but fails to produce adiponectin(insulin sensitive)

d) Enlarged fat - insulin resistant

- Glucotoxitcity: Chronic elevated plasma glucose impair β cell function.

- IAPP (islet amyloid polypeptide):

↑ Secretion of IAPP and amyloid deposition in pancreas

↓

progressive β cell failure

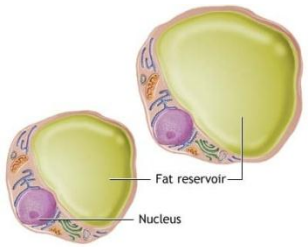
Amylin secreted in a one to one ratio with insulin and IAPP oligomer are toxic to β cell.

GUT

↓ Incretin effect

Fat cell

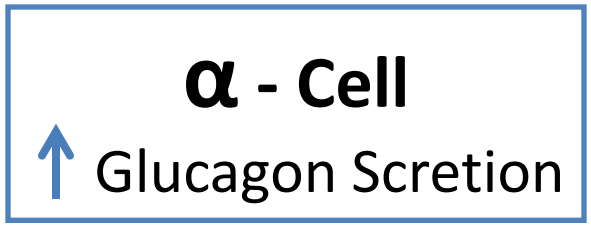
↑ Lipolysis



Hyperglycemia

- **Gut hormone – incretin effect**
  - GLP-1 deficient but GIP increased.
  - GLP-1 → Glucagon suppressor
  - GIP → insulin resistance → β- cell failure

Hyperglycemia



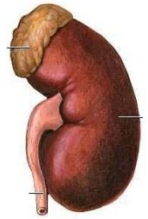
- **Pancreatic α-cell:**

  Basal glucagon elevated in Type2 DM

  ↓

  ↑ HGP

Hyperglycemia



↑ **α - Cell**
Glucagon Scretion

Kidneys
↑ Glucose reabsorption

Kidney:

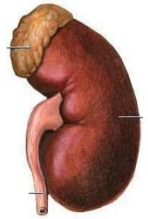
- Filters ± 162gm glucose/day. reabsorbed 100% by high capacity $SGLT_2$ transporter from proximal tubules.

In DM reabsorptive capacity increased

↓

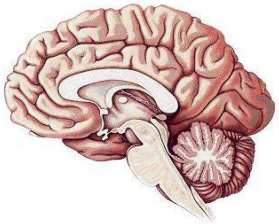
hyperglycaemia

Hyperglycemia



Kidneys

↑ Glucose reabsorption



Brain

Neurotransmitter dysfunction

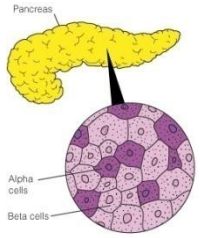
- **Brain:**
  - Epidemic of DM is related to epidemic of obesity.
  - Insulin is a powerful appetite suppressant.
  - In obesity:

    Hypothalamic area which regulate appetite is not suppressed despite hyperinsulinemia.

    - Indicating Insulin resistance
    - Leading to increased HGP

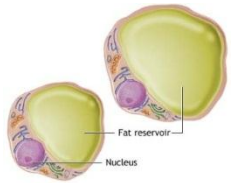
Hyperglycemia

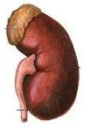
B - Cell
↓ Insulin secretion



GUT
↓ Incretin effect

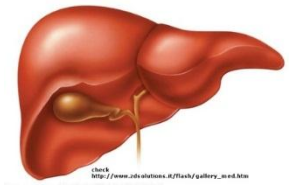
Fat cell
↑ **Lipolysis**





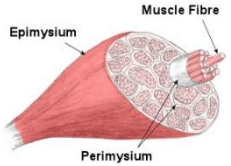
α - Cell
↑ Glucagon Scretion

Kidneys
↑ **Glucose reabsorption**



Liver
↑ HGP

Brain
Neurotransmitter dysfunction



Muscle
↓ Glucose uptake

Treatment

- **As multiple pathology** → Multiple drugs in combination

- **Reverse of known pathogenic abnormality:**

  Not simply reducing HbA1c

- **To prevent slow progressive β cell failure:**

  Thereby must start early.

Treatment paradigm shift

in combination with diet/exercise.

- **Insulin resistance:** Exercise, metformin, TZD

  (Liver, muscle and fat cell)

  - improves insulin sensitivity,
  - anti atherosclerogenic and
  - TZD

    preserve β cell.

- **β cell failure:** *Sulphonylurea & Glinides ??*

  initial improvement → •enhance β cell failure

  •↑HbA1c

- Amylin based: Pramalintide,

  synthetic analogue along with insulin regimen ↓HbA1c and ↓Body weight for longtime.

- **Incretin effect:**

  Liraglutide (GLP-1 analogue)

  Exenatide (DPP-4 inhibitor)

  → Preserve β cell,

  ↓ Appetite

  ↓ Gastric emptying

- **Pancreatic α cell:**
  - GLP-1 analogue
  - DPP-4 inhibitor

- **Kidney:**

  $SGLT_2$ transporter inhibitor- Dapagliflozin

  UTI, Polyuria, electrolyte imbalance

- **Brain:**
  - Metformin
  - GLP-1 analogue
  - Ghrelin inibitior??

Thank you