Diabetes mellitus

Objectives

1. To study the Pathogenesis of T2D.

2. To illustrate differences between T1D and T2D.

3. To illustrate the diagnosis of diabetes mellitus.

4. To give an account on impaired glucose tolerance and impaired fasting glycaemia

5. To give an account on assessment of glycaemic control

Pathogenesis of T2D:

T2D is a more complex condition than T1D because there is a combination of:

1. Insulin Resistance.

with:

2. Beta – Cell Failure.

leading to *'relative' insulin deficiency*

Genetic predisposition

Genetic factors are important in type 2 diabetes, as shown that the concordance rate for T2D in monozygotic twins approach 100%.

1. Insulin Resistance (IR)

The primary cause of IR remains *unclear*.

1. Intra-abdominal 'central' adipose tissue: is metabolically active, and releases large quantities of FFAs which may induce IR because they compete with glucose as a fuel supply for oxidation in peripheral tissues such as muscle.

2. Adipokines: Adipose tissue releases a number of hormones (adipokines) which act on specific receptors to influence sensitivity to insulin in other tissues.

3. *Central obesity: may have a particularly potent influence on insulin sensitivity in the liver, and thereby adversely affect gluconeogenesis and hepatic lipid metabolism.*

4. Physical activity: is another important determinant of insulin sensitivity. Inactivity is associated with down-regulation of insulin-sensitive kinases and may promote accumulation of FFAs within skeletal muscle. Sedentary people are therefore more insulin-resistant than active people with the same degree of obesity.

2. Pancreatic B-cell failure

In the early stages of T2D, reduction in the total mass of pancreatic islet tissue is modest.

At the time of diagnosis, around 50-65 % of β-cell function has been lost and this declines progressively with time.

Some pathological changes are typical of T2D, the most consistent of which is deposition of amyloid.

Elevated plasma glucose and FFAs exert toxic effects on pancreatic β cells to impair insulin secretion.

Comparison between T1D & T2D

Feature	Type 1 diabetes	Type 2 diabetes
Age at onset	Younger "mostly in children" (usually < 30 years)	Mostly in adults (usually > 30 years)
Onset of symptoms	Sudden (days or weeks)	Gradual (months or years ' asymptomatic')
Body weight	Lean	Over weight or obese
Prevalence	~10%	~90%
Ethnicity risk	Northern European	Asian, African, American-Indian
Pathogenesis	Autoimmune disease	No immune disturbance
Heredity	HLA-DR3 and DR4 in > 90%	No HLA link
Concordance in identical twins	50%	>90%

Feature	Type 1 diabetes	Type 2 diabetes
Family history of DM	Uncommon	Common
Other autoimmune diseases	Common	Uncommon
Autoantibodies	Present	Absent
Clinical	1. Insulin deficiency 2. ± Ketoacidosis 3. Ketonuria 4. Always need insulin	1. Partial insulin deficiency initially 2. No ketonuria 2. ± Hyperosmolar state 3. Need insulin with gradual *B*-cell failure
Biochemical	C- peptide disappears	C- peptide persists
Rapid death without insulin	Yes	No
Diabetic complications at diagnosis	No	25%

Diagnosis of DM:

**** In patients complains from symptoms suggesting DM:**

1. Test urine for Glucose and ketones.

2. Measure RBG or FBG. Diagnosis confirmed by:

FPG: ≥ 7.0 mmol/l (≥ 126 mg/dl)

PPG: ≥ 11.1 mmol/l (≥ 200 mg/dl)

Hb A1c: ≥ 6.5 %

NOTES:

Two readings are needed in asymptomatic people.

The oral glucose tolerance test (OGTT) :

The OGTT is required for borderline cases and for diagnosis of gestational diabetes.

INDICATIONS OF OGTT:

1. **IFG: 6.1 - 6.9 mmol/l (110 - 125 mg/dl)***
2. **IGT: *7.8* – 11.0 mmol/l (140 - 199 mg/dl)**
3. **Borderline blood sugar values**
4. **Symptoms suggesting DM with normal blood sugar values**
5. **Gestational diabetes**

Notes:

- ***A lower cut-off of 5.6 mmol/L "100 mg/dl " (rather than 6.1 mmol/L) has been proposed.**

HOW TO PERFORM OGTT:

Adult: 75 g glucose in 300 ml water.

Child: 1.75 g glucose/kg body weight.

Only a fasting and a 120-min samples are needed

Interpretation of OGTT:

Normal OGTT:

FPG: <6.1 mmol/l

PPG: <7.8 mmol/l

Impaired glucose tolerance:

FPG: < 7.0 mmol/l

PPG: ≥ 7.8, < 11.1 mmol/l

Diabetes mellitus:

FPG: ≥ 7.0 mmol/l

PPG: ≥ 11.1 mmol/l

Impaired glucose tolerance:

FPG: < 7.0 mmol/l

(< 126 mg/dl)

PPG: ≥ 7.8 mmol/l, < 11.1 mmol/l

(≥ 140 mg/dl, < 200 mg/dl)

Hb A1c: 5.7 – 6.4 %

Impaired fasting glycaemia:

FPG: > 6.1 mmol/l , < 7.0 mmol/l

(> 110 mg/dl, < 126 mg/dl)

PPG: < 7.8 mmol/l

(< 140 mg/dl)

Notes:

- **These patients have increased risks of progression to frank diabetes with time and of macrovascular atheromatous disease**
- **A lower cut-off of 5.6 mmol/L "100 mg/dl " (rather than 6.1 mmol/L) has been proposed; this would triple the prevalence of this condition.**

Other Definitions:

Potential Diabetes: **Normal OGTT but have an increased risk of developing DM for genetic reasons like individuals who have 1st degree relative with DM**

Latent Diabetes: **Normal OGTT but develop abnormal OGTT in conditions imposing burden on *Beta*-cells like pregnancy, infections, MI, stress, drugs.**

Assessment of Glycaemic Control:

1. Plasma glucose measurement:

Self monitoring of blood glucose. "*Diabetic Calendar*"

2. Hb A1c: **Assess glycaemic control in the previous 6-8 weeks.**

Interpretation of Hb A1c:

1. Optimal Control: **Hb A1c: 6.5 – 7.0 %**

2. Sub-optimal (Acceptable) Control: **Hb A1c: 7.0-8.0 %**

3. Poor Control: **Hb A1c ≥ 8.0 %**

3. Glycated albumin (Fructosamine):

Assess glycaemic control over shorter period (in the last 2-3 weeks)