

Pathogenesis of Diabetes Mellitus (DM), Type II

Unhealthy Lifestyle: i.e. over-eating, obesity, inactivity

Intraperitoneal cavity accumulates "visceral fat" (aka. "abdominal fat"), which is an endocrine organ that secretes:

Inflammatory mediators

Adipokines

Free fatty acids (FFAs)

Note: "adipokines" are inflammatory mediators released from adipose tissue (e.g. TNFalpha). The more adipose tissue a patient has, the more adipokines are released.

Genetic Susceptibility:

Polygenetic or monogenetic factors (i.e. maturity-onset diabetes of the young (MODY)) can predispose insulin resistance

Aging: Beta-cell mass declines with aging, so those predisposed to insulin resistance may develop Type II DM as they age.

Medications: i.e. corticosteroids, anti-psychotics, highly-active anti-retrovirals, progestin-only oral contraceptives

Complex, unclear actions on body tissue

Insulin resistance

(liver, muscle, adipose tissue become less responsive to insulin, and thus less able to use glucose as a fuel source)

Upototoxicity:

FFAs inhibit function of GLUT2 on Beta-cells, ↓ glucose import

Beta-cells do not recognize high blood glucose → ↓ insulin secretion

Initially, beta-cells of the pancreas work overtime to ↑ insulin secretion

Blood [glucose] is kept normal

Glucotoxicity: hyperglycemia is directly toxic to Beta-cells

Hyperglycemia

Over many years, as insulin resistance worsens, Beta-cells "tire out", ↓ insulin secretion (relative insulin deficiency)

Over many more years: Beta-cells deteriorate until they finally stop producing insulin, (absolute insulin deficit)

Since cells can't use glucose, body perceives a state of "starvation", thus mobilizing triglycerides into FFAs, to be used as fuel by cells.

Type II Diabetes Mellitus

Note: There is a HUGE genetic basis for Type II DM: high concordance rate between family members (90% for monozygotic twins), and if a first-degree relative is affected, the risk for other family members is 5-10x above baseline.

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Pathogenesis And Treatment Of Diabetes Mellitus

ML Morrison



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