**Diabetes Mellitus: Pathology**

Diabetes Mellitus (DM) is not a single disease entity but rather a group of metabolic disorders sharing the common feature of hyperglycaemia.

Normal blood glucose levels range from 70-120mg/dL.

The diagnosis of diabetes is established by noting an elevation of blood glucose by any one of the 3 criteria:

1. A random glucose concentration of greater than 200mg/dL with classical signs and symptoms.
2. A fasting glucose concentration of greater than 126mg/dL on more than one occasion.
3. An abnormal oral glucose tolerance test in which the glucose concentration is greater than 200mg/dL 2 hours after the standard CHO load.

*Classification of DM*

The majority of cases fall into 2 particular types:

Type 1 Diabetes Mellitus (T1DM)

It is an autoimmune disease characterised by pancreatic β-cell destruction and an absolute deficiency of insulin. It accounts for 5-10% of all DM cases.

Type 2 Diabetes Mellitus (T2DM)

It is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response to pancreatic β-cells. 90-95% of all cases are composed of T2DM.

*Glucose Homeostasis*

Normal glucose homeostasis is determined by 3 processes:

1. Glucose production in the liver
2. Glucose uptake and utilisation by peripheral tissue (skeletal muscle)
3. Actions of insulin and counter-regulatory hormones including glucagon on glucose uptake and metabolism

Insulin and glucagon have opposing regulatory effects on glucose homeostasis. In fasting states, high glucagon levels but low insulin levels facilitate gluconeogenesis and glycogenolysis. In meal times, insulin levels rise and glucagon decreases in response to a large dose of glucose.

The skeletal muscle is the major insulin-responsive site for post-prandial glucose use and is critical for preventing hyperglycaemia and maintaining glucose homeostasis.

*Pathogenesis of T1DM*

T1Dm is an autoimmune disease in which islet destruction is caused by immune effector cells reacting against endogenous β-cell antigens.

There is some evidence of genetic susceptibility. Moreover environmental factors such as viral infections may involved in triggering islet destruction in T1DM.

The clinical onset of T1DM is often hasty. However, the cell destruction is often progressive with often 90% of β-cells destroyed when the disease presents. The fundamental immune abnormality in T1DM is a failure of self-tolerance in T-cells.

*Pathogenesis of T2DM*

T2DM is a prototypic multifactorial complex disease which incorporates both genetic and environmental factors. Environmental factors include a heavily sedentary lifestyle and obesity.

The 2 metabolic defects that characterise T2DM are:

1. A decreased response of peripheral tissues to insulin.
2. β-cell dysfunction that is manifested as inadequate insulin secretion in the face of insulin resistance and hyperglycaemia.

*Pathogenesis of the Complications of DM*

Formation of Advanced Glycation End (AGE) Products

AGEs are formed as a result of nonenzymatic reactions between intracellular glucose derived from dicarbonyl precursors with amino groups or both intra and extracellular proteins.

This may lead to effects of:

1. Release of pro-inflammatory cytokines and growth factors from intimal macrophages.
2. Generation of reactive O species.
3. Increased procoagulant activity on endothelia cells and macrophages
4. Proliferation of vascular smooth muscle cells and synthesis of extracellular matrix

Intracellular Hyperglycaemia and Disturbances in Polyol Pathways

Activation of Protein Kinase C.

The effects include:

* Production of proangiogenic vascular endothelial growth factor (VEGF)
* Elevated levels of vasoconstrictor endothelin-1 and decreased levels of vasodilator NO
* Production of profibrogenic factors like TGF-β leading to increased deposition of extracellular matrix and basement membrane material
* Production of PAI-1 leading to reduced fibrinolysis and possible vascular occlusive episodes
* Production of pro-inflammatory cytokines by vascular endothelium

*Clinical Presenation*

* Macrovascular Complications – myocardial infarction, renal vascular insufficiency, cerebrovascular accidents.
* Diabetic Neuropathy
* Visual Impairment
* Diabetic Neuropathy
* Increased susceptibility of infections of the skin, and to TB, pneumonia and pyelonephritis

*Long Term Complications – Morphology*

***Pancreas.*** Lesions in the pancreas are inconstant and rarely of diagnostic value. Distinctive changes are more commonly associated with type 1 than with type 2 diabetes. One or more of the following alterations may be present:

* **Reduction in the number and size of islets.** This is most often seen in type 1 diabetes, particularly with rapidly advancing disease. Most of the islets are small and inconspicuous.
* **Leukocytic infiltrates in the islets** (insulitis) are principally composed of T lymphocytes, as is also seen in animal models of autoimmune diabetes. Lymphocytic infiltrates may be present in type 1 diabetics at the time of clinical presentation. The distribution of insulitis may be strikingly uneven. Eosinophilic infiltrates may also be found, particularly in diabetic infants who fail to survive the immediate postnatal period.
* **In type 2 diabetes there may be a subtle reduction in islet cell mass,** demonstrated only by special morphometric studies.
* **Amyloid deposition within islets in type 2 diabetes** begins in and around capillaries and between cells. At advanced stages, the islets may be virtually obliterated; fibrosis may also be observed. Similar lesions may be found in elderly nondiabetics, apparently as part of normal aging.
* **An increase in the number and size of islets** is especially characteristic of nondiabetic newborns of diabetic mothers. Presumably, fetal islets undergo hyperplasia in response to the maternal hyperglycemia.