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Second stage/ Lecture 1

Metabolic Syndrome

The characteristic features are abdominal obesity and insulin resistance or decreased glucose tolerance. The body cannot properly use glucose even in presence of normal insulin level. In other words, body cannot use insulin efficiently. Therefore, the metabolic syndrome is also called the insulin resistance syndrome. People with the Met S are at increased risk of coronary heart disease and type 2 diabetes. The MetS has become increasingly common in the developing countries.

Causes for Mets or Associated Conditions Include:

obesity; alcoholism; sedentary lifestyle with lack of physical exercise; polycystic ovarian syndrome (PCOS); hypercortisolism (e.g. steroid use or Cushing's disease); certain drugs and genetic causes such as mutations of the insulin receptors.

Effects of Insulin Resistance:

hydrolysis of stored triglycerides or fats, which elevates free fatty acids (FFA) in the plasma; reduction of glucose uptake or glucose utilization among muscle cells and reduction of glycogenesis (glycogen formation) or decreasing glucose storage in the liver cells with both effects leading to elevation of blood sugar levels. In obese patients especially those with high visceral fat, compensatory hyperinsulinemia causes the down regulation of the insulin receptors potentiated by the inherent defects within the target cells itself. Both aspects play a role in the development of insulin resistance.

Laboratory Tests for MetS:

The fasting insulin level greater than 60 pmol/L is considered to be positive evidence of insulin resistance. Further, hyperinsulinemic euglycemic clamp test may be done in selected cases; however, this is rarely performed in the clinical setting. But this is considered to be the gold standard because it measures the exact amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia.

Management of the Metabolic Syndrome

i. Weight loss to achieve a desirable weight.

ii. Moderate exercise every day.

iii. Reduced intake of saturated fats, trans fatty acids and cholesterol.

Diabetes Mellitus

Diabetes mellitus is the third leading cause of death (after heart disease and cancer) in many developed countries. It affects about 6 to 8% of the general population. The complications of diabetes affect the eye, kidney and nervous system. Diabetes mellitus is a clinical condition characterized by increased blood glucose level (hyperglycemia) due to insufficient or inefficient (incompetent) insulin on the target tissues. As a consequence, the blood glucose level is elevated which spills over into urine in diabetes mellitus (Greek: diabetes—a siphon or running through; mellitus—sweet).

Sources of Blood Glucose

1. Dietary sources: The dietary carbohydrates are digested and absorbed as monosaccharides (glucose, fructose, galactose etc.). The liver is capable of converting fructose and galactose into glucose.

2. Gluconeogenesis: The degradation of glycogen in muscle results in the formation of lactate. Breakdown of fat in adipose tissue will produce free glycerol and propionate. Lactate, glycerol, propionate and some amino acids are good precursors for glucose synthesis (gluconeogenesis) that actively occurs in liver and kidney. Gluconeogenesis continuously

adds glucose to the blood. Cori cycle is responsible for the conversion of muscle lactate to glucose in liver.

3. Glycogenolysis: Degradation of glycogen in liver produces free glucose. This is in contrast to muscle glycogenolysis where glucose is not formed in sufficient amount due to lack of the enzyme glucose 6- phosphatase. However, the contribution of liver glycogenolysis to blood glucose is rather limited and can meet only the short intervals of emergency. This is due to the limited presence of glycogen in liver. An adult liver (weighing about 1.5 kg) can provide only 40-50 g of blood glucose from glycogen, that can last only for a few hours to meet the body requirements. the sources of blood glucose during a normal day (24 hours) are given. Glucose is primarily derived from glycogenolysis (of hepatic glycogen) between the meals. Gluconeogenesis becomes a predominant source of glucose in late night (after depletion of hepatic glycogen). During day time, gluconeogenesis may be more or less active, depending on the frequency of consumption of snacks, coffee, tea, fruit juices etc.

Utilization of blood glucose

Certain tissues like brain, erythrocytes, renal medulla and bone marrow are exclusively dependent on glucose for their energy needs. When the body is at total rest, about two-thirds of the blood glucose is utilized by the brain. The remaining one-third by RBC and skeletal muscle. A regular supply of glucose, by whatever means it may be, is absolutely required to keep the brain functionally intact. The different metabolic pathways (glycolysis, glycogenesis, HMP shunt etc.) responsible for the utilization of blood glucose, The synthesis of fat from acetyl CoA and glycerol. Kidney plays a special role in

the homeostasis of blood glucose. Glucose is continuously filtered by the glomeruli, reabsorbed and returned to the blood. If the level of glucose in blood is above 160-180 mg/dl, glucose is excreted in urine (glycosuria).

This value (160-180 mg/dl) is referred to as renal threshold for glucose.

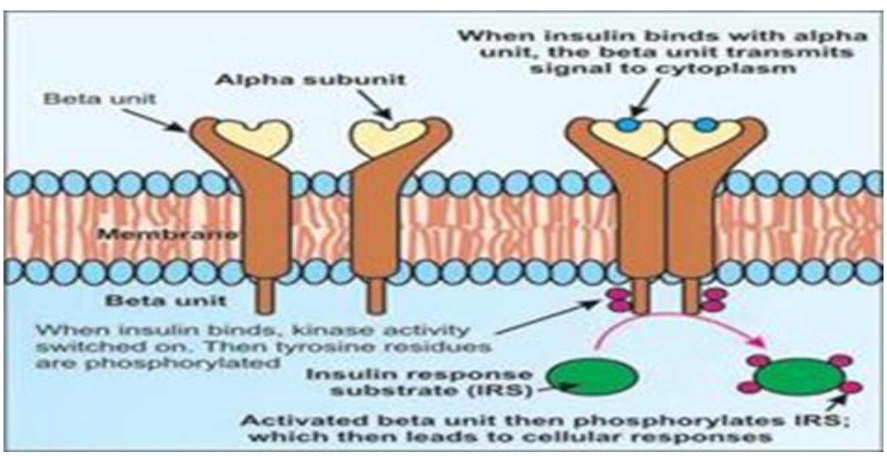
Role of Hormones in Blood Glucose Homeostasis

Hormones play a significant role in the regulation of blood glucose concentration, Primarily, insulin lowers blood glucose level (hypoglycemic) while the rest of the hormones oppose the actions of insulin (hyperglycemia) are Glucagon, Epinephrine, Thyroxine, Glucocorticoids, Growth hormone and adrenocorticotropic hormone (ACTH).

Insulin

Insulin is the most important hormone controlling plasma glucose concentrations. A plasma glucose concentration of greater than about 5 mmol/L acting via the glucose transporter 2 stimulates insulin release from the pancreas b-cell. These cells produce proinsulin, which consists of the 51-amino-acid polypeptide insulin and a linking peptide (C-peptide).

Insulin binds to specific cell surface receptors on muscle and adipose tissue, thus enhancing the rate of glucose entry into these cells. Insulin-induced activation of enzymes stimulates glucose incorporation into glycogen (glycogenesis) in liver and muscle. Insulin also inhibits the production of glucose (gluconeogenesis) from fats and amino acids, partly by inhibiting fat and protein breakdown (lipolysis and proteolysis).



Classification of Diabetes Mellitus

1. Type 1 Diabetes Mellitus :(formerly known as Insulin-dependent diabetes mellitus; IDDM). About 5% of total diabetic patients are of type Here circulating insulin level is deficient.

2. Type 2 Diabetes Mellitus (formerly known as non-insulin dependent diabetes mellitus; NIDDM). Most of the patients belong to this type. Here circulating insulin level is normal or mildly elevated or slightly decreased, depending on the stage of the disease. This type is further classified as: Obese, non-obese, and Maturity onset diabetes of young (MODY).

3. Diabetic prone states: Gestational diabetes mellitus (GDM), Impaired glucose tolerance (IGT), and Impaired fasting glycemia (IFG)

4. Secondary to other known causes: endocrinopathies (Cushing's disease, thyrotoxicosis, acromegaly), drug induced (steroids, beta blockers, etc.), and pancreatic diseases (chronic pancreatitis, fibro calculus pancreatitis, hemochromatosis, cystic fibrosis).

Diabetes mellitus is associated with several metabolic alterations. Most important among them are hyperglycemia, ketoacidosis and hypertriglyceridemia