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OXIDATIVE STRESS AND DIABETES: A REVIEW

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ABSTRACT

Oxidative stress results from an imbalance between radical-generating and radical-scavenging systems, i.e. increased free radical production or reduced activity of antioxidant defenses or both. Implication of oxidative stress in the pathogenesis of diabetes is suggested, not only by oxygen free-radical generation, but also due to nonenzymatic protein glycosylation, auto-oxidation of glucose, impaired glutathione metabolism, alteration in antioxidant enzymes, lipid peroxides formation and decreased ascorbic acid levels. In addition to GSH, there are other defense mechanisms against free radicals like the enzymes superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT) whose activities contribute to eliminate superoxide, hydrogen peroxide and hydroxyl radicals.

Humans have evolved with antioxidant systems to protect against free radicals. These systems include some antioxidants produced in the body (endogenous) and others obtained from diet (exogenous).

Keywords: Oxidative stress, defense mechanisms, antioxidant, free radicals

DIABETES MELLITUS

The term "Diabetes mellitus" is derived from the Greek words dia (=through), bainein (=to go) and diabetes literally means pass through. The disease causes loss of weight as if the body mass is passed through the urine. Although it was known for centuries that the urine of patients with diabetes was sweet, it was not until 1674 that physician named Willis coined the term Diabetes Mellitus (from the Greek word for honey) [1].

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. [2] besides hyperglycemia, several other factors like hyperlipidemia and enhanced oxidative stress play a major role in diabetic pathogenesis. The disease is progressive and is associated with high risk of complications. [3]

CLASSIFICATION OF DIABETES MELLITUS:

Different forms of Diabetes Mellitus are:-

1 General:

Type 1 diabetes mellitus (formerly called insulin dependent diabetes mellitus, or IDDM).

- Auto-immune type 1 diabètes mellitus (type 1A)
- Non-autoimmune or idiopathic type 1 diabetes mellitus (type 1B)

Type 2 diabetes mellitus (formerly called non-insulin dependent diabetes mellitus or NIDDM)

2 Specific – defined gene mutations:
Maturity-onset diabetes of youth (MODY)

PATHOPHYSIOLOGY:

Carbohydrates and glucose in particular are an important source of energy for most living organisms. During fasting, most of the glucose in the blood is supplied by the liver and is used by the brain, independently of insulin. After a meal, the rise in blood glucose level rapidly stimulates insulin secretion, which results within minutes in an increased glucose transport, metabolism and storage by muscle and adipocytes. In addition, insulin inhibits glucagon secretion and lowers serum free acid concentrations, contributing to the sharp decline in hepatic glucose production. In a normal person about half the glucose ingested is converted into energy through the glycolytic pathway and about half is stored as fat and glycogen with the help of insulin and other enzymes. Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is primarily triggered by food, chiefly food containing absorbable glucose. The chief trigger is a rise in blood glucose levels after eating. (Figure 1)

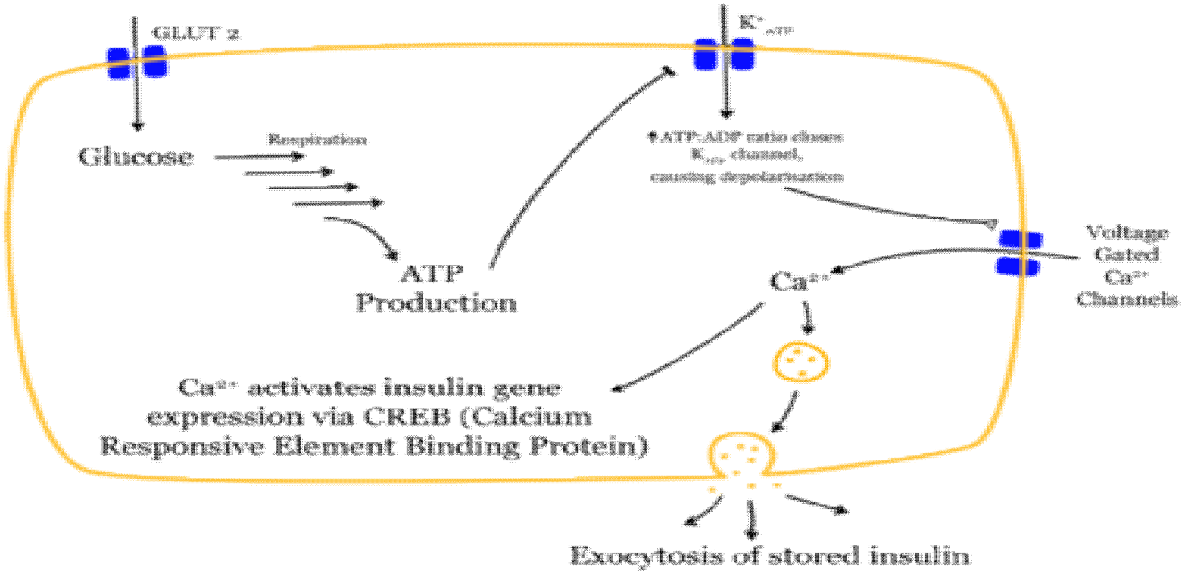


Figure 1: Mechanism of insulin release in normal pancreatic beta cells

There are two main types of diabetes, Type I and Type II, described below. [4]

A) Type I Diabetes: (Juvenile Onset Diabetes, Insulin-Dependent Diabetes)

Three interlocking mechanisms are responsible for the islet cell destruction:

1. Genetic Susceptibility
2. Auto-Immunity
3. Environmental

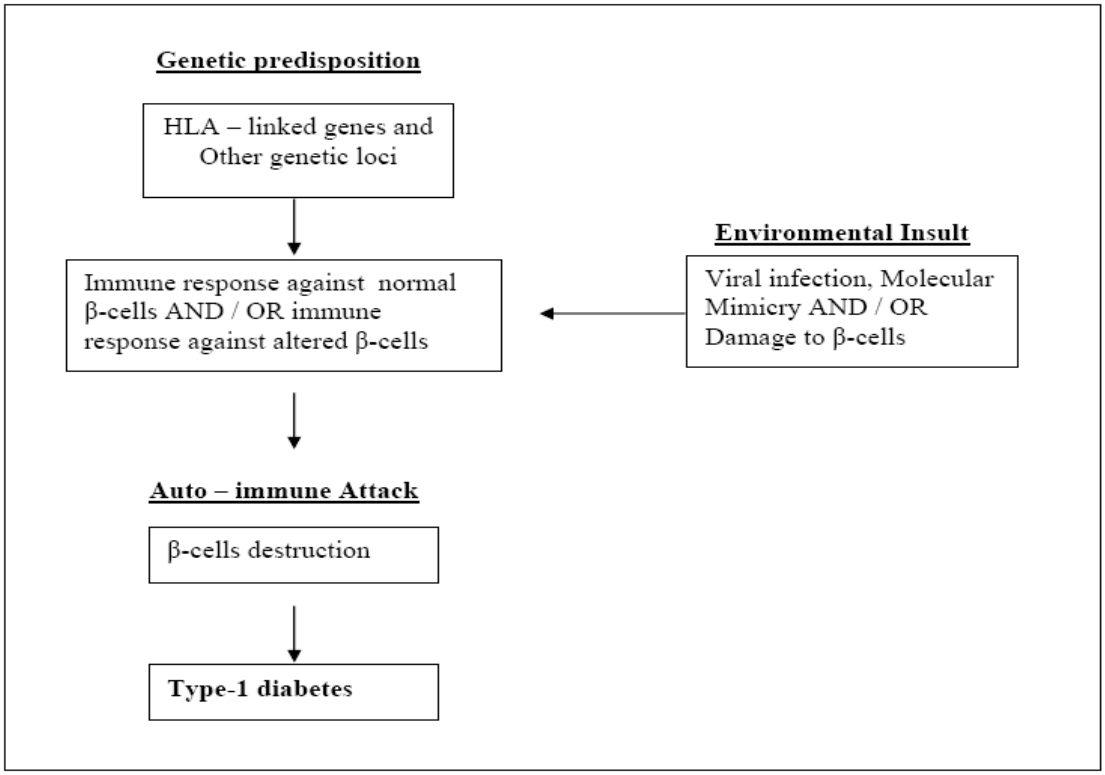


Figure 2: Pathogenesis of Type-1 diabetes mellitus

B) Pathogenesis of Type-2 diabetes mellitus

The two metabolic defects that are characterize type-2 diabetes mellitus are:

1. A derangement in β-cell secretion of insulin
2. A decrease response of peripheral tissue to respond to insulin (Insulin resistance)

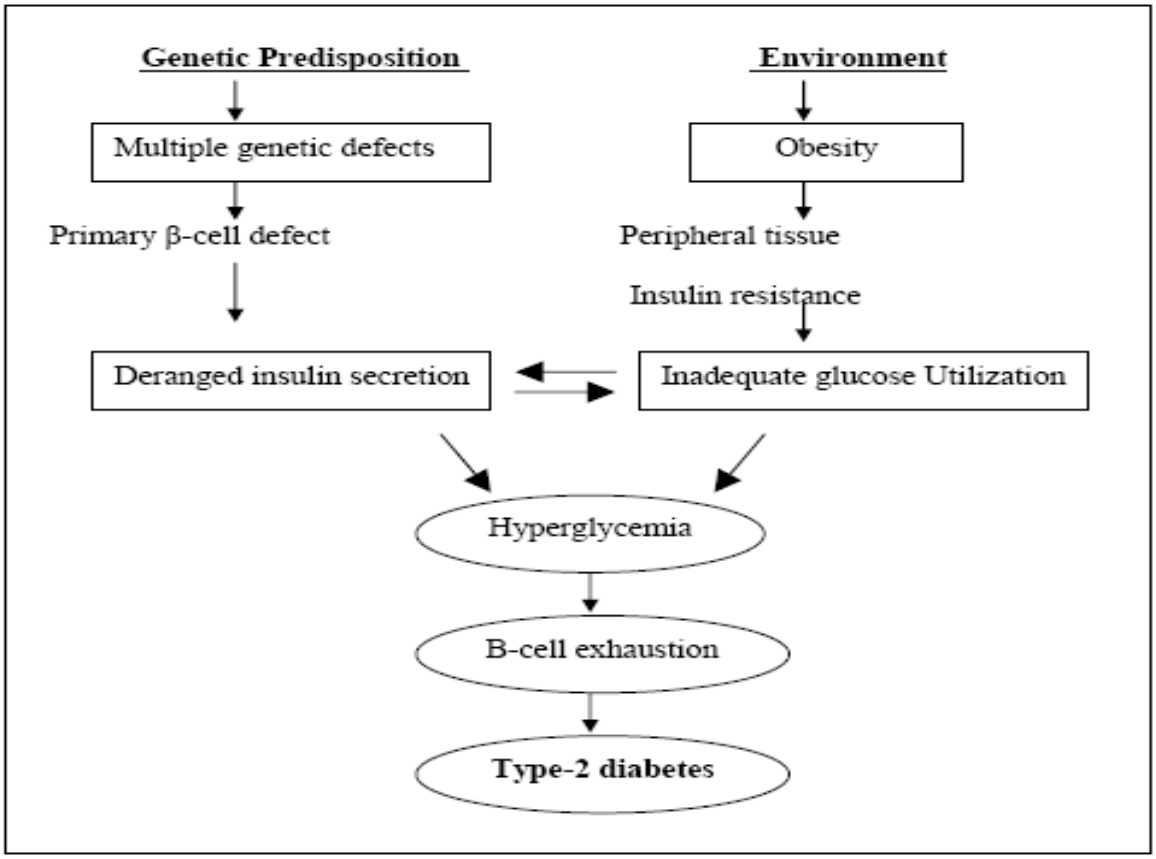


Figure 3: Pathogenesis of Type-2 diabetes mellitus

COMPLICATIONS OF DIABETES

Persons with diabetes are at increased risk for macrovascular disease includes cerebrovascular disease, coronary artery disease and peripheral vascular disease and are due to atherosclerosis of large vessels; and microvascular disease, including retinopathy and nephropathy; peripheral and autonomic neuropathies; and lower extremity disease.

Both the type of diabetes mellitus may develop complications which are divided into 2 major groups, [5]

1. Acute metabolic complications: These include diabetic ketoacidosis, hyperosmolar nonketonic coma and hypoglycemia.

2. Late systemic complications: These are atherosclerosis, diabetic microangiopathy, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and infections.

Diabetes is also accompanied by a substantial increase in atherosclerotic disease of large vessels, including cardiac, cerebral, and peripheral vascular disease (cardio vascular diseases.)

OXIDATIVE STRESS AND DIABETES:

Oxidative stress and oxidative damage to the tissue are common end points of chronic diseases, such as atherosclerosis, diabetes and rheumatoid arthritis. [6] Oxidative stress is currently suggested as mechanism underlying diabetes and diabetic complications. [7] During diabetes, persistent hyperglycemia causes increased production of free radicals, especially reactive oxygen species (ROS),

for all tissues from glucose auto-oxidation and protein glycosylation. The increase in the level of ROS in diabetes could be due to their increased production and/ or decreased destruction by nonenzymic and enzymic catalase (CAT), reduced glutathione (GSH), and superoxide dismutase (SOD) antioxidants. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes. [8]

Oxidants are generated as a result of normal intracellular metabolism in mitochondria and peroxisomes, as well as from a variety of cytosolic enzyme systems. In addition, a number of external agents can trigger ROS production. A sophisticated enzymatic and non-enzymatic antioxidant defense system (Figure 4) including catalase (CAT), superoxide dismutase (SOD) and reduced glutathione (GSH) counteracts and regulates overall ROS levels to maintain physiological homeostasis. Lowering ROS levels below the homeostatic set point may interrupt the physiological role of oxidants in cellular proliferation and host defense. Similarly, increased ROS may also be detrimental and lead to cell death or to acceleration in ageing and age-related diseases. Traditionally, the impairment caused by increased ROS is thought to result from random damage to proteins, lipids and DNA. In addition to these effects, a rise in ROS levels may also constitute a stress signal that activates specific redox-sensitive signaling pathways. Once activated, these diverse signaling pathways may have either damaging or potentially protective functions. [9]

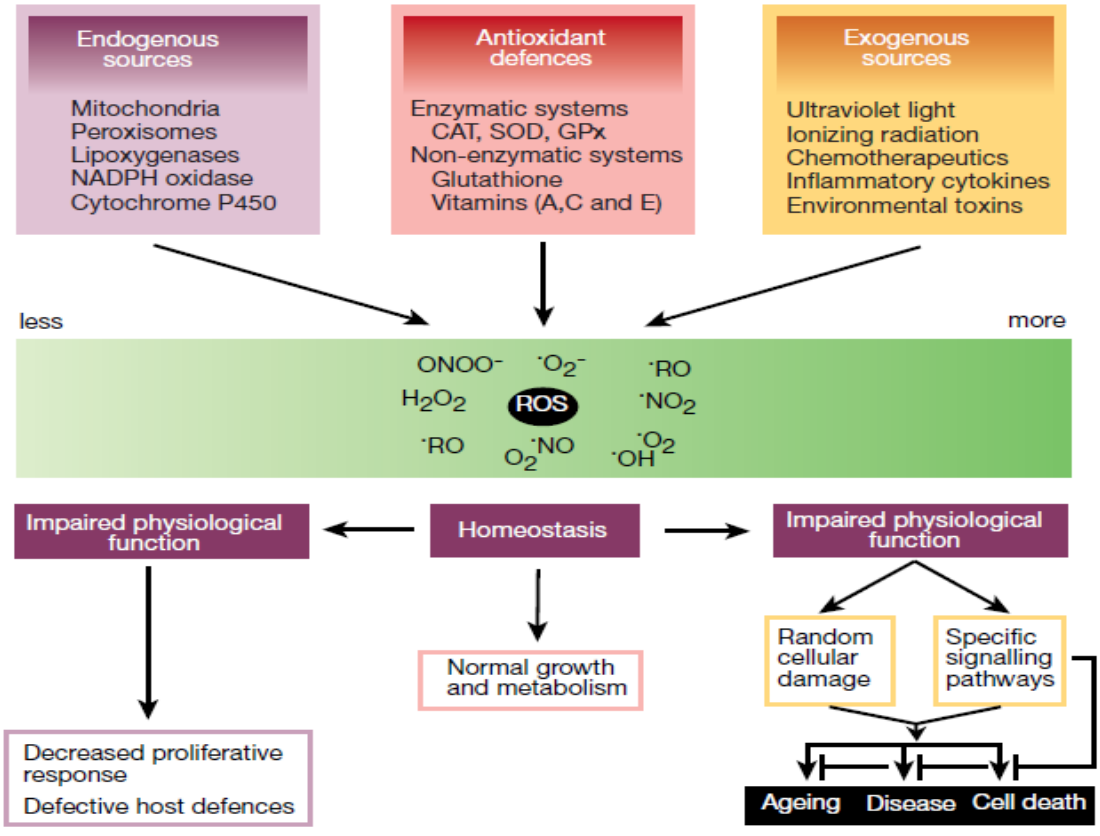


Figure 4: The sources and cellular responses to reactive oxygen species (ROS)

Oxidative stress can occur as a result of either excess ROS production, or impaired antioxidant system, or a combination thereof. The primary ROS produced in the course of oxygen metabolism is superoxide, which is a highly reactive, cytotoxic ROS. Superoxide is dismutated to a far less reactive product, hydrogen peroxide (H_2O_2), by a family of metalloenzymes known as superoxide dismutase (SOD). [10] The ubiquitous superoxide dismutase's (SODs) catalyze the disproportionation of superoxide to molecular oxygen and peroxide and thus are critical for protecting the cell against the toxic products of aerobic respiration.

$$2O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2$$

The primary ROS produced in the course of oxygen metabolism is superoxide, which is a highly reactive, cytotoxic ROS. O_2^- is commonly produced within aerobic biological systems, and superoxide dismutases (SODs) provide an important defense against it. Thus, SOD is the front line of defense against ROS-mediated injury.

GSH is by far the most important antioxidant in most mammalian cells. This ubiquitous tripeptide, γ-Glu-Cys-Gly, performs many cellular functions. In particular, the thiol containing moiety is a potent reducing agent. [11]

$H_2O_2 + GSH \xrightarrow{GPX} H_2O + GSSG$

$GSSG + NAD(P)H \xrightarrow{GR} GSH + NAD(P)^+$

Intracellular GSH is converted to GSSG by selenium-containing GSH peroxidase, which catalyzes the reduction of H_20_2 in the presence of GSH and GSH peroxidase is coupled with oxidation of glucose-6-phosphate and of 6-phosphogluconate, which provides NADPH for reduction of GSSG by GSSG reductase. This is a major pathway of H_20_2 metabolism in many cells. It is thus important for the protection of membrane lipids against oxidation. Intermediates such as O_2 and H_2O_2 are formed extensively in biological systems, and these produce reactive oxygen species that can lead to organic peroxide formation. GSH has the important function of destroying reactive oxygen intermediates and free radicals that are constantly formed in metabolism. [12]

Catalase (CAT, H_2O_2: H_2O_2 oxidoreductase) is an enzyme that decompose hydrogen peroxide (H_2O_2) to molecular oxygen (O_2) and water (H_2O). This activity of catalase is known as catalytic activity. It also exhibits peroxidatic activity and catalyses the oxidation of various hydrogen donors in the presence of relatively lower concentrations of hydrogen peroxide.

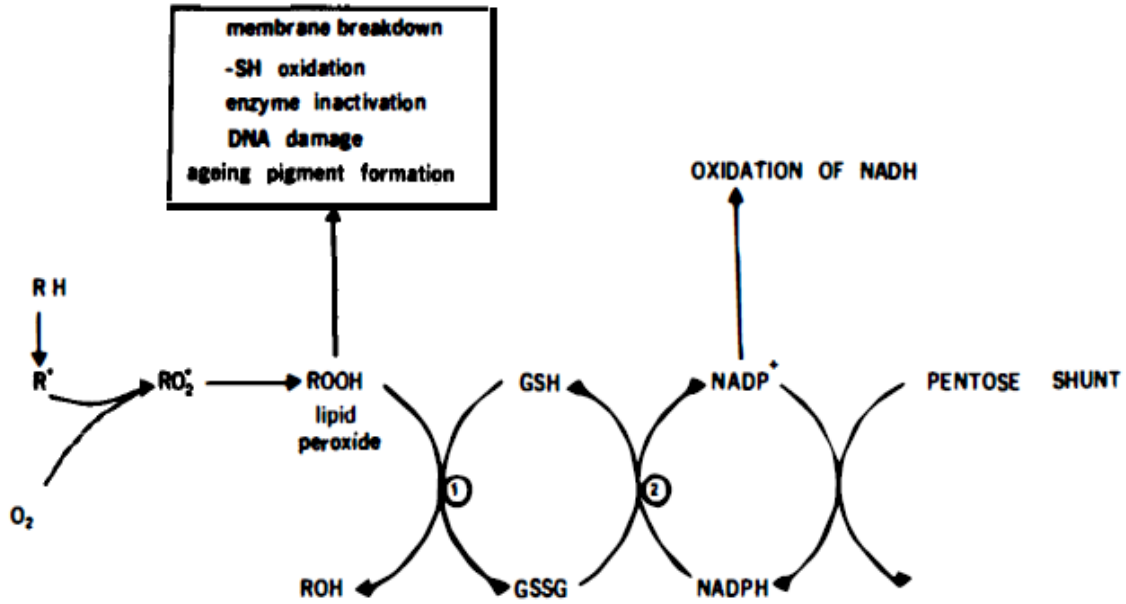
$CAT + H_2O_2 \longrightarrow (CAT - H_2O_2)$ (Complex I)

$(CAT + H_2O_2) + H_2O_2 \longrightarrow CAT + 2\ H_2O + O_2$ (Catalytic activity)

$(CAT + H_2O_2) + AH_2 \longrightarrow CAT + 2\ H_2O + A$ (Peroxidative activity) [13]

Lipids when react with free radicals, they undergo peroxidation to form lipid peroxides. Lipid peroxides decompose to form numerous products including malondialdehyde. [14] The toxicity of oxygen, or of its radical derivatives, is often accompanied by the peroxidation of lipids. Lipid peroxidation as induced by low-level exposures to nitrogen dioxide appears to proceed either by hydrogen atom abstraction or by nitrogen dioxide addition to the olefin. The

reaction course is largely influenced by the presence of radical trapping species, particularly oxygen. [15]



Summary of some of the events leading to the production and breakdown of lipid peroxides.

The most common way to measure lipid peroxides is to estimate malondialdehyde (MDA) content. MDA is formed during lipid peroxidation after rupture of the carbon chain of unsaturated fatty acids. The amount of malondialdehyde is then determined colorometrically after reaction with thiobarbituric acid. [16]

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Humans have evolved with antioxidant systems to protect against free radicals. These systems include some antioxidants produced in the body (endogenous) and others obtained from diet (exogenous). The first includes (a) enzymatic defenses, such as glutathione peroxidase, catalase, and super oxide dismutase, which metabolize superoxide, hydrogen peroxide, and lipid peroxides, thus preventing most of the formation of the toxic OH • and (b) nonenzymatic defenses, such as glutathion, histidine-peptides, the iron binding proteins transferrin and ferritin, dihydrolipoic acid, melatonin, urate, and plasma protein thiols.[17]

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