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Interaction between type 1 diabetes patient and obesity by assay LDL and CAT enzymes

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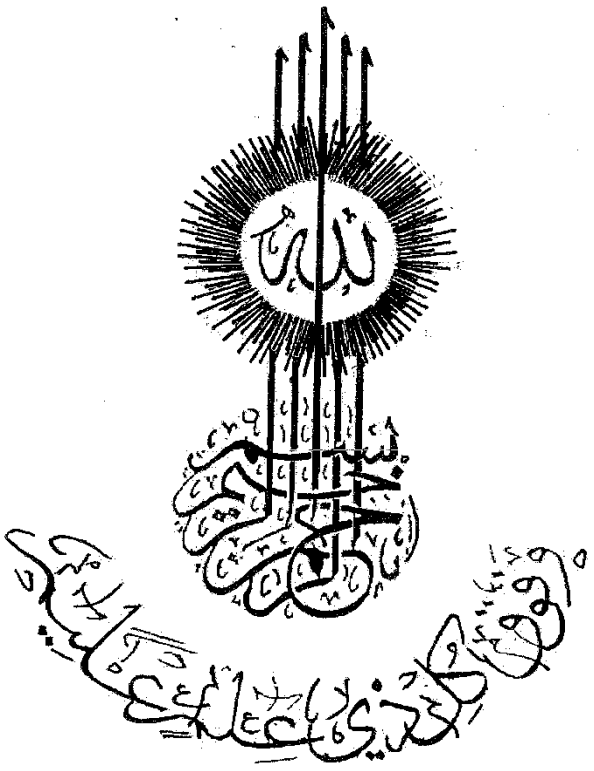

صدق الله العلي العظيم

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الاهداء

إليك يا أمي يا من علمتني العطاء دون انتظار المقابل، يا من زرعتي في قلبي أسمى المعاني الأفاضل ..

إلى ذلك الصرح العظيم الذي علمني الخلق الكريم ، والدي صاحب الفضل الكبير ..

إليك يا أستاذي الكريم الذي علمتني أن تشجيع المعلم لتلميذه دافع قوي له على التقدم ..

إلى إخوتي وأخواتي سندي في حياتي . إلى كل من دعمني وشجعني في حياتي وأعطاني دفعة نحو الأمام ..

حوراء اسد و تبارك حمودي و تبارك انس

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. the origin and etiology of DM can vary greatly but always include defects in either insulin secretion or response or in both at some point in the course of disease.
when characteristic symptoms of DM are clearly present and blood glucose levels are high enough, the diagnosis is usually unequivocal. However, it is important to remember that the diagnosis is made in asymptomatic patients in most cases,based on the results of routine test.the prevalence of DM, its specific complications and the presence of other diseases that often accompany DM make this disease one of today's main social and public health problems .
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Diabetes is a major cause of morbidity and mortality, though these outcomes are not due to the immediate effects of the disorder. They are instead related to the diseases that develop as a result of chronic diabetes mellitus. These include diseases of large blood vessels (macrovascular disease, including coronary heart disease and peripheral arterial disease) and small blood vessels (microvascular disease, including retinal and renal vascular disease), as .well as diseases of the nerves

Several studies have suggested that reactive oxygen species (ROS) are implicated in the etiology of type 1 diabetes as well as in the development of severe microangiopathic complications such as diabetic retinopathy and diabetic nephropathy. Chronic extracellular hyperglycemia in diabetes stimulates ROS production and increases oxidative stress. The oxidation of high levels of glucose inside diabetic cells produces more electron donors (NADH and FADH2) and increases the electron transfer, thereby generating superoxide

Excess generation of ROS such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$) and reactive nitrogen species such as

nitric oxide oxidize target celular proteins, nucleic acids, or membrane lipids and damage their cellular structure and function.

Hyperglycemia stimulates the expression of inducible nitric oxide synthase (iNOS) and increases production of nitric oxide, an intracellular second messenger. Increased nitric oxide generation accompanied by the superoxide overproduction favors the formation of peroxynitrite, a highly reactive oxidant. Evidence suggests that ROS also regulate the expression of genes encoding for proteins involved in inflammation, immune response, and cell death.

Antioxidant enzymes such as manganese superoxide dismutase (MnSOD) and catalase (CAT) directly eliminate ROS, while glutathione-S-transferases (GSTs) detoxify cytotoxic secondary metabolites of ROS. Together they represent a protective mechanism against the damage caused by the oxidative stress. Most of the enzymes involved in the .defense against oxidative stress are polymorphic

In type 1 diabetic patients with diabetic ketoacidosis, quantitative lipid .abnormalities are observed, due to insulin deficiency

Triglyceride-rich lipoproteins (chylomicrons, VLDLs) are increased leading to hypertriglyceridemia. This is mainly due to decreased lipoprotein lipase activity (Vergès, 2001; Dullaart, 1995). Diabetic ketoacidosis is a situation of severe insulin deficiency with reduced lipoprotein lipase activity as a consequence, because insulin usually stimulates its activity.

Decreased lipoprotein lipase activity leads to profound reduction of triglyceride-rich lipoprotein catabolism (Taskinen, 1987). In this condition of severe insulin deficiency, reduced catabolism of triglyceride-rich lipoproteins is, by far, the main factor involved in hypertriglyceridemia. This hypertriglyceridemia resolves rapidly after .well titrated insulin therapy (Weidman et al., 1982)

LDL-cholesterol is decreased during diabetic ketoacidosis (Weidman et al., 1982). This fall in plasma LDL-cholesterol level is the direct consequence of the reduction of triglyceride-rich lipoprotein catabolism, due to decreased lipoprotein lipase activity.

In diabetic ketoacidosis, HDL-cholesterol level is significantly decreased (Weidman et al., 1982). This is a consequence of hypertrigliceridemia observed in this condition. Indeed, the augmented level of plasma triglyceride-rich lipoproteins drives, through CETP, the transfer of triglycerides from triglyceride-rich lipoproteins to HDLs leading to the formation of triglyceride-rich HDL particles. HDLs enriched in triglycerides become very good substrate for hepatic lipase, leading to increase their catabolism and, thus, to decrease plasma HDL-cholesterol level. This low HDL-cholesterol condition resolves rapidly after well titrated insulin therapy.

Causes:

Insulin is a hormone secreted by beta cells, which are located within clusters of cells in the pancreas called the islets of Langerhans. Insulin's role in the body is to trigger cells to take up glucose so that the cells can use this energy-yielding sugar.

Patients with diabetes may have dysfunctional beta cells, resulting in decreased insulin secretion, or their muscle and adipose cells may be resistant to the effects of insulin, resulting in a decreased ability of these cells to take up and metabolize glucose. In both cases, the levels of glucose in the blood increase, causing hyperglycemia (high blood sugar).

As glucose accumulates in the blood, excess levels of this sugar are excreted in the urine. Because of greater amounts of glucose in the urine, more water is excreted with it, causing an increase in urinary volume and frequency of urination as well as thirst.

(The name diabetes mellitus refers to these symptoms: diabetes, from the Greek diabainein, meaning "to pass through," describes the copious urination, and mellitus, from the Latin meaning "sweetened with honey," refers to sugar in the urine.) Other symptoms of diabetes include itching, hunger, weight loss, and weakness

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Classification of Diabetes mellitus:

Type I - is an autoimmune disease which destroys insulin producing pancreatic cells, whereby no insulin is secreted as a result of pancreatic β-cell deterioration and reliance on exogenous insulin for survival .

About 10% of all diabetics are type 1 with dependence on insulin for survival with risk of ketoacidosis (ADA, 2010). Since this type is auto-.immune, a preventive regime is yet to be known

Type Π- is a progressive disease typified by insufficient production of insulin or insulin resistance (Mohamed et al., 2016). About 90% of all diabetes incidences are type 2 and it is the second highest risk factor for developing Alzheimer's disease (Breteler, 2000 and CDCP., 2011). Oxidative stress has been implicated in the pathology of type 2 diabetes .(Evans et al., 2002 ; Giacco and Brownlee, 2010)

Gestational diabetes- is most common in pregnant women. It is characterized by a rise in glucose level and insufficient insulin which reduces glucose level. A large number of individuals develop pre .diabetes before a diabetic condition is diagnosed

Prediabetes, the glucose level is consistently above normal and often progresses to type 2 diabetes. Gestational diabetes is characterized by a .slight resistance to insulin (Metzger et al., 2007)

Monogenic Diabetes - has been newly diagnosed and which is characterized by a single gene mutation in the mitochondrial DNA or the autosomal dominant inheritance pattern. It is most common in young ..individuals (Chan, 2016)

Acute Clinical Manifestation

Hyperglycemia itself can cause symptoms but usually only when blood glucose concentrations are approximately 180 mg per 100 ml (10 mmol per litre) or higher. When blood glucose concentrations increase, more glucose is filtered by the glomeruli of the kidneys than can be reabsorbed by the kidney tubules, resulting in glucose excretion in the urine.

High glucose concentrations in the urine create an osmotic effect that reduces the reabsorption of water by the kidneys, causing polyuria (excretion of large volumes of urine). The loss of water from the circulation stimulates thirst. Therefore, patients with moderate or severe hyperglycemia typically have polyuria and polydipsia (excessive thirst).

The loss of glucose in the urine results in weakness, fatigue, weight loss, and increased appetite (polyphagia). Patients with hyperglycemia are prone to infections, particularly vaginal and urinary tract infections, and .an infection may be the presenting manifestation of diabetes

There are two acute life-threatening complications of diabetes:

hyperglycemia and acidosis (increased acidity of the blood), either of which may be the presenting manifestation of diabetes. In patients with type 1 diabetes, insulin deficiency, if not recognized and treated properly, leads to severe hyperglycemia and to a marked increase in lipolysis (the breakdown of lipids), with a greatly increased rate of release of fatty acids from adipose tissue.

In the liver, much of the excess fatty acid is converted to the keto acids beta-hydroxybutyric acid and acetoacetic acid. The increased release of fatty acids and keto acids from adipose, liver, and muscle tissues raises the acid content of the blood, thereby lowering the pH of the blood.

The combination of hyperglycemia and acidosis is called diabetic ketoacidosis and leads to hyperventilation and to impaired central nervous system function, culminating in coma and death. Patients with diabetic ketoacidosis must be treated immediately with .insulin and intravenous fluids

Risk factors of type1 diabetes :

Viral infections: Researchers have found that certain viruses may trigger the development of type 1 diabetes by causing the immune system to turn against the body—instead of helping it fight infection and sickness. Viruses that are believed to trigger type 1 include: German .measles, coxsackie, and mumps

Race/ethnicity: Certain ethnicities have a higher rate of type 1 diabetes. In the United States, Caucasians seem to be more susceptible to type 1 than African-Americans and Hispanic-Americans. Chinese people have a lower risk of developing type 1, as do people in South .America

Geography: It seems that people who live in northern climates are at a higher risk for developing type 1 diabetes. It's been suggested that people who live in northern countries are indoors more (especially in the winter), and that means that they're in closer proximity to each other—.potentially leading to more viral infections

Conversely, people who live in southern climates—such as South America—are less likely to develop type 1. And along the same lines, researchers have noticed that more cases are diagnosed in the winter in .northern countries; the diagnosis rate goes down in the summer

Family history: Since type 1 diabetes involves an inherited susceptibility to developing the disease, if a family member has (or had) type 1, you .are at a higher risk

If both parents have (or had) type 1, the likelihood of their child developing type 1 is higher than if just one parent has (or had) diabetes. Researchers have noticed that if the father has type 1, the risk of a child developing it as well is slightly higher than if the mother or .sibling has type 1 diabetes

Early diet: Researchers have suggested a slightly higher rate of type 1 .diabetes in children who were given cow's milk at a very young age

Other autoimmune conditions: As explained above, type 1 diabetes is an autoimmune condition because it causes the body's immune system to turn against itself. There are other autoimmune conditions that may share a similar HLA complex, and therefore, having one of those .disorders may make you more likely to develop type 1

Other autoimmune conditions that may increase your risk for type 1 .include: Graves' disease, multiple sclerosis, and pernicious anemia

Complications

Over time, type 1 diabetes complications can affect major organs in your body, including heart, blood vessels, nerves, eyes and kidneys. Maintaining a normal blood sugar level can dramatically reduce the risk .of many complications

Eventually, diabetes complications may be disabling or even life-.threatening

Heart and blood vessel disease. Diabetes dramatically increases your risk of various cardiovascular problems, including coronary artery disease with chest pain (angina), heart attack, stroke, narrowing of the .arteries (atherosclerosis) and high blood pressure

Nerve damage (neuropathy). Excess sugar can injure the walls of the tiny blood vessels (capillaries) that nourish your nerves, especially in the legs. This can cause tingling, numbness, burning or pain that usually begins at the tips of the toes or fingers and gradually spreads upward. Poorly controlled blood sugar could cause you to eventually lose all .sense of feeling in the affected limbs

Damage to the nerves that affect the gastrointestinal tract can cause problems with nausea, vomiting, diarrhea or constipation. For men, .erectile dysfunction may be an issue

Kidney damage (nephropathy). The kidneys contain millions of tiny blood vessel clusters that filter waste from your blood. Diabetes can damage this delicate filtering system. Severe damage can lead to kidney failure or irreversible end-stage kidney disease, which requires dialysis .or a kidney transplant

Eye damage. Diabetes can damage the blood vessels of the retina (diabetic retinopathy), potentially causing blindness. Diabetes also increases the risk of other serious vision conditions, such as cataracts .and glaucoma

Foot damage. Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated, cuts and blisters can become serious infections that may ultimately require toe, .foot or leg amputation

Skin and mouth conditions. Diabetes may leave you more susceptible to infections of the skin and mouth, including bacterial and fungal .infections. Gum disease and dry mouth also are more likely

Pregnancy complications. High blood sugar levels can be dangerous for both the mother and the baby. The risk of miscarriage, stillbirth and birth defects increases when diabetes isn't well-controlled. For the mother, diabetes increases the risk of diabetic ketoacidosis, diabetic eye problems (retinopathy), pregnancy-induced high blood pressure and preeclampsia

.Catalase, CAT

Catalase (CAT) is a key antioxidant enzyme in the body's defense against oxidative stress. Furthermore, Catalase is a heme enzyme which is present in the peroxisome of virtually all aerobic cells. Catalase converts the reactive oxygen species hydrogen peroxide to water and oxygen and thus diminishes the toxic effects of hydrogen peroxide. Catalase stimulates growth of cells including T-cells, B-cells, myeloid leukemia cells, melanoma cells, mastocytoma cells and normal and transformed fibroblast cells. Catalase gene polymorphisms are linked with decreases

in catalase activity nevertheless, to date, acatalasemia is the only .disease known to be caused by the CAT gene

LDL

Low-density lipoprotein (LDL) is one of the five major groups of lipoprotein which transport all fat molecules around the body in the extracellular water.These groups, from least dense to most dense, are chylomicrons (aka ULDL by the overall density naming convention), very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein and high-density lipoprotein (HDL). LDL delivers fat molecules to cells. LDL can contribute .to atherosclerosis if it is oxidized within the walls of arteries

Overview

Lipoproteins transfer lipids (fats) around the body in the extracellular fluid, making fats available to body cells for receptor-mediated endocytosis.Lipoproteins are complex particles composed of multiple proteins, typically 80–100 proteins per particle (organized by a single apolipoprotein B for LDL and the larger particles). A single LDL particle is about 220–275 angstroms in diameter, typically transporting 3,000 to 6,000 fat molecules per particle, and varying in size according to the number and mix of fat molecules contained within. The lipids carried include all fat molecules with cholesterol, phospholipids, .and triglycerides dominant; amounts of each varying considerably

Transport into the cell

When a cell requires additional cholesterol (beyond its current internal HMGCoA production pathway), it synthesizes the necessary LDL receptors as well as PCSK9, a proprotein convertase that marks the LDL receptor for degradation. LDL receptors are inserted into the plasma membrane and diffuse freely until they associate with clathrin-coated pits. When LDL receptors bind LDL particles in the bloodstream, the .clathrin-coated pits are endocytosed into the cell

Vesicles containing LDL receptors bound to LDL are delivered to the endosome. In the presence of low pH, such as that found in the

endosome, LDL receptors undergo a conformation change, releasing ,LDL. LDL is then shipped to the lysosome

The role of LDL and CAT enzymes in DM patient

Lipid peroxides are thought to be formed by free radicals and may play an important role in the development of atheromatous vascular diseases. The relationship between serum lipids, lipoproteins, lipid peroxides [thiobarbituric acid reactive substances (TBARS)] and erythrocyte antioxidant enzymes [catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD)] was investigated in non-insulin-dependent diabetic patients with and without coronary heart disease (CHD), and a comparison was made for all the above parameters with non-diabetic patients with CHD. Lipid peroxide concentrations were significantly increased in both groups of diabetic patients and also in non-diabetic patients with CHD, compared to those in control subjects. Diabetic patients with CHD had higher levels of TBARS compared to those diabetics without CHD. Hyperlipidaemia and abnormal lipoprotein levels were observed in all three groups of patients. Increased total cholesterol and LDL-cholesterol were observed in diabetics with CHD compared to those without CHD. Among the erythrocyte antioxidant enzymes, CAT activity was increased, GPx activity was decreased and no change was observed in SOD activity in both groups of diabetic patients and non-diabetic patients with CHD compared to those in controls. A clear correlation was observed between the CAT activity and lipid peroxide concentrations in all the diabetic patients. These observations suggest that there are similar abnormalities in lipid metabolism and erythrocyte antioxidant enzymes in diabetic patients and non-diabetic patients with CHD

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Obesity and type1 diabetes:

In the past 20 years, the prevalence of obesity has tripled worldwide, to the extent that it is now being considered an epidemic.Obesity, defined as a body mass index (BMI) of ≥30 kg/m2, affects approximately 35% of men and 40% of women in the USA.It has recently been reported that obesity in particular is rising at a greater rate than overweight.

Though patients with type 1 diabetes (T1D) have traditionally been thought to have lower BMI, current research has shown otherwise. The trend of increasing obesity prevalence has increased at a faster rate in .patients with T1D compared to the general population .

Currently, around 50% of patients with T1D are either overweight or . obese. They also have higher waist and hip circumferences when compared to healthy controls. In the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, which followed adult patients with T1D for an average of 18 years, prevalence of overweight increased from 29 to 42% and prevalence of obesity increased sevenfold from 3 to 23%. Weight gain appeared to be unrelated to aging and instead related to clinical factors such as insulin therapy.

Comorbidities, often associated with excess body weight, reduce the benefits of good metabolic control. Thus, controlling body weight in patients with T1D is necessary due to the well-known relationship between obesity and cardiovascular disease (CVD). Metabolic abnormalities related to obesity, such as the pro-inflammatory state, are likely to modify CVD risk in this population. So far, complications related to CVD have been the leading cause of mortality in patients with T1D .

The mechanism and relationship between obesity and type1 diabetes :

Body mass index has a strong relationship to diabetes and insulin resistance. In obese individuals, the amount of nonesterified fatty acids, glycerol, hormones, cytokines, proinflammatory markers, and other

substances that are involved in the development of insulin resistance, is increased. The pathogenesis in the development of diabetes is based on the fact that the β-islet cells of the pancreas are impaired, causing a lack of control of blood glucose.

The development of diabetes becomes more inevitable if the failure of β-islet cells of the pancreas is accompanied by insulin resistance. Weight gain and body mass are central to the formation and rising incidence of type 1 and type 2 diabetes

The association between type 1 diabetes and weight gain was first . investigated by Baum et al20 in 1975. The Baum et al study suggested that there was an association related to overfeeding or to hormonal dysregulation.20

The “accelerator hypothesis” proposed by Wilkin21 is considered one of the most accepted theories that demonstrates the association between body mass and type 1 diabetes. The authors of this theory suggested that increasing body weight in young age groups increases the risk of developing type 1 diabete.

There is an inverse relationship between body mass index and age at diagnosis. Furthermore, as young children gain more weight, diabetes can be diagnosed earlier. This is explained by the fact that more weight accelerates insulin resistance, leading to the development of type 1 diabetes in individuals who are predisposed genetically to diabetes.

Following this study, many papers were published supporting Wilkin’s accelerator hypotheses. One study conducted in the United States in 2003 showed a significant increase in the prevalence of being overweight in children with type 1 diabetes, from 12.6% in the period 1979–1989 to 36.8% in the period 1990–1998. To date, the exact mechanism and relationship between type 1 diabetes and obesity remains inconclusive and needs further explanation

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