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Review Article

Obesity As A Major Risk Factor in the Pakistan.

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Abstract

Objectives: Obesity is commonly associated with diabetes mellitus. It is one of the major risk factor that contributes to the onset of non insulin dependent diabetes mellitus in the local population. Our aim was to compare the levels of obesity related proteins that play role in the development of insulin resistance in the diabetic obese and non diabetic individuals.

Methods: For this purpose the study was carried out on 100 diabetic obese and 100 controls sex and age matched persons were recruited from sheikh zayed hospital, Lahore. Initially the body mass index of all the subjects was measured and diabetic subjects with the BMI greater than 30 were included in the study. Serum fasting glucose levels, microalbuminurea, fasting total cholesterol, triglyceride, LDL, VLDL and HDL levels were measured for samples of all subjects by following the standard protocols.

Results: Total protein estimation was done by Bradford Assay. 10% SDS gel was performed for the protein analysis between control and obese diabetics. Blood glucose levels of all diabetic obese subjects were found to be greater than 126mg/dl. BMI values correlated positively with total cholesterol, LDL, and triglyceride levels. HDL levels were observed to be markedly decreased in diabetic subjects when compared to controls. Presence of obesity related proteins in diabetic subjects with BMI greater than 30 was confirmed.

Conclusion: In the next step we intend to estimate the level of obesity related proteins responsible for the diabetic subjects and compare them with the levels found in the controls.

Key Words: obesity, lipid profile, Pakistani, diabetes, BMI

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Introduction:

Diabetes mellitus is a world health problem and affects all human society at various stages of development. It is more common amongst developed countries where affluent and overweight individual lives longer than human being of under developed countries. The incidence of this disease in a society , whether in Pakistan or any developed country is difficult to judger but it is quiet obvious that the disease is multiplying geometrically more or less, because of genetic and environmental factors).Diabetes mellitus is a group of metabolic diseases characterizedby hyperglycemia resulting from defects in insulin secretion,insulin action, or both. The chronic hyperglycemia of diabetes associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the ß-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Type 2 diabetes is most common form of the diabetes accounting for 90% of cases.[1]

Regulation of Blood Glucose Levels

The maintenance of the blood sugar at normal levels is brought about by an efficient regulatory mechanism. The main organs in this mechanism are the liver, the autonomic nervous system, and certain glands of internal secretion called endocrine glands. Maintenance of blood glucose homeostasis is of paramount importance to the survival of the human organism. The predominant tissue responding to signals that indicate reduced or elevated blood glucose levels is the liver. Indeed, one of the most important functions of the liver is to produce glucose for the circulation. Both elevated and reduced levels of blood glucose trigger hormonal responses to initiate pathways designed to restore glucose homeostasis. Low blood glucose triggers release of glucagon from pancreatic beta-cells. High blood glucose triggers release of insulin from pancreatic beta-cells.[2]

Despite intermittent ingestion of dietary carbohydrates, serum glucose levels remain relatively steady throughout the day. This requires the concerted actions of several different tissues. Pancreatic ß-cells, for example, secrete insulin in response to the elevations in glucose that occur after eating. Insulin promotes glucose disposal in adipose tissue and muscle, and also prevents the liver from producing more glucose by suppressing glycogenolysis and gluconeogenesis. In the fasting state, low insulin levels combined with elevated counter-regulatory hormones such as glucagon, adrenaline and corticosteroids promote hepatic glucose production. Recently, evidence has emerged that the brain coordinates many of these effects as well, through direct and indirect glucose sensing and neural outputs to peripheral organs. Inputs to serum glucose levels include absorption from the intestine and release from the liver. The latter occurs by breakdown of preformed glycogen as well as

gluconeogenesis, and both processes are inhibited by insulin. Glucose is removed from the system by uptake into virtually all cell types, but most importantly into muscle and adipose tissue, which requires insulin. Recent evidence suggests that the CNS can also sense glucose and act to affect systemic glycaemia, at least in part by regulating gluconeogenesis.[3]

Diabetes results from the dysregulation of multiple glucoregulatory hormones that normally act to maintain glucose homeostasis. These hormonal imbalances lead to chronic hyperglycemia, which results in an array of microvascular complications including retinopathy, nephropathy, and neuropathy. Any defect in insulin production leads to improper regulation of glucose in the blood and result in diabetes. Similarly, in patients with type 1 and type 2 diabetes, postprandial glucagon secretion is abnormally elevated. This inappropriate secretion of glucagon leads to excess hepatic glucose production and is an important contributor to postprandial hyperglycemia in patients with diabetes.

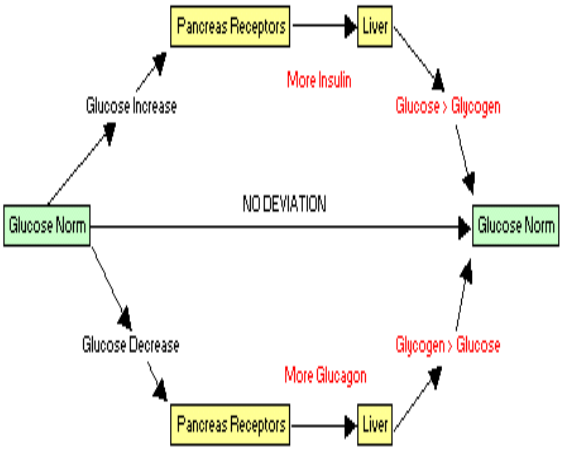

Fig 1:*Glucose Homeostasis*

Insulin

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects. It is synthesized in the β cells of the pancreatic islets of langherhans as its precursor,proinsulin.Glucose is the principal stimulus for insulin secretion, though other macronutrients, hormones, humoral factors and neural input may modify this response. Insulin, together with its principal counter-regulatory hormone glucagon, regulates blood glucose concentrations. Pancreatic β cells secrete 0.25–1.5 units of insulin per hour during the fasting (or basal) state, sufficient to enable glucose insulin-dependent entry into cells.[4,5]

Insulin resistance

Insulin is released by the pancreas in response to the presence of sugar (glucose) in the blood stream. Glucose gets into the blood through consumption of sugar or sugar-containing foods or via the breakdown of carbohydrates into simple sugars. Insulin is a chemical messenger that acts on the walls of the cells to cause the release, from within the cell, of special protein molecules – the so-called GLUT-4 transporters. The GLUT-4 transporters rise to the cells' outer membranes where they grab hold of the glucose molecule and transport it into the interior of the cell. Here the glucose is used to produce energy and any excess is converted into fat Insulin resistance is

defined where a normal or elevated insulin level produces an attenuated biological response; classically this refers to impaired sensitivity to insulin mediated glucose disposal Insulin resistance in most cases is believed to be manifest at the cellular level via post-receptor defects in insulin signalling. Possible mechanisms include down-regulation, deficiencies or genetic polymorphisms of tyrosine phosphorylation of the insulin receptor, IRS (insulin receptor substrate) proteins or may involve abnormalities of GLUT 4 function.[4,5,6]

TYPES OF DIABETES

There are several different types of diabetes, varying very slightly from one another. Different types are classified as follows.

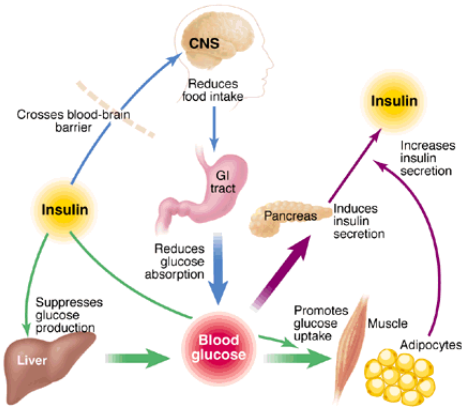

Fig 2:*Mode Of Action Of Insulin And Normal Regulation Of Blood Glucose Levels.*

Type 1 diabetes

This form of diabetes, which accounts for only 5–10% ofthose with diabetes, previously encompassed by the terms insulin-dependentdiabetes, type I diabetes, or juvenile-onset diabetes, resultsfrom a cellular-mediated autoimmune destruction of the ß-cellsof the pancreas. Autoimmune destruction of ß-cells has multiple geneticpredispositions and is also related to environmental factorsthat are still poorly defined. Although patients are rarelyobese when they present with this type of diabetes, the presenceof obesity is not incompatible with the diagnosis. [7]

Type 2 diabetes

This form of diabetes, which accounts for ~ 90–95% of thosewith diabetes, previously referred to as non-insulin-dependentdiabetes, type II diabetes, or adult-onset diabetes, encompassesindividuals who have insulin resistance and usually have relative(rather than absolute) insulin deficiency.Most patients with this form of diabetes are obese, and obesityitself causes some degree of insulin resistance. Patientswhoare not obese by traditional weight criteria may have an increasedpercentage of body fat distributed predominantly in the abdominalregion.[7]

Obesity

Obesity represents an increase in adipose tissue mass or it specifically refers to an excess amount of body fat. Every individual needs a certain amount of body fat for energy, heat insulation and shock absorption. However, excessive deposition of fat in the body, which is usually referred to as overweight or obesity, is dangerous. Overweight specifically refers to an excess

body weight compared to set standards, while obesity is to have an abnormally high proportion of total body fat. Obesity is a state of low-grade chronic inflammation, asindicated by the increased concentrations of C-reactive protein,IL-6, and other inflammatory markers identified in the plasmaof obese individuals.

Obesity is a major health hazard all over the world and is becoming a major health threat in Pakistan. There are a number of health hazards associated with obesity, including diabetes, hypertension, cardiovascular disease, arthritis, anesthesia risk, respiratory problems, breast cancer, menstrual abnormalities, ovarian dysfunction along with poor social image and rejection.[8]

MEASURE OF OBESITY

Obesity can be assessed in several ways. Each method has advantages and disadvantages, and the appropriateness and scientific acceptability of each method will depend on the situation

- Body mass index (BMI)
- Waist circumference
- Waist to hip ratio

The BMI (Body Mass Index)

BMI which describes relative weight for height correlates with both morbidity and mortality. The relative risk for diabetes and CVD (cardio vascular diseases) incidence increase in a graded fashion with increasing BMI in all population groups. BMI is significantly correlated with total body fat content. Moreover, calculating BMI is simple, rapid, and inexpensive, and can be applied generally to adults. Body mass index (BMI) has traditionally been used to identify individuals who are the most likely to be overweight or obese. It is calculated by dividing the weight (in kilograms) by the height (in meters) squared. Generally, a high value indicates excessive body fat and consistently relates to increased health risks and mortality.[9]

BMI is then calculated by using following formula.

$$\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meter})^2}$$

Waist Circumference

Fat located in the abdominal region is associated with greater health risks than that in peripheral regions. Nonetheless, the presence of increased total abdominal fat appears to be an independent risk predictor when BMI is not markedly increased. Therefore, waist or abdominal circumference, as well as BMI, should be measured for the initial assessment of obesity. [10]

Waist to hip ratio

Waist-to-hip ratio (WHR) is the ratio of the circumference of the waist to that of the hips. It is calculated by measuring the hip circumference at its widest part and dividing that into the waist circumference (located just above the upper hip bone). WHR is 0.7 for women and 0.9 for men have been shown to correlate strongly with

generalhealth and fertility. Women within the 0.7 and men with 0.9 ranges are less susceptible to major diseases such as diabetes, and cardiovascular disorders. WHR is a better predictor of mortality in older people than waist circumference or BMI. If obesity is redefined using WHR instead of BMI, the proportion of people categorized as at risk of heart attack worldwide increases threefold.[10]

Diabetes and Obesity

A worldwide epidemic exists with respect to diabetes mellitus,primarily because of increased rates of obesity. Obesity has become widespread in developed countries along witha corresponding increase in the prevalence of diabetes mellitus. Epidemiological studies have shown that, compared to lean individuals, very obese men and women (body mass index >35) have a 60- and 90-fold increased probability of developing diabetes, respectively. Although the precise underlying mechanisms inthedevelopment of diabetes are as yet unknown, the initial patho-physiologicalevent is usually insulin resistance, which involves a geneticcomponent that is exacerbated by obesity and a sedentary lifestyle.There is a significant correlation between obesity and insulinresistanceinnondiabetic subjects, and obesity exacerbatesinsulin resistance indiabetic subjects. However,the degree of insulin resistance that accompanies obesity variesconsiderably, and the relation among obesity, insulinresistance,and diabetes mellitus is not well understood.[11]

The pancreas secretes insulin in order to help metabolize glucose and carbohydrates. When a non-diabetic person consumes excessive calories and gains weight, tissues become insensitive to insulin, and the body becomes less able to convert glucose into energy and other metabolites. One study has shown a decline in insulin sensitivity (or effectiveness) of 30 to 40 percent when a person exceeds 35 to 40 percent above their ideal weight. The body compensates by producing more insulin, a condition called hyperinsulinemia. Many studies have shown that obese adults have much higher insulin levels in their blood than leaner.[12]

Increased adipose tissue especially that in an upper body or “android” deposition was first associated with diabetes and vascular disease by French endocrinologist Jean Vague in 1956. Insulin resistance increases with increasing body mass index, waist circumference and in particular waist-hip ratio.[13]

Proteins Secreted by Adiposites in Obese Condation

Recentstudies have established adipose tissue as an endocrine organcapable of hormone and cytokine secretion. Knowledge about this metabolic syndromehas moved forward with the description of numerous adipocytesecretary products. Adipocytes express and secrete several adipokines that are similar in their function to endocrine hormones such as leptin and adiponectin. Many secreted proteins are derived from the nonadipocyte fraction of adipose tissues.) Knowledge of adipocyte biology is therefore crucial for understanding the

pathophysiological basis of obesity and metabolic diseases such as diabetes mellitus

TABLE 1:*Adiposites Secreted Proteins*

Serial no	Category of protein	Name of protein	Expression in diabetics
1	Cytokines and cytokine-related proteins	Leptin TNF- alpha IL-6	+ + +
2	Other immune-related proteins	MCP-1	+
3	Proteins involved in fibrinolytic system	PAI-1 Tissue factor	+ +
4	Complement and complement-related proteins	Adipsin (complement factor D) ASP Adiponectin	+ + -
5	Lipids and proteins for lipid metabolism or transport	Lipoprotein lipase (LPL) Apolipoprotein E Apolipoprotein A1, Apolipoprotein A2 Apolipoprotein B Apolipoprotein H Apolipoprotein C1, C2 NEFAs Cholesterol ester transferase protein (CETP	+ + - - + - - + +

Proteins Up Regulated in Obesity and Diabetes:

Leptin

Leptin, a 16000 dalton protein was the first adipokine discovered to have a role in modulating adiposity, and it remains the best studied. This obesity-related hormone is a molecule criticalto the regulation of energy balance and body weight. Likeadiponectin, it is secreted mainly by adipocytes. However, unlikeadiponectin, which is inversely proportional to body fat, leptinlevels have a direct correlation with total body fat and withincreased serum levels in those with diabetes mellitus. Leptin also improves glucose homeostasis in lipodystrophic mice, and in humans with lipodystrophy or congenital leptin deficiency.[13]

C reactive protein

C-reactive protein (CRP) is an acute-phase protein which can have both pro- and anti-inflammatory effects.CRP is a member of the pentarxin family of proteins and is composed of five identical subunits, non-covalently linked to form a symmetrical disc of approximately 115000 Dalton. First identified in 1930, C-reactive protein is a nonglycosylated protein. C-reactive protein plays a role in destroying infectious agents, minimizing tissue damage, and facilitating tissue repair and regeneration. The concentration of CRP in the blood of healthy human beings ranges from 0 to 1.0 mg/dL, but during acute inflammation, the CRP levels may increase 1000-fold. In humans, CRP level is an important indicator for the early, rapid diagnosis of a disease, especially for acute typhlitis, cholecystitis, and pancreatitis. In addition the C-reactive protein is also used as a novel predictor of cardiovascular events and of progression to diabetes mellitus in pre-diabetic individuals.

Apolipoprotein B

Apolipoprotein B (apoB) is the primary apolipoprotein of low density lipoproteins (LDL) which are called bad cholesterol and are responsible for carrying cholesterol to tissues. This 250000 dalton protein is the primary apolipoprotein component of LDL and is absolutely required for its formation. What is clear is that the apoB on the LDL particle acts as a ligand for LDL receptors in various cells throughout the body. Through a mechanism that is not fully understood, high levels of apoB can lead to plaques that cause heart disease (atherosclerosis). High plasma levels of apoB are positively corelated to serum LDL cholesterol level and thus are risk factors for atherosclerosis, a leading cause of death in the population and important marker to check the progression of obesity related diabetes mellitus.[13]

Apolipoprotein E

Apolipoprotein E (apoE) is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. ApoE was initially recognized for its importance in lipoprotein metabolism and cardiovascular disease. ApoE is 34000 dalton protein and transports lipoproteins, fat-soluble vitamins, and cholesterol into the lymph system and then into the blood. However, increased expression of apoE increases the rate of hepatic VLDL (very-low-density lipoprotein), triacylglycerol secretion and is associated with hypertriglyceridaemia. In humans and experimental animals, plasma apoE levels are correlated with plasma triacylglycerol levels.[14]

Alpha 2 macroglobulin

Alpha 2-macroglobulin (α2-M), a proteinase inhibitor in blood and tissue, is known to act as such a binding protein for numerous cytokines and growth factors. Recently, we have shown that α2-M is also involved in binding and transport of human growth hormone. These biologically important polypeptides mainly bind to transformed α 2-M (a2-Mt), which is the receptor recognizable form of the inhibitor. The receptor of α 2-M (α 2-M-R) was found to be identical to the low density lipoprotein receptor-related protein (LRP). The proteinase inhibitor, a2-M, may act as a

leptin-binding protein in human plasma. Binding of leptin to transformed a2-M and its rapid clearance by the a2-M receptor may significantly influence the bioavailability of leptin in human plasma. [14]

Lipoprotein lipase

Lipoprotein lipase is a key enzyme in lipid homeostasis in humans, providing intravascular release of fatty acid from circulating triacylglycerol. Lipoprotein lipase is the primary enzyme that converts lipoprotein triglyceride (TG) to FFAs (free fatty acids). A genetic deficiency of LPL results in hyperlipoproteinemia. LPL is produced by heart, adipose tissue, muscle, as well as in small amounts by many other tissues. It is a glycoprotein anchored on the luminal surface of capillary endothelium through its interaction with cell surface glycosaminoglycans. The normal targets for LPL action are the triacylglycerol-rich lipoproteins, especially chylomicrons and very low density lipoproteins (VLDL). Abnormalities in LPL function have been found to be associated with a number of pathophysiological conditions, including atherosclerosis, chylomicronaemia, obesity, Alzheimer's disease, and dyslipidaemia associated with diabetes, insulin resistance, and infection.[12]

Tumor necrosis factor alpha

Tumor necrosis factor α (TNF-α) is a pleiotropic cytokine that plays an important role in immunity and inflammation. During chronic illness, markedly elevated TNF-α secretion can contribute to hemorrhage, necrosis, and in severe cases, death. Overproduction of TNF-α is thought to play a role in a number of disease processes including arthritis, periodontal disease,inflammatory bowel disease, and chronic obstructive pulmonary disease. In each case, TNF-α is associated with persistent inflammation and tissue destruction. The inflammatory events stimulated by TNF-α can lead to connective tissue destruction by the release of lytic enzymes produced by resident cells as well as by recruited inflammatory cells. Diabetes is associated with excessive TNF-α expression. This may result from constitutive overproduction by adipose tissue in diabetes mellitus, the effects of hyperglycemia and advanced glycation end products and an exaggerated or more persistent response to stimuli such as bacteria or wound healing.TNF-α overexpression in diabetes is thought to contribute to several complications in diabetes, including retinopathy, nephropathy, neuropathy, and diabetes-enhanced periodontal disease.Delayed or incomplete healing of wounds has been well documented in diabetic humans and in animal models of diabetes [14]

Proteins Down Regulated in Obesity and Diabetes:

Adiponectin

One of the adipokinesadiponectin, molecular weight 30000 dalton is a collagen-like plasma protein produced and secretedexclusively by adipose tissue, has been shown to have compellinganti-atherogenic, and insulin-sensitizingproperties. Cross-sectional studies

of human subjectshave reported decreased concentrations of adiponectininpatientswith diabetes mellitus, hypertension, dyslipidemia, and cardiovasculardisease compared with healthy individuals,and weight reduction has resulted inincreasesinadiponectin. In addition, inverse correlations of adiponectinwith BMI, percent body fat, waist-to-hip ratio, glucose, insulin,and triglyceride and positive correlations with HDL and directmeasures of insulin sensitivity have been consistently demonstrated.[14]

ApolipoproteinA-I

Apolipoprotein A1 (ApoA-I) is the major protein component of high density lipoprotein (HDL) in plasma. This protein, of molecular weight 28000 dalton, promotes cholesterol efflux from tissues to the liver for excretion. The level of apo A1 is positively corelated with HDL cholesterol in the serum and negitivelycorelated with LDL cholesterol. ApoA-I is synthesized in both the intestine and the liver, but the relative contribution of the intestine and the liver to the plasma apoA-I pool in humans remains.[15]

Apolipoprotein AII

Apolipoprotein AII (ApoA-II) constitutes approximately 20% of HDL protein, is present on about two-thirds of HDL particles in humans, and is synthesized only in the liver. ApoA-II is also required for normal HDL biosynthesis and metabolism. This protein just like apoA1 is present in low concentration in obese person .

Apolipoprotein H

Apolipoprotein H (ApoH), also known as β2-glycoprotein I, is a plasma glycoprotein either circulating as a free protein or associated to lipoproteins. ApoH is a 54000 dalton single-chain glycoprotein consisting of five carbohydrate chains. Reports show that ApoH may have an important function in blood coagulation and clearance of apoptotic bodies from the circulation. Some works indicate that the binding of ApoH with target membranes containing anionic phospholipids could induce agglutination and precipitation. The interactions of ApoH with phospholipids are considered crucial in explaining its physiological or clinical roles.[14]

Aims and objective of the study

The study was carried out to check the effect of obesity on diabetes and how certain proteins which have their origin in the adipose tissues can cause the aggravation and progression of diabetes mellitus. In our study, firstly, we have focused on the effect of obesity on the lipid profile and other biochemical parameters such as protein concentration and fasting blood glucose level of the of diabetic individuals. Secondly we have checked the expression level of various proteins which are secreted by adipose tissues in the serum of diabetic obese subjects and the possible effect they have on glucose homeostasis or generally on the progression of diabetes mellitus.[15]

Plan of work

The study was conducted by first collecting the serum samples of 50 confirmed diabetic subjects from the hospital. The weight, height, waist and hip circumference was measured and the BMI, waist to hip ratio was calculated. 25 of these subjects were obese by all the three criteria which we measured and were grouped as diabetic obese. The other 25 diabetics were grouped as diabetic non obese. 25 healthy, normal subjects were also included in the study as control. The biochemical tests such as total serum protein concentration, fasting blood sugar and lipid profile was performed. The statistical analysis was performed with the help of SPSS computer program and level of significance was taken as < 0.05. After the physical and biochemical parameters were measured, the protein profile was obtained by running the serum samples on 10% SDS PAGE. The gels were stained both with coomassie R-250 stain and with silver nitrate. By studying the gels we can tell which protein is over expressed and which protein is under expressed in diabetic obese, diabetic non obese and control samples.

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