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TO CORRELATE LEVELS OF TNF-α, INSULIN, INSULIN RESISTANCE, ANTIOXIDANT ENZYMES AND LIPOPROTEIN PROFILE IN OBESE WITH TYPE 2 DM SUBJECTS

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ABSTRACT: Obesity has become a matter of quality to health care administrators. The busy lifestyle of people made them prefer fast food instead of taking healthy food. But the people are not aware that fast food habits convert to diseases like obesity, type 2 diabetes mellitus (T2DM), dyslipoproteinemia *etc*. This case-control study was carried out in the Department of Biochemistry in collaboration with the Department of General Medicine, Madhav Prasad Tripathi Medical College, Siddhartnagar to explore the status of blood sugar fasting (BSF), tumor necrosis factor-α (TNF- α), Insulin, Insulin resistance, antioxidant enzymes and lipoprotein profile by standard spectrophotometric kit methods, as well as anthropometric measurements, blood pressure (BP) with the help of suitable instruments and equipment's in Control group and Obese with T2DM group. A marked impairment observed in levels of lipoprotein profile accompanied by an increase in the lipids and apo-protein levels of serum β lipoproteins, lipid peroxide, Insulin and Insulin resistance, blood pressure, anthropometric measurements following the decrease in lipid and apo-protein constituents of α lipoprotein. Also observed in decrease of levels of serum-reduced glutathione as well as the level of antioxidant enzymes in the obese with T2DM group with respect to control group. Thus, it is clear that obesity with T2DM is a risk factor for diabetic dyslipoproteinemia and coronary artery disease (CAD) in patients suffering from obese with T2DM.

INTRODUCTION: In a history of 3.5 billion years of existence of life, man evolved only 5 million years ago, and that nurturing of modern man began just 10 thousand years back with the emergence of virtues of social, cultural, and health values. The latter became a prime concern as it formed the fundamental basis for development. The primeval scriptures, as old as "Atharva Veda" written about 5000 - 6000 years ago, vividly and brilliantly narrate about health care, consciousness, concern, and control.

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As the man grew mentally and spiritually, he became more and more concerned about old age and elderly people. This is perhaps the genesis for the increasing interest in age-related diseases such as aging, cardiovascular diseases (CVD), diabetes mellitus (DM), and cancer. Obesity is defined as excess body weight (>20% of ideal weight) due to accumulation of fat [1-5].

In recent years, however, two more parameters have been found in frequent use waist/hip ratio and waist circumference. Insulin resistance and impairments in anthropometric measurements, lipoprotein profile, decreased levels of antioxidant enzymes, increased levels of lipid peroxides are cardinal features of DM. Insulin resistance and dyslipo-proteinemia both have mutual bondage with each other. The reasons for this covenant

equation for hyperglycemia and dyslipoproteinemia are many but one of the causes attributed to it is pro-oxidant and antioxidant balance. There is gathering evidence that infuriating pro-oxidant milieu, either due to provoked FR generation or waning antioxidant defense, induces DM in experimental animal. However, presence of such an atrocious ambience in human system in general and β cells of Langerhen‘s in pancreas is still a polemic issue Man has always dreamt of an ideal state of health and his efforts to fulfill this desire have been perpetually thwarted away by the ever-changing spectrum of the diseases. DM still remains a major health problem and its prevalence is increasing day by day [6].

Diabetic Dyslipoproteinemia: Prolonged free radical mediated lipotoxicity and abnormal glucose tolerance are involved in the pathogenesis of diabetes mellitus. Excess circulation of lipid, mainly non-esterified fatty acids (NEFA), glucose or both act on cells and tissues to counteract insulin mediated glucose uptake, hepatic regulation of glucose output and insulin secretion [7]. Diabetic dyslipoproteinemia is characterized by the level of cholesterol (normal to borderline), LDL-cholesterol levels with oxidized LDL (OX-LDL) and small dense particles that are associated with increased apolipoprotein (apoB), reduced HDL and high triglyceride (TG) levels [8].

Altered surface conformation and functionality of apo LDL (apoB) and apo HDL (apoE) of these lipoproteins interact with proteoglycans in arterial wall, with subsequent modification as by oxidation, leading to foam cell formation. The positively charged apoB and apoE interact with negatively charged carboxylic acid residues or sulphate groups on the side chain of the proteoglycans and initiate propogate atherosclerosis. In insulin sensitive persons both C - reactive protein (CRP) and Serum amyloid A (SAA) levels are increased with increasing insulin resistance.

Proteoglycans synthesis is increased by glucose and inhibited by thiazolidinediones. Oxidized LDL is believed to increase the risk of diabetes. However, treatment with antioxidant vitamin E and others was not found to control this type of lipid abnormalities [9]. The dyslipoproteinemia associated with diabetic nephropathy and renal injury is characterized by the major lipoprotein abnormalities of increased VLDL remnants, increased lipoprotein (a), low HDL-cholesterol and abnormal particle composition with oxidized carbamylated LDL, increased VLDL apoC III and increased small dense LDL. All these atherogenic abnormalities are associated with proteinurea, increased LDL production and decreased removal. Acetylcholine esterase inhibitors decreased the proteinuria and also deceased LDL-cholesterol levels. Statins are effective in nephritic syndrome, persons with diabetic nephropathy and persons on dialysis generally well tolerate it with low incidence of myopathy [10].

The evidence suggests that treatment with lipid lowering drugs may be associated with regression of microalbumin urea among patients with type-I diabetes. Statin treatment also improves survival in observational studies of dialysis populations. Higher glycemic load carbohydrates. The social aspects influencing the caloric intake are overzealous advertising of sweetened beverages and foods. Sedentary life is another determing factor. For example T.V., movies and computers and more confinement at home encourages less walking and physical exercise [11]. All these factors in concert tend to alter metabolism and appetite [12].

The production of TNF-α, a pro-inflammatory adipocytokineis noticeably enhanced in obesity [13]. TNF-α is a pleotropic cytokine with diverse functions and occurs in many pathological diseases like cancer, cardiovascular disease, type 2 diabetes mellitus etc [14]. Macrophages produce it in response to inflammation, endotoxemia and cancer and plays a key role in the pathogenesis of peripheral insulin resistance in obesity. TNF-α inhibits tyrosine kinase activity at the insulin receptor level and cause obesity induced insulin resistance [15-16]. Many studies have shown increased serum levels of TNF-α in obese patients in comparison with lean subjects [17].

Emerging clinical data shows that, inflammation precedes the development of clinically overt diabetes and also predicts the subsequent cardiovascular events [18]. TNF-α may serve as aninflammatory biomarker and as an important risk indicator for the future development of type 2 diabetes mellitus and provide a novel target for

therapeutic intervention. This study was undertaken to estimate the TNF-α levels in type 2 diabetes mellitus and to analyse the association with the anthropometric (BodyMass Index; BMI and Waist Hip Ratio; WHR) and clinical variables (fasting glucose and insulin) related to insulin resistance (IR), in obese and obese with diabetes.

Due to the aforesaid reasons resulting in the tilted and excess energy intake, the body starts gaining weight. This gain is practically confined to the accumulation of fat in adipocytes which are the center of adiposity from where aberrant signals originate to initiate various abnormal biochemical outcomes resulting in insulin resistance, metabolic syndrome, diabetes, CVD, and others [19].

The struggle begins between physiological and unphysiological forces and diseases set in when physiological processes are overwhelmed. The single most important process regulating "Energy Homeostasis" is "Glucose Homeostasis" in blood and tissues. The major consumers of glucose are peripheral tissue cells. Insulin is undisputedly a key regulator of this process.

However, there is an array of hormones and cytokines to countercheck its regulatory function. Unfortunately, in obesity, these counter switches get disturbed. Among these TNF-is one of the major switches. It gradually diminishes insulin potency in the peripheral tissues with the result cells do not obediently respond to commands of insulin for flow of glucose from extracellular milieu inside the cell. This refusal of the cells to listen to the commands of insulin is known as "Insulin Resistance". Initially beta-cells send more insulin to combat this situation causing "Hyper insulinemia". However, the capacity of beta-cells is limited. Gradually they start getting exhausted and beta-cell dysfunction develops. While these three processes are in progress numerous other unfavorable factors such as proinflammatory cytokines, mitochondrial stress through altered redox status intervene along with TNF-. In chronic and persistent obesity, insulin alone fails to combat the opposite forces culminating in multiple abnormalities. The above proposed hypothesis of text position among TNF-, insulin resistance is quite sound and appealing but its veracity is not proven in all populations or in all patients [20].

MATERIAL AND METHODS:

Study Design: Subjects were divided in to two groups of 50 subject each: Group 1: Healthy Control (n=50), Group 2: Obese with T2DM (n=50). Who attended for their periodic health checkups. All individuals were subjected to a complete medical evaluation by a physician, including a full medical history and physical examination. Only males between 35-65 years of age were included in the study. Patients with evidence of acute or chronic inflammatory or infectious disease, or cancer, were excluded from the study.

Collection of Blood Samples: Fasting blood samples were collected, from the ante mediancubital vein of the subjects following overnight fasting, using disposable plastic syringes with all aseptic precautions. Blood was transferred immediately in to a dry clean plastic test tube with a gentle push to avoid hemolysis. Blood was collected from both groups (Healthy Control & obese with T2DM\), for biochemical estimations influoride (sodium fluoride and potassium oxalate, 5.4 mg NaF and 3.0 mg K-oxalate in each vial), EDTA (3 mg/ vial) and plain vials.

Separation of Serum and Plasma: Plasma was separated by centrifuging anticoagulant mixed whole blood at 1500 rpm for 15 minutes at 4 °C in Eppendorf centrifuge machine. On the other hand, for separating serum, the whole blood was kept in plain vacuutainer at 37 °C for 30 minutes after which this coagulated blood was centrifuged at 1500 rpm for 15 minutes at 4°C in Eppendorf centrifuge machine. The supernatant was pipetteout in a new tube and kept at - 20 °C till analysis.

Preparation of RBC Lysate: 3 ml whole blood of EDTA vacuutainer was taken and centrifuged at1500 rpm for 15 minutes at 4 °C in Eppendorf centrifuge machine. The whole supernatant from the tubes was pipette out, and then added 1 ml of normal saline (0.9% Nacl, isotonic solution). It was then again centrifuged at 1500 rpm for 15 minutes at 4°C in Eppendorf centrifuge machine.

Anthropometric Measurement: Height (cm), Weight (kg), Waist and hip circumferences (cm) were noted using a measuring tape to the 0.1 cm. Waist circumference was measured at the midpoint

between the lower border of rib cage and the iliac crest. Hip circumference was measured at the level of trochanter, the widest part of the hip region. Weight (kg) was measured to the nearest 0.1 kg using a weighing machine simultaneously. Waist hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

BMI was calculated as weight (kg) divided by height (m). Obesity is defined as BMI> 30kg/ m^2 [21].

Biochemical Analysis of Serum, Plasma and Lysate: The blood was centrifuged and plasma was separated. The fasting blood sugar (FBS) [22] was analyzed in plasma while glycosylated hemoglobin (HbA1C) [23], Super oxide dismutase (SOD) [24], Catalase (CAT) [25], Glutathione peroxidase (GPx) [26] and Glutathione reductase (GR) [27] were estimated in RBC lysate, serum total cholesterol (TC) [28], triglyceride (TG) [29], high density lipoprotein total cholesterol (HDL-TC) [30] were assayed by standard spectrophotometric methods. Low density lipoprotein total cholesterol (LDL-TC) and very low density lipoprotein total cholesterol (VLDL-TC) were calculated by Friedewald's equation [31].

Serum was also used for the assay of lipid peroxide (LPO) [32], reduced glutathione (GSH) [31]. A portion of serum was fractionated into very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) by polyanionic precipitation methods [32]. TNFα and Insulin had estimated by the standard ELISA kit method [33]. Insulin resistance will be calculated by formula given below-

Homa Index = Fasting Insulin concentration (Unit/ml) x Fasting Glucose concentration (mili mol/l)/ 22.5. Normal young subjects have an Insulin resistance of 1 [34]. All samples were processed and examined according to principles of good laboratory practice at clinical biochemistry

Statistical Analysis:

Statistical Analysis: One-way-analysis of variance (ANOVA- Newman's student test) was performed by comparison of values for CAD with T2DMgroup with control. All hypothesis testing were two-tailed. P <0.05 was considered statistically significant and the results were expressed as mean± SD. The Graph pad INSTAT 3.0 software was used to carried out the statistical analysis [35].

RESULTS:

Status of Blood Sugar Fasting, TNF α, HOMA-IR, Insulin and HbA1c, in Obese with T2DM Patients: The data in **Table 1** shows that, in Obese with T2DM patients, showed markedly increased levels of Blood Sugar Fasting, TNF α, HOMA-IR, Insulin and HbA1c 103%, with respect to healthy control.

Status of Serum Lipoprotein Constituents in Obese with T2DM Patients: The data in *Table 2* shows that, in Obese with T2DM patients, showed markedly increased levels of VLDL-TC 47.27%, VLDL-PL 90%, VLDL-TG 90%, VLDL-Apo 6.6%, and increased in levels of LDL-TC 93.69%, LDL-PL 40%, LDL-TG 85%, LDL-Apo 34 % as well as decrease in levels of HDL-TC 34%, HDL-PL 41%, HDL-TG 25% and HDL-Apo 13% with respect to Healthy Control.

Status of GSH, LPO, SOD, Catalase, GPX and GR in Obese with T2DM Patients: The data in **Table 3** shows that, in Obese with T2DM patients, showed markedly increased levels of GSH 47%, LPO 211%, as well as decrease in the level of SOD 50 %, CAT 45%, GPx 24%, GR 48% with respect to Healthy Control.

RESULTS:

TABLE 1: STATUS OF TNF-A, INSULIN, AND INSULIN RESISTANCE IN OBESE WITH T2DM SUBJECTS

Variables → Groups ↓	BMI (Kg/m2)	Body Surface Area (m2)	Waist Hip Ratio	Blood Pressure (mm hg)		Blood Sugar Fasting (mg/dl)	TNF α (pg/Ml)	HOMA-IR	Insulin (μ Unit /ml)	Glyco-sylated Hemo-globin (g%)
				Systolic Blood Pressure	Diastolic Blood Pressure					
Healthy Control (n=50)	18.75 ±3.25	1.88±1.76	0.87 ±0.06	118.53 ±4.66	78.20±4.21	91.27 ±7.87	22.31 ±10.45	31.01 ±12.22	7.67±3.07	3.98±0.30
Obese with	30.45±3.	2.27±	0.89±	142.67±	96.47±	187.61±	195.18±	305.08±	38.67±	9.65±

T2DM (n=50)	84*** (+62.4%)	0.17*** (+39.0%)	0.08NS	7.14*** (+20.34%)	4.50*** (+17.38%)	35.32*** (+105%)	34.23*** (+774%)	85.12*** (+883%)	6.75*** (+404%)	0.880*** (+142.40%)

Values expressed as mean ± SD of 50 subjects. Values in the parenthesis are percent change in comparison to healthy control. ***p<0.001, NS= Non-significant.

TABLE 2: LIPOPROTEIN PROFILE IN OBESE SUBJECTS WITH T2DM

	Very low-density lipoprotein (VLDL)				Low-density lipoprotein (LDL)				High-density lipoprotein (HDL)			
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	Apo-protein (mg/dl)
Control (n=50)	21.11 ±3.66	16.80 ±2.06	120.10 ±3.29	15.02 ±2.99	111.64 ±5.59	25.97 ±3.43	20.60 ±3.76	60.87 ±2.37	60.87 ±2.73	51.18 ±3.36	16.90 ±2.51	168.82 ±11.63
Obese with T2DM (n=50)	31.09±1.20*** (+47.27%)	21.92 ±2.48*** (+90%)	228.76±5.70*** (+90%)	16.00 ±0.57NS (+6.6%)	215.71 ±3.75*** (+93.69%)	35.59 ±1.43*** (+ 40%)	37.21 ±6.29*** (+85%)	81.55 ±1.46*** (+34%)	40.68 ±8.65*** (-34%)	30.52 ±2.27*** (-41%)	12.55 ±1.28*** (-25%)	147.42 ±12.33* (-13%)

Values expressed as mg/dl are mean ± SD of 50 subjects. Values in the parenthesis are percent change in comparison to healthy control. ***p<0.001, *p<0.01, NS= Non-significant.

TABLE 3: STATUS OF OXIDATIVE MARKERS IN SERUM AND ANTIOXIDANT ENZYMES IN RBC LYSATE OF OBESE WITH T2DM SUBJECTS

Experimental Schedule	Status of Markers used for oxidative stress in Serum	Status of Antioxidant Enzymes in RBC Lysate				
	Reduced Glutathione: GSH (mg/dl)	Lipid Peroxide: LPO (nmol MDA/ml)	Super oxide dismutase: SOD (unit/minute/ mg protein)	Catalase (unit/minute/m g protein)	Glutathioe Peroxidase: GPx (n mole NADPH oxidized/ min/mg protein)	Glutathionr Reductase: GR (n mole NADPH oxidized/ min/mg protein)
Control (n=50)	31.00 0± 5.76	2.28± 0.54	4.10 ± 0.19	3800 ± 252.00	345.38±180.00	2450.00±38.88
Obese with T2DM (n=50)	15.79 ± 3.62*** (- 47%)	7.10 ± 2.37*** (+211%)	2.00 ±0.18*** (-50%)	2090± 267.08*** (-45%)	250.00 ± 97.56*** (-24%)	1255.00 ± 40.12*** (-48.70%)

Values expressed as mean ± SD of 50 subjects. Values in the parenthesis are percent change in comparison to healthy control. ***p<0.001.

DISCUSSION: Pre-existing studies of human and animal models have indicated that, TNF-α expression in the adipose tissues is significantly elevated in obesity [19, 20, 29]. In our study TNF-α concentration was significantly high in obese T2DM than in non-obese subjects. Our results demonstrated that, increased level of TNF-α were associated with increased level of glucose in obese with T2DM and was related to the degree of obesity. Nilksson *et al* reported that, the plasma TNF-α levels were increased by 23% in lean T2DM compared to 51% in obese T2DM subjects with more severe insulin resistance [35].

Interestingly the results are very stirring. In the present study the average glycosylated hemoglobin (HbA1c) was significantly higher in obese with T2DM subjects, when compare with healthy control ($p < 0.001$). On the contrary shown HDL cholesterol level were significantly lower. These observations clearly indicated that in these obese with T2DM subjects lopsided dyslipidemia also existed. In another exercise constituent (total cholesterol, phospholipids, triglycerides and apoprotein) of VLDL, LDL and HDL were examined. While lipid fractions were adversely affected in patients and required correction, the three most important features needing focus are low HDL cholesterol, low HDL apoprotein fraction **Table 2** and low GSH, SOD, CAT, GPx and GR **Table 3.** There is consistent evidence that HDL choledterol is a potent predictor of cardiovascular events independently and also in obese with T2DM subjects [36]. The cardio protective effect of HDL is attributed to its role in reverse cholesterol transport. It removes excess cholesterol from peripheral tissues towards the liver for excretion in to bile or else for steroid hormone synthesis in steroidogenic organs. Further effects of HDL are proteotropic as it also exerts most importantly as antioxidant and anti-inflammatory agent [28]. Apoprotein-1 is quantitatively a major component of HDL. Glycation of apoprotein A-1 in HDL alters and

reduces LCAT activity in proportion to the extent of apoprotein A-1 glycation. Indeed, there is convincing evidence that hyperglycemia induces several pathways generating more ROS. This ROS increase glycation potential [37]. In this clinical study, apoprotein-1 significantly decreased and concomitantly OS also increased. Furthermore, in both VLDL and LDL components total cholesterol and triglycerides levels were consistently and considerably higher in obese with T2DM subjects. Although cells usually exist in a reductive environment, oxidation and reduction reactions are essential and crucial for every cell. In normal cells at any given time, oxidative processes yielding Reactive oxygen species (ROS) are slightly more than reduction processes.

This oxidative potential is termed as OS. ROS and antioxidants are major oxidative stress (OS) determinants as other cellular oxidative reductive processes are in balance. OS is raised in obese with T2DM patients through numerous pathologies. Our study indicates the pivotal role of oxidative stress in pathogenesis and progression of obese with T2DM. In the present study, LPO, an accepted marker of OS in obese with T2DM patients was significantly raised.

The average increase was more than threefold to that of controls. This alluded and signified to provoke OS in obese with T2DM subjects. Consequently, this must be disturbing the redox box. The raised OS was accompanied with reduction in GSH level and lower SOD, Catalase, GPx and GR activities. On the contrary endogenous antioxidants are reducible and try to balance cellular antioxidants, thereby maintaining cellular redox homeostasis. In light of these report, the observation stated in **Table 3** purport perturbed redox box in obese with T2DM subjects. This clearly suggested that increased oxidative stress abnormal lipid and lipoprotein profile are major independent risk factors in the patho-mechanisms in obese with T2DM subjects. All these data provide strong associative evidence supporting subclinical inflammation as a unifying factor accelerating the progression of Insulin resistance and T2DM. Our data suggest a possible role of TNF-α in the pathophysiology of Insulin Resistance particularly in obese with T2DM subjects [38-42].

CONCLUSION: The definition of the cutoff value for "normal" BMI in a population would depend on identifying the risk associated with a disorder strongly associated with BMI. Further, such types of studies will specially help health workers and clinicians to suggest health and therapeutic regimens in a particular population. Our study also indicates the pivotal role of anthropometric measurement, blood pressure, TNF α, insulin, HOMA IR, blood glucose, oxidative stress, and impaired carbohydrate and lipid metabolism in the pathogenesis and progression of obesity and obesity with T2DM. This study also shows a significant boost in oxidative stress, β lipoproteins, blood glucose, and glycosylated hemoglobin followed with the decrease in α lipoproteins, antioxidant enzymes, reduced glutathione activities observed in obese with T2DM patients with respect to healthy control. This is suggested that increased oxidative stress, hyperglycemia, abnormal lipoprotein constituents and decreased activity of antioxidant enzymes, reduced glutathione are risk factors in the pathomechanism of artherosclerosis in obese with T2DM subjects.

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