RETINOL-BINDING PROTEIN-4 AND INSULIN RESISTANCE IN GLUCOSE INTOLERANT OBESE PATIENTS

By

Nearmeen M. Rashad, Mohsen M.A. Eldarawy, Mohamed M. M. Hassan, Abd EL-Azeem M. Gomaa

Internal medicine department, Medical Biochemistry, faculty of medicine, Zagazig University, Egypt

ABSTRACT

Objective: Obesity associated insulin resistance is a major risk factor for type 2 diabetes and cardiovascular disease. The disturbances of adipokines secretion are associated with the pathogenesis of insulin resistance and type 2 diabetes. Retinol-binding protein-4 (RBP4), a new adipokine, was recently reported to provide a link between obesity and insulin resistance. The aim of this study was to study the relation between retinol-binding protein 4 and insulin résistance in obese patients with or without glucose intolerance. **Research Design And Methods:** We studied from august 2008 to august 2010, The study population included 100 subjects, 20 of them were healthy lean subjects (control group) and 80 obese patients (their BMI were >30) and they were divided into three groups According to glucose tolerance: normal glucose tolerance (NGT; *n* = 20), impaired glucose tolerance (IGT; *n* = 20), and type 2 diabetes (*n* = 40). Plasma RBP4 concentrations were compared with various parameters related to insulin resistance .Insulin resistance and B cell function, were assessed by using the homeostasis model.

Results: Plasma RBP4 concentrations were higher in obese groups As compared to lean group. Plasma RBP4 concentrations were higher in IGT (23.78±SD 10.57) and diabetic (26.3±SD 10.0) patients as compared to lean (6.12±SD 1.03) and NGT (16.64±SD 8.04) with more significant changes in diabetic group. However, no difference was found between plasma RBP4 concentrations in the IGT and type 2 diabetic groups. Plasma RBP4 concentrations were found to be correlated with Systolic and diastolic blood pressure, BMI .while Plasma RBP4 concentrations were not correlated with Age and sex .Of these, BMI, fasting serum insulin, fasting plasma glucose levels and HOMA.IR were found to be independent determinants of plasma RBP4 concentrations. **Conclusions**: Plasma RBP4 concentrations were found to be elevated in obese subjects with IGT or type 2 diabetes with more significant changes in diabetic group and to be related to various clinical parameters known to be associated with insulin resistance.

Keywords: Adipocyte, adipokines, insulin resistance, homeostasis model.

INTRODUCTION

Insulin resistance is an early and strong determinant of type 2 diabetes. Insulin resistance in obesity and type 2 diabetes is manifested by decreased insulin stimulated glucose transporter and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output (1).These functional defects may result, in part, from impaired insulin signaling in all three target tissues and, in adipocytes, also from downregulation of the major insulin- responsive glucose transporter, GLUT4.in both muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity, and phosphorylation of IRSs are reduced. There are also tissue- specific alterations in adipocytes from obese subjects with type 2 diabetes(2).Obesity and diabetes are epidemic worldwide(3). Obesity is a major cause of insulin resistance; however, its exact mechanism is still undergoing investigation (4).Adipose tissue is now recognized as an endocrine organ that contributes to the physiopathology of type 2 diabetes. Adipokines, proteins produced by adipose tissue, have been identified as potential contributors to insulin resistance in humans(5).Over the past few years,

emerging evidence has shown that adipokines are produced both by adipocytes and macrophages in human adipose tissue, and that diverse paracrine and autocrine pathways are involved in their regulation (5).Adipose tissue has been demonstrated to secrete various adipokines that relate to insulin resistance(6), Such adipokines include adiponectin, leptin, and, recently, retinol- binding protein 4 (RBP4) (6).Adipocyte-derived cytokines (adipokines) provide an important link between obesity related disorders and insulin resistance(7). Retinol-binding protein-4 (RBP4) is an adipokine that may play a role in regulating glucose metabolism and insulin sensitivity (8). Experimental studies revealed that a decrease of adipose tissue GLUT4 expression leads to an increase in RBP4 synthesis and secretion. RBP4 stimulates hepatic gluconeogenesis and inhibits insulin signaling in the muscle (8).Thus, RBP4 might be a signal linking adipose tissue with an induction of insulin resistance in the liver and muscle. RBP4 binds to retinol and transthyretin (TTR) homotetramer to form a tertiary protein complex that reduces renal clearance of RBP4. Several studies have demonstrated that circulating RBP4 concentration is elevated in humans with insulin resistance (9).

In contrast, other studies have shown normal serum RBP4 concentration in obese menopausal women and low concentration in individuals with type 2 diabetes mellitus, and that RBP4 concentration are unrelated to insulin sensitivity in calorie-restricted obese individuals (10).

SUBJECTS AND METHODS

The ethical committee of our institution approved this study to be conducted at diabetes and endocrinology outpatient clinic of Internal Medicine and Biochemistry Departments, Faculty of Medicine, Zagazig University Hospitals. In the period from august 2008 to august 2010.

It included total number of 100 subjects, 20 of them were healthy lean subjects (control group) and 80 obese patients (their BMI were >30) and they were divided into three groups According to 75-g oral glucose tolerance test, according to the diagnostic criteria of the American Diabetes Association: normal glucose tolerance (NGT; n = 20), impaired glucose tolerance (IGT; n = 20), and type 2 diabetes (n = 40).

The patients were among patients attending diabetes and endocrinology outpatient clinic of Zagazig university hospital .Written informed consent was obtained from all participants after exclusion of:

1- Subjects suffering from fever, acute illness, chronic disease or taking medications that affect glucose metabolism.
2- Subjects who are participating in a dietary or exercise programs or taking medications for weight reduction.

METHODS

All patients included in this study were subjected to the following:

Full clinical assessment including history taking and clinical examination;Blood pressure and weight were measured. Plasma glucose levels were determined using the glucose oxidase method. Total cholesterol, triglyceride, and HDL cholesterol concentrations were measured enzymatically using an autoanalyzer. Low density lipoprotein cholesterol (LDL-cholesterol) was calculated according to (Fried ward-Fredrickson equation) HbA1c (A1C) was measured by affinity chromatography, and plasma insulin concentrations were measured by ELISA. Homeostasis model assessments of insulin resistance (HOMA-

IR) and B-cell function (HOMA-B) were performed.

ELISA for RBP4:

RBP4 standards of concentration 0.001–2.5 μ g/ml, 50 μ l human plasma at a dilution of 1:100, which was collected from subjects who had fasted overnight Then, 50 μ l anti-RBP4 was added to each well and incubated at 37°C for 1 h. Each well was then washed three times with PBS containing 0.05% Tween-20. The secondary antibody reaction was performed at 25°C for 1 h, and then each well was washed three times with PBS containing 0.05% Tween-20. Colorimetric reaction was performed for 20 min with the use of horseradish peroxidase– conjugated streptavidin diluted 1:1,000 in PBS and 2,2'azino-bis(2-ethylbenzothiazoline-6-sulfonic acid) as substrate. Optical densities were measured at 450 nm. The ELISA system had an intra-assay coefficient of variation of 4–8% and an interassay coefficient of variation of 5–10%.

STATISTICAL ANALYSIS

Data are presented as means ± SD comparisons between groups were performed by analysis of variance (ANOVA), post hoc tests (least significance of difference) were performed for multiple comparisons between groups, while X^2 tests were used for categorical variable, Pearson's correlation analyses, and multiple linear regression analyses were performed using statistical package for social sciences (SPSS) for windows version 17.

RESULTS

Study of clinical data of different groups are shown in Table1**.**There were highly significant difference between mean values ±SD of different studied groups as regard to systolic and diastolic blood pressure (F=5.50, P<0.01 and F=4.27, P<0.01 respectively). While no significant difference between mean values ±SD of different studied groups as regard to age.

As regards BMI, Show statistically highly significant difference of the mean values ±SD of BMI in Control group (26.8±1.9) as compared to NGT (35.3±2.72) and IGT (34.5±1.9), and Type 2 diabetes (34.1±SD2.0) ,(P<0.01) .Also there was statistically highly significant increase of the mean values ±SD of BMI in Type 2 diabetes (34.1±2.0) as compared to NGT (35.3±2.72) and IGT (34.5±1.9) ,(P<0.01) while there were no significant differences in this respect between other groups of the study.

Results of oral glucose tolerance test (OGTT) as shown in Table1: shows the mean values ±SD of blood glucose levels (mg/dl) during oral glucose tolerance test (75 gm load) in different groups of the study, application of ANOVA test revealed that, there were statistically highly significant differences among different groups of the study as regard to (fasting, blood glucose and, blood glucose at 120 minutes), (F=136.2, P<0.001, and F=93.6, P<0.001 respectively).

Lipid profile study shows the mean values ±SD of serum (total cholesterol, LDL.c, HDL.c and Triglycerides) (mg/dl) in different studied groups, application of ANOVA test revealed statistically highly significant difference among different group of the study as regard to HDL.c and Triglycerides (F=11.3, P<0.001 and F=8.8, P<0.001). While no significant difference between mean values ±SD of serum cholesterol and LDL.c among different studied groups p>0.05.

Table (1): Simple analysis of variance of mean values ± SD for clinical data in different studied groups.

items	Control N=20	NGT N=20	IGT N=20	Type 2 diabetes N=40	F	p
Age (years)	39.3 ±SD 9.5	43.1±SD 8.8	46.4 ±SD 8.39	45.9 ±SD 11.1	2.43	0.070
Systolic blood pressure(mm/Hg)	120.7±SD 8.7	129.4±SD 13.3	134.4 ±SD 13.5	133.6 ±SD 13.3	5.50	.002
diastolic blood pressure(mm/Hg)	80.7 ±SD 5.1	81.0 ±SD 6.198	86.9 ±SD 8.92	86.7 ±SD 9.5	4.27	0.007
BMI (Kg/m^2)	26.8±SD 1.9	35.3±SD 2.72	34.5±SD 1.9	34.1±SD 2.0	69.3	0.000
Fasting blood glucose	87.9±SD 3.5	92.6±SD 4.5	107.1±SD 11.2	176.9±SD 29.9	136.2	0.000
Blood glucose at 120 min	117.9 ±SD 7.6	119.2 ±SD 8.6	145.2 ±SD 17.4	211.5±SD 36.8	93.6	0.000
Fasting serum insulin	8.15±SD 1.6	11.09±SD 3.5	14.5± SD 4.6	17.1± SD 6.2	17.84	0.000
Serum cholesterol (mm/Hg)	196.8±SD 22.7	207.1±SD 34.2	220.9±SD 25.1	208.6±SD 38.7	1.81	0.149
Serum LDL.c (mm/Hg)	119.25±SD 24.7	122.77±SD 34.6	135.90±SD 25.4	128.36±SD 38.2	.992	0.400
Serum HDL.c (mm/Hg)	41.95±SD 6.3	42.50±SD 6.5	41.15±SD 6.75	34.78±SD 5.08	11.3	0.000
Serum Triglycerides(mm/Hg	178.2±SD 23.9	209.1±SD 40.4	219.2±SD 29.9	229.4±SD 42.7	8.8	0.000
HBA1c	6.3±SD 0.3	6.6±SD 0.4	6.9±SD 0.5	7.4±SD 0.5	25.8	0.000
HOMA.IR	1.7±SD 0.3	2.5±SD .7	3.8±SD 1.3	7.4±SD 3.0	46.3	0.000
β cell function %	119.19± SD 27.86	54.69 ±SD12.2	48.84 ±SD10.9	38.2±SD 6.0	21.55	0.000
RBP4	6.12±SD 1.03	16.64±SD 8.04	23.78±SD 10.57	26.3±SD 10.0	26.12	0.000

HOMA-IR, homeostasis model assessment of insulin resistance.

As regards RBP4 (μg/ml) there were statistically highly significant differences among the different groups of the study (F=26.12, P<0.001). Also there was highly significant difference of the mean values ±SD of RBP4 (μg/ml) (P<0.001) in control group (6.12±SD 1.03) as compared to NGT (16.64±SD 8.04), IGT (23.78±SD 10.57) and Type 2 diabetes (26.3±SD 10.0). Also significant difference was obtained when comparing NGT (16.64±SD 8.04) to IGT (23.78±SD 10.57) and Type 2 diabetes (26.3±SD 10.0). While, there was no significant difference in this respect between other groups of the study.

There were statistically highly significant differences among the different groups of the study as regards HBA1c (F=25.8, P<0.001).

B cell function %(HOMA B) was highly significant difference among the different groups of the study (F=21.55, P<0.001).

Table (2): **Correlations between plasma retinol binding protein 4(µg/ml) and various clinical parameters in different studied groups**.

Items	r	p
Age (years)	**0.143**	**0.155**
sex	**0 .115**	**0.255**
Systolic blood pressure (mm/hg)	**0.358**	**0.000**
diastolic blood pressure (mm/hg)	**0.332**	**0.001**
BMI(kg/m)	**0.481**	**0.000**
Fasting blood Glucose (mg/dl)	**0.506**	**0.000**
2 hour post prandial blood Glucose (mg/dl)	**0.485**	**0.000**
Fasting serum insulin (µU/ml)	**0 .417**	**0.000**
HOMA .IR	**0.45**	**0.000**
HB A1C%	**0.387**	**0.000**
B CELL Function (HOMA .B)	**-0.215**	**0.031**

HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B HOMA of B cell Function

Table (2**)** shows Plasma RBP4 concentrations(µg/ml) were Highly correlated with Systolic blood pressure (mm/hg), diastolic blood pressure (mm/hg) ,BMI(kg/m**)** , P <0.001 .fasting blood Glucose mg/dl, two hours post prandial blood Glucose (mg/dl), fasting serum Insulin(µU/ml), HOMA .IR and HB A1C, P <0.001. While Plasma RBP4 concentrations were modestly correlated with Beta CELL Function (HOMA -B)**,** P <0.05. while Plasma RBP4 concentrations were not correlated with Age (years) and sex (P >0.05).

Table (3) shows Multivariate analysis revealed that BMI, fasting serum insulin, fasting plasma glucose levels and HOMA.IR were independently associated with plasma RBP4 concentrations**.**

Table (3): Multivariate analysis for the relationship between metabolic parameters and plasma RBP4 level (µg/ml).

	Unstandardized coefficients		Standardized coefficients		
	β	**Std. Error**	**β**	***t***	***P***
Constant	**-40.644**	**9.829**		**-4.135**	**0.000**
AGE	**-3.176**	**0.110**	**-0.028**	**-0.289**	**0.773**
GENDER	**1.419**	**2.301**	**0.059**	**0.617**	**0.539**
Glucose 0 min	**0.254**	**0.062**	**0.985**	**4.091**	**0.000**
Insulin 0 min	**1.785**	**0.584**	**0.908**	**3.057**	**0.003**
BMI(kg/m)	**0.700**	**0.305**	**0.228**	**2.294**	**0.024**
HOMA.IR	**-4.422**	**1.583**	**-1.203**	**-2.794**	**0.006**

HOMA-IR, homeostasis model assessment of insulin resistance

DISCUSSION

Obesity is associated with the global increase in type 2 diabetes (11) and metabolic syndrome, features of which include insulin resistance, impaired insulin secretion, hepatic steatosis, dyslipidemia, and atherosclerosis(12). Insulin resistance is the central feature of this syndrome (13)

The number of obese individuals worldwide has reached 2.1 billion, leading to an explosion of obesity-related health problems associated with increased morbidity and mortality .Obese individuals develop resistance to the cellular actions of insulin, characterized by an impaired ability of insulin to inhibit glucose output from the liver and to promote glucose uptake in fat and muscle (14).

Type 2 diabetes is one of the fastest-growing diseases in NorthAmerica and in many developing countries, and it is closely associated with both insulin resistance and obesity. Although the discovery of various adipokines has shed light on the causes of this disease, the molecular link between obesity, insulin resistance, and type 2 diabetes in humans is still largely unknown (15).

Insulin resistance is a key etiological factor for type 2 diabetes mellitus (T2DM), which has reached epidemic proportions the association between obesity and insulin resistance is likely a cause-and-effect relationship since human and animal studies indicate that weight loss/gain correlates closely with increasing/decreasing insulin sensitivity, respectively .

Increased adipose tissue mass is strongly associated with the pathogenesis of insulin resistance and type 2 diabetes.Adipose tissue may be viewed as an endocrine organ that secretes many types of adipokines (such as leptin, tumor necrosis factor α, interleukin 6, and adiponectin) that modulate the action of insulin in other tissues (16).

It appears that RBP4 is a factor that acts to induce insulin resistance in the liver and skeletal muscle of rodents; however, the mechanism through which this adipokine acts and the role that adiposity status plays in humans are still unclear (8).

Moreover, retinol-binding protein-4 (RBP4), a new fat-derived adipokine that specifically binds to retinol, has recently been reported to provide a link between obesity and insulin resistance (8)

Retinol binding protein 4 (RBP4) is a novel protein secreted by adipose tissue which might be involved in the pathogenesis of insulin resistance (8).

Retinol-binding protein 4 (RBP4), also known as plasma retinol-binding protein, is a lipocalin superfamily molecule that transports vitamin A (retinol) in the serum (17). Dietary retinol is metabolized to retinaldehyde, multiple isomers of retinoic acid, and retinyl esters (18).

Experimental studies revealed that a decrease of adipose tissue GLUT4 expression leads to an increase in RBP4 synthesis and secretion. RBP4 stimulates hepatic gluconeogenesis and inhibits insulin signaling in the muscle (8).

Studies in humans showed the relationship between insulin sensitivity and serum RBP4 in insulin-resistant states, i.e. obesity; type 2 diabetes (9), nonalcoholic fatty liver disease (19), family history of type 2 diabetes (20), and polycystic ovary syndrome (21).

Our study showed that there was NO a significant change of age between different studied groups.

This was in agreement with Muscelli et al., (2008) (22) who reported that there was NO a significant changes between (NGT, IGT and DM) as regard to age.

In the study by CHO et al., (2006) (23) there was significant increase of Plasma RBP4 levels in women over the age of 50 as compared to those under the age of 50. However, no such age associated difference in RBP4 plasma levels was observed in men. Moreover, women over the age of 50 had significantly lower plasma RBP4 levels than men.

Tapp et al., (2010) (24) disagreed as they reported that age was significant increase diabetic patients as compared to NGT and IGT patients.

In our study, we observed that there was significant elevation of systolic and diastolic blood pressure in patients with diabetes mellitus compared to other groups of the study.

Similar results was observed by Magliano et al., *(2008*) (25) who reported that there was highly a significant difference between mean values ±SD of different studied groups as regard blood pressure.

Also similar results were obtained by Tapp et al., (2010) (24) who observed that was highly a significant difference between mean values ±SD of systolic and diastolic blood pressure in diabetic patients as compared to NGT and IGT.

CHO et al., (2006) (23) disagreed as they reported that there was no significant difference of the mean values ±SD of systolic and diastolic blood pressure in diabetic patients as compared to NGT and IGT.

As regard to BMI, our study shows that there was highly significant difference of the mean values ±SD of BMI in diabetic patients as compared to lean, NGT and IGT.

This was in agreement with Magliano et al., *(2008*) (25) who reported that diabetic patients had higher BMI than non diabetic.

Similar results were observed by ENGBERG et al., (2009) (27) who found that there was highly significant increase of the mean values ±SD of BMI in diabetic patients as compared to lean, NGT and IGT.

Also similar results were obtained by Chavez et al., (2009) (28) who observed that was highly a significant increase of mean values ±SD of BMI in diabetic patients as compared to lean NGT and obese NGT.

Muscelli et al., *(*2008) (22) disagreed as they reported that there was no significant difference of the mean values ±SD of BMI in diabetic patients as compared to lean, NGT and IGT.

Our study observed that, there was highly significant difference among different groups of the study as regard to (fasting, blood glucose at 60 minutes , blood glucose at 120 minutes and fasting serum insulin levels) as there was significant increase in IGT and diabetic patients as compared to lean and NGT with more significant changes in diabetic group.

This was in agreement with CHO et al., (2006) **(**23) who reported that diabetic obese patients had significant difference of the mean values ±SD of fasting, two hour post prandial and fasting serum insulin levels in diabetic patients as compared to lean, NGT and IGT.

Similar results were observed by Chavez et al., (2009) (28)who reported that that was highly a significant increase of mean values ±SD of fasting ,two hour post prandial and fasting serum insulin levels in diabetic patients as compared to lean NGT and obese NGT.

Tapp et al., (2010)(24) also agree with our results as they suggested that fasting, two hour post prandial and fasting serum insulin levels were highly a significant increase in diabetic patients as compared to lean, NGT and IGT.

Our study showed that, there was highly significant difference as regard to HDL.c and Triglycerides in IGT and diabetic patients as compared to lean and NGT with more significant changes in diabetic group. While no significant difference between mean values ±SD of serum cholesterol and LDL.c among different studied groups.

Similar results were observed by Chavez et al., (2009) (28**)** who reported that there was highly significant difference of HDL.c and Triglycerides in diabetic patients as compared to Lean NGT and Obese NGT patients. While no significant difference between mean values ±SD of serum cholesterol and LDL.c among different studied groups.

Cho et al., (2006) **(**23) disagreed as they reported that there was significant increase of serum cholesterol and LDL.c (mg/dl) in IGT and diabetic patients as compared to lean and NGT with more significant changes in diabetic group. While no significant difference between mean values ±SD of HDL.c and Triglycerides (mg/dl) among different studied groups.

Muscelli et al., *(*2008)(22) observed that there was significant increase of Triglycerides (mg/dl) While no significant difference between mean values ±SD of HDL.c and LDL.c (mg/dl) among different studied groups.

Magliano et al., *(2008*)(25) reported that there was highly significant difference of HDL.c, total cholesterol and Triglycerides (mg/dl) in diabetic patients as compared to non diabetic patients.

In our study, we observed that there was significant increase of the mean values ±SD of HBA1c% in IGT and diabetic patients as compared to lean and NGT with more significant changes in diabetic group.

This was in agreement with Muscelli et al., *(*2008)(22) who reported that there was significant increase of the mean values ±SD of HBA1c% in diabetic patients as compared to NGT and IGT.

Similar results were observed by Magliano et al., *(2008*)(25) who observed that there was significant increase of the mean values ±SD of HBA1c% in diabetic patients as compared to non diabetic patients.

Also similar results were observed by Chavez et al., (2009) who observed that there was significant increase of the mean values ±SD of HBA1c% in diabetic patients as compared to Lean NGT and Obese NGT.

CHO et al., (2006) **(**23) disagreed as they observed that there was no significant change between NGT, IGT and DM as regard to HBA1c%.

Our study showed that the mean values ±SD of insulin resistant % (HOMA) was highly significant difference in IGT and diabetic patients as compared to lean and NGT with more significant changes in diabetic group.

Cho et al., (2006) **(**23) reported that there was modestly significant difference between NGT, IGT and DM as regard to insulin resistant % (HOMA IR).

Our study observed that there was significant increase of the mean values ±SD of Plasma RBP4 concentrations in obese groups As compared to lean group. Moreover there was significant increase of the mean values ±SD of Plasma RBP4 concentrations among different groups of the study.

Similar results were observed by Yang et al., (2005)(8) who reported that Obese human subjects with elevated serum RBP4 levels had unequivocally higher BMI than lean control subjects they suggested that obesity, but not hyperglycemia, is an important determinator of circulating RBP4 levels. However, they could not examine the

quantitative relation between plasma RBP4 and blood glucose levels.

Yang et al., (2005)(8) explained that possible mechanism underlying increased fasting plasma glucose levels in subjects with higher plasma RBP4 levels probably concerns increased hepatic glucose output, as RBP4 has been reported to up regulate the expression of PEPCK, a key enzyme in hepatic gluconeogenesis, in the liver.

Janke et al., (2006) (31) disagreed as they observed that RBP4 serum levels were not different between lean, overweight, and obese Subjects.

Also Broch et al., (2007) (26) disagreed as they reported that, Serum RBP4 concentration was found to be similar among lean, overweight and obese subjects.

Borengasser et al., (2007) (29) observed that Plasma RBP4 levels did not correlate with BMI.

In our study Plasma RBP4 concentrations were Highly correlated with Systolic blood pressure (mm/hg), diastolic blood pressure (mm/hg) BMI(kg/m) .while Plasma RBP4 concentrations were not correlated with Age (years) and sex .

Stefan et al., (2007)(33) reported that ,Plasma RBP4 levels were not significantly associated with sex, age, weight, or height .while No significant associations of RBP4 levels with fasting and 2-h glycemia, FFAs, or suppression of lipolysis in univariate analyses and after adjustment for age, sex, height, and body fat were detected.

Gavi et al. (2006) (30)showed that RBP4 values were lower in females compared with males' .RBP4 levels were found to correlate negatively with insulin sensitivity and positively with age while RBP4 levels did not correlate with BMI, trunk fat, or percent body fat.

Hahn et al. (2007)(32) reported that, RBP 4 levels were positively correlated with body mass index (BMI), body fat, waist circumference, fasting glucose, and area under the curve for glucose, but not with indices of insulin resistance.

Borengasser et al., (2007)(29) observed that there were no differences between insulin sensitive and insulin resistance groups in BMI or age, yet there were significant differences in Insulin sensitivity (S_I) and 2-h glucose, as expected. There was no significant difference in RBP4 expression in SAT (sc adipose tissue) between the insulin sensitive and insulin resistance groups although the average plasma RBP4 level of the insulin sensitive group was lower than that in the insulin resistance group.

Our study showed that there was significant increase of the mean values ±SD of Plasma RBP4 concentrations in IGT and diabetic patients as compared to lean and NGT with more significant changes in diabetic group. Also our study reported that No difference in plasma RBP4 levels was observed between the IGT and type 2 diabetic groups.

This was in agreement with Cho et al., (2006) **(**23**)** who reported that Plasma RBP4 concentrations were higher in the IGT and type 2 diabetic groups than in the NGT group.

Similar to our study, Cho et al., (2006) **(**23) reported that No difference in plasma RBP4 levels was observed between the IGT and type 2 diabetic groups.

In our study we observed that , Plasma RBP4 concentrations were Highly correlated with fasting blood Glucose mg/dl, two hours post prandial blood Glucose (mg/dl), fasting serum Insulin , HOMA .IR, HB A1C and Beta CELL Function (HOMA -B).

Cho et al., (2006) (23) reported that, Plasma RBP4 concentrations were modestly correlated with waist circumference, fasting plasma glucose, and HOMA-IR in the NGT group Moreover; fasting plasma glucose levels were found to be an independent determinant for plasma RBP4 concentrations. While Plasma RBP4 concentrations were not correlated with two hours post prandial blood Glucose (mg/dl), fasting serum Insulin, HB A1C and Beta CELL Function (HOMA -B).

Our study showed that, Plasma RBP4 concentrations were highly correlated with Serum Triglycerides and Serum Cholesterol (mg/dl). While Plasma RBP4 concentrations were modestly correlated with Serum LDL.c and Serum HDL.c (mg/dl).

Cho et al., (2006) (23) disagreed as they reported that, Plasma RBP4 concentrations were not correlated with Serum Triglycerides, Serum Cholesterol, Serum LDL.c and Serum HDL.c (mg/dl).

Broch et al., (2007) (26)reported that, in all subjects as a whole, circulating RBP4 was not found to be associated with age, BMI, waist-to-hip ratio, blood pressure, or circulating lipids.

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