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Retinol Binding Protein 4: Possible Relation between Insulin Resistance in Type 2 Diabetes and Visceral Obesity

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Abstract

Introduction: Retinol Binding Protein 4 (RBP-4), an adipokine, that was identified as key regulator of obesity related insulin resistance and type 2 diabetes, and certain components of metabolic syndrome.

Objectives: To study the relation of RBP4 and insulin resistance in patients with visceral obesity and type 2 diabetes mellitus.

Patients and Methods: This study was conducted on 74 subjects; classified according to their Body Mass Index (BMI) and Waist Circumference (WC) into three main groups: Group 1: included 27 obese diabetic subjects Group 2: included 28 obese non diabetic subjects. Group 3: included 19 healthy non-obese subjects, serving as control. All patients were assessed for Insulin Resistance (IR) index by HOMA-IR and Assessment of B cell function by HOMA-β, RBP4.

Results: RBP4 was significantly higher in group 1 and group 2 compared to group 3($p>0.05$) and was non-significant in group 1 compared to group 2. There was non-significant correlation between RBP4 & (anthropometric parameters, lipid profile, FBG, 2HPP, HBA1C, FI, HOMA-IR, HOMA-B) in group 1. RBP4 was significantly negative correlated with (BW, HDL) and significant positive correlated with FI, HOMA-IR in the group 2. In viscerally obese subjects HOMA-B% was lower than diabetes group and control group.

Conclusion: RBP4 was correlated to insulin resistance in viscerally obese subjects. Viscerally obese subjects had impaired B cell function they are liable for type 2 diabetes and other metabolic risks.

Keywords: Type 2 diabetes mellitus; Retinol Binding Protein 4 (RBP4); Insulin resistance; Obesity

Introduction

Retinol Binding Protein 4 (RBP4), secreted mostly by liver and adipocytes, is a member of lipocalin family transporting vitamin A from liver to peripheral tissues [1], so it is linked to obesity and its co-morbidities especially insulin resistance, type 2 diabetes, and certain components of metabolic syndrome [2]. Obesity especially visceral obesity is the major contributor for insulin resistance, type 2 diabetes and cardiovascular diseases [3]. The present study aimed to assess serum level of RBP4 and its correlation with insulin resistance in patients with visceral obesity and type 2 diabetes mellitus.

Materials and methods

This case control study was conducted on 74 subjects "aged from 38 to 50 years" being collected from November 2015 to June 2016 after taking an informed consent and approval by the Ethics Committee for medical research. Patients were divided into 3 groups:

Group 1: Included 27 type 2 diabetic patients treated by sulphonylurea.

Group 2: Included 28 viscerally obese patients (according to International Diabetes Federation (IDF) 2016 criteria for elevated waist circumference) [4].

Group 3: "Control group": Included 19 apparently healthy age and sex matched subjects. Individuals excluded from the study were diabetics taking insulin or insulin sensitizers (e.g.: metformin and glitazones), type 1 diabetics, pregnant and postmenopausal females, patients taking hormonal contraception and steroids as well as those taking medications affecting plasma lipid profile (e.g.: statins and fenofibrate), subjects with liver dysfunction, renal impairment, infection, and malignancy. Patients were subjected to medical history and clinical examination for signs of insulin resistance, anthropometric measurements [including body weight (kg), height (cm) using a fixed stadiometer, Body Mass Index (BMI) "kg/m^2", Waist Circumference (WC) "cm", Hip Circumference HP "cm" and Waist Hip Ratio (WHR) "cm". Waist circumference was measured with a tape midway between costal margin and iliac crest in mid-axillary line [5], in addition to analytical methods, which included:

1. Fasting glucose, 2 Hour postprandial, Total cholesterol (TC), HDL cholesterol (HDLc), and triglycerides (TG) measured by enzymatic assays, LDL-cholesterol levels calculated using Friedewald's equation: LDLc = TC-HDLc-TG/5 (mg/dl).

2. Hemoglobin A1c percentage using ion-exchange high-performance liquid chromatography (HPLC) technique.

3. Fasting serum insulin (FI) (μIU/mL) measured with a two-site chemiluminescent enzyme immunometric assay.

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Variables	Group 1(DM)	Group 2 (Visc. obese patients)	Group 3 (Control)
	N: 27	N: 28	N: 19
	Mean ± SD	Mean ± SD	Mean ± SD
Age (ys)	44.7 ± 6.26	41.43 ± 8.07	40.84 ± 4.67
BW (kg)	99.74 ± 31.34	93.71 ± 11.34	61.63 ± 8.35
BMI (kg/m²)	38.62 ± 10.86	36.05 ± 4.58	22.9 ± 2.41
WC (cm)	111.67 ± 13.91	108.14 ± 7.17	79.37 ± 7.57
HC (cm)	111.67 ± 15.26	112.34 ± 8.07	95.53 ± 5.09
WHR	1 ± 0.05	0.96 ± 0.07	0.83 ± 0.06
(BW: Body Weight, HT: Height, BMI: Body Mass Index, WC: Waist Circumference, HC: Hip Circumference, WHR: Waist Hip Ratio.			

Table 1: Descriptive data of the 3 studied groups regarding age and anthropometric measurements.

Variables	Group 1	Group 2	Group 3	P-value		
	(DM)	(Visc. Obese patients)	(Control)			
	N: 27	N: 28	N: 19			
	Mean ± SD	Mean ± SD	Mean ± SD	P1	P2	P3
FBG (mg/dl)	170.48 ± 71.27	103.11 ± 18.65	90.84 ± 70	0	0	0
2hpp (mg/dl)	267.04 ± 103.65	130.54 ± 28.56	120.5 ± 15.95	0	0	>0.05
HBA1C (%)	7.73 ± 1.22	5.72 ± 0.43	4.87 ± 0.4	0	0	0
FI (µIU/ml)	10 ± 9.76	2.3 ± 3.4	9.8 ± 5.6	0	>0.05	0
HOMA- IR	4.2 ± 4.48	0.57 ± 0.87	2.21 ± 1.34	0	>0.05	0
HOMA-B (%)	58.35 ± 64.4	26.57 ± 37.99	135.56 ± 75.65	0.035	0.001	0
Cholesterol (mg/dl)	209.44 ± 53.4	193.54 ± 23.38	139.16 ± 16.47	>0.05	0	0
Triglycerides (mg/dl)	155.67 ± 57.69	127.86 ± 49.32	130.42 ± 12.63	>0.05	>0.05	>0.05
HDL (mg/dl)	40.24 ± 10.85	43 ± 12.67	66.37 ± 51.98	>0.05	0	0
LDL (mg/dl)	125.53 ± 25.29	122.71 ± 21.93	103.53 ± 8.76	>0.05	0.001	0.001
RBP4 (µg/ml)	52.72 ± 25.79	52.48 ± 20.96	19.85 ± 16.31	>0.05	0	0
(FBG: Fasting Blood Glucose, 2HPP: 2 Hours Post Prandial, FI: Fasting Insulin, IR: Insulin Resistance, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein., RBP4: Retinol Binding Protein 4)						

Table 2: Comparison between the 3 studied groups regarding FBG, 2HPP, HBA1C, FI, HOMA-IR, HOMA-B%, cholesterol, Triglycerides, HDL, LDL and RBP4.

4. Insulin resistance (IR) index using Homeostatic Model Assessment HOMA-IR and B-cell function assessment using HOMA-β (9):

- HOMA-IR=Fasting Insulin (µU/ml) x fasting glucose (mg/dl) /405.
- HOMA- β= 360 × fasting insulin (µIU/ml)/fasting glucose (mg/dl)-63.

5. RBP4, expressed in ng/mL (normal range 2-28 ng/ml), measured with a competitive enzyme-linked immunoassay kit supplied by (Phoenix Pharmaceuticals, Inc., Belmont, CA).

6. CT scan of abdomen to measure visceral and subcutaneous fat amount.

Statistical methods

All data were analyzed using software (version 11, SPSS Inc., Chicago, Illinois). Parametric data were expressed as mean and standard deviation (X ± SD). Comparative statistics was done between two groups by Chi squared test and across all cohorts (Lean, Obese and Diabetics) by one-way ANOVA and post-hoc Tuckey analysis. Correlation analysis was performed by Pearson's correlation (r). P values <0.05 were considered significant, whereas values <0.01 or <0.001 were considered highly significant

Results

Study subjects were classified according to their BMI and WC into 3 main groups: Group 1: 27 obese diabetics, 12 males (44.4%) and 15 females (55.6%), Group 2: 28 Obese non diabetics, 12 males (42.9%) and 16 females (57.1%). Group 3 "control": 19 healthy non-obese, 8 males (42.1%) and 11 females (57.9%). Descriptive data of the 3 studied groups including anthropometric measurements (BW, BMI, WC, HC, WHR) are shown in Table 1. Lab results shown in Table 2: FBG, HBA1c % and 2 hr-pp blood glucose were significantly higher in group 1 and 2 compared to group 3. Fasting insulin (FI) and HOMA-IR were significantly higher in group 1 and 3 compared to group 2 but were non significantly different in group 1 compared to group 3. HOMA-B % was significantly higher in group 3 compared to group 1 and 2, it was significantly higher in group 1 compared to group 2. Cholesterol and

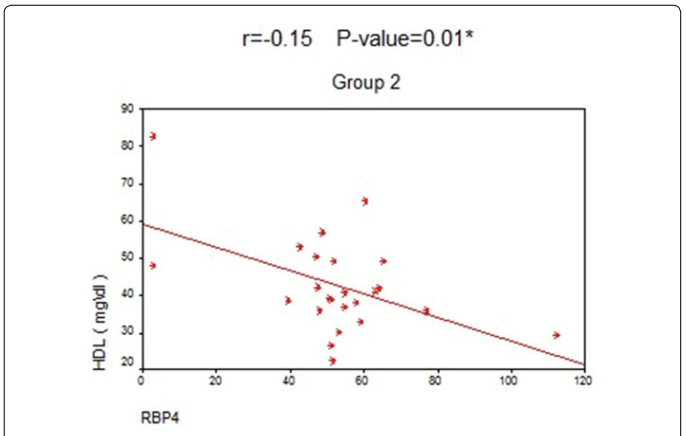

Figure 1: RBP4 was significantly negative correlated with BW and HDL.

LDL were significantly higher in group 1 and 2 compared to group 3 while HDL was significantly lower in group 1 and group 2 compared to group 3. RBP4 level was significantly higher in group 1 and 2 with mean (52.72 ± 25.79, and 52.48 ± 20.96 µg/ml) respectively compared to group 3 mean (19.85 ± 16.31 µg/ml) while there was non significant difference in group 1 compared to group 2.

There was non significant correlation between RBP4 & (anthropometric parameters, lipid profile, FBG, 2HPP, HBA1C, FI, HOMA-IR, HOMA-B) in group 1. RBP4 was significantly negative correlated with BW and HDL and significant positive correlated with FI, HOMA-IR in the group 2. (Figures 1 and 2) (Table 3)

Visceral and subcutaneous fat at level of L1 and L5 that were

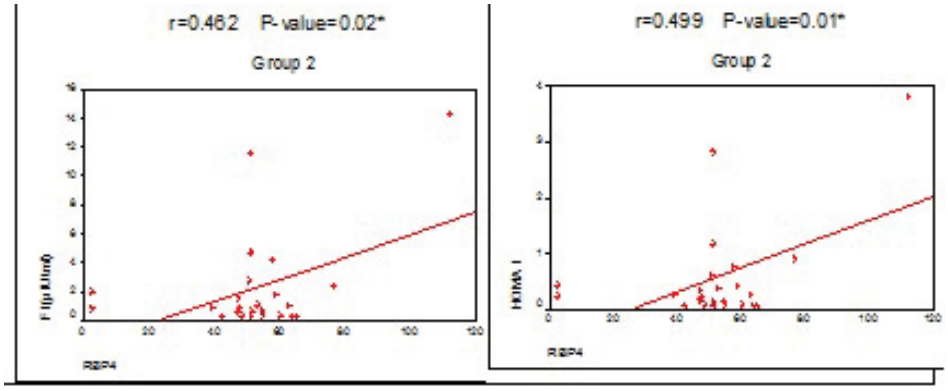

Figure 2: Significant positive correlated with FI, HOMA-IR in the Group 2.

Variables	RBP4 (µg/ml)			
	Group 1 (DM)		Group 2 (Visc. Obese Patients)	
	R	P	R	P
BW (kg)	0.02	>0.05	-0.41	0.049*
BMI (kg/cm²)	0.01	>0.05	-0.29	>0.05
WC (cm)	-0.095	>0.05	-0.07	>0.05
HC (cm)	-0.2	>0.05	-0.33	>0.05
WHR	0.34	>0.05	0.26	>0.05
Cholesterol (mg/dl)	0.11	>0.05	-0.37	>0.05
Triglycerides (mg/dl)	0.12	>0.05	0.16	>0.05
HDL (mg/dl)	0.05	>0.05	-0.15	0.01*
LDL (mg/dl)	-0.04	>0.05	-0.23	>0.05
FBG (mg/dl)	0.1	>0.05	0.16	>0.05
2hpp (mg/dl)	0.23	>0.05	0.08	>0.05
HBA1C %	-0.14	>0.05	-0.124	>0.05
FI (µIU/ml)	0.05	>0.05	0.462	0.02*
HOMA- IR	0.04	>0.05	0.499	0.01*
HOMA B %	0.11	>0.05	0.32	>0.05
Area 2 L1 (ml)	0.2	>0.05	0.39	>0.05
Area 2 L5 (ml)	-0.434	0.03*	0.21	>0.05
Area 6 L1 (ml)	-0.25	>0.05	-0.13	>0.05
Area 6 L5 (ml)	-0.349	>0.05	-0.37	>0.05

(BW: Body weight, BMI: body mass index, WC: Waist Circumference, HC: Hip Circumference, WHR: Waist Hip Ratio, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, FBG: Fasting Blood Glucose, 2 HPP: 2 Hours Post Prandial, FI: Fasting Insulin, Area 2 L1: Visceral Fat at the level of L1, Area 2 L5: Visceral Fat at the level of L5, Area 6 L1: Subcutaneous fat at the level of L1, Area 6 L5: Subcutaneous fat at the level of L5).

Table 3: Correlation between RBP4 and anthropometric measurements as well as lipid profile, studied Biochemical parameters and values of CT measurement of visceral & subcutaneous fat in group 1 and group 2.

Variables	Group1 (DM)	Group 2 (Visc. Obese Patients)	Group 3 (Control)	P-value		
	N: 26	N: 26	N: 19			
	Mean ± SD	Mean ± SD	Mean ± SD	P1	P2	P3
Area 2 L1(ml)	39.7 ± 18.48	38.36 ± 16.09	10.75 ± 7.84	>0.05	0	0
Area 2 L5 (ml)	37.59 ± 15.8	36.08 ± 12.83	10.97 ± 4.84	>0.05	0	0
Area 6 L1 (ml)	63.85 ± 37.01	63.02 ± 25.82	13.83 ± 8.94	>0.05	0	0
Area 6 L5 (ml)	101.46 ±53.07	114.94 ± 43.35	31.42 ± 18.46	>0.05	0	0

Table 4: Comparison between Values of CT measurements of visceral and sub-cutaneous fat (in ml) among studied groups.

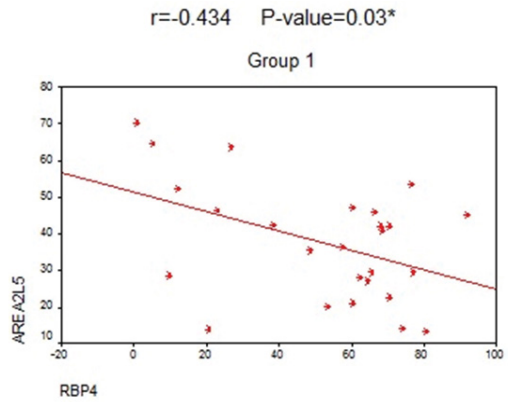

Figure 3: There was significant negative correlation between RBP4 and visceral fat.

significantly higher in group 1 and 2 compared to group 3 while there were non-significant difference in group 1 compared to group 2. Table 4 at level of L5 in group 1, there was significant negative correlation between RBP4 and visceral fat (area 2) (Figure 3).

Discussion

RBP4 may contribute to insulin resistance and type 2 diabetes by impairing insulin-stimulated glucose uptake in muscles and elevating hepatic glucose production [6, 7]. It also inhibits insulin-induced phosphorylation of insulin receptor substrate 1 (IRS1), and its expression is inversely related to glucose transporter 4 (GLUT4) in adipocytes [8].

Various adipokines, including RBP4, are considered as endogenous signal molecules involved in glucolipid metabolism, disturbing insulin signal pathways and promoting development of type 2 diabetes [9]. Therefore, this study aimed to assess serum level of RBP4 and its correlation with insulin resistance in patients with visceral obesity and type 2 diabetes mellitus.

FBG and HbA1c were significantly higher in visceral obese compared to control groups. This may be explained by high level of FFA, IR and impairment of glucose metabolism due to effect of some adipokines as RBP4. Bilir et al. studied the effects of fat distribution and some adipokines on insulin resistance in subjects with overweight and high WC (viscerally obese persons) in Turkey [10]. He reported that there was significantly higher FBG and 2hr-pp blood glucose in this group compared to controls.

In the current study, there were significantly higher level of serum cholesterol, LDL and lower level of HDL in visceral obese group compared to control group. This can be explained by high WC and BMI above the recommended values by WHO which had adverse effects on lipid profile. The same results were reported by Bora et al. who attributed the dyslipidemia to the effect of high BMI and WC [11].

In the current study, FI and HOMA-IR were significantly higher in diabetics compared to viscerally obese group but there was non-significant differences between diabetics and controls. Also Gomez-Ambrosi et al. [12] reported that there were higher FI, HOMA-IR and c-peptide in diabetic obese group with high WC compared to obese patients with normal and impaired glucose tolerance.

Regarding HOMA-B%, it was significantly higher in control and diabetic groups compared to viscerally obese group. This result is in agreement with Awad et al. [13] who found significantly higher HOMA-B% in lean normal glucose tolerant subjects compared to obese subjects with normal and impaired glucose tolerance, but in disagreement with them, they found that obese type 2 diabetics had lower HOMA-B% compared with obese normal glucose tolerance and impaired glucose tolerance subjects.

In the present study, there was significantly higher RBP4 in diabetics and viscerally obese groups compared to control group with no difference between diabetic and viscerally obese groups. This increase in the RBP4 could be explained by the fact that RBP4 levels are linked to increased visceral adipose tissue content. It is expressed preferentially in visceral fat when compared with subcutaneous fat which is high in diabetic and visceral obese groups [14]. These results were consistent with Budhitresna et al. [15] who found higher RBP4 in type 2 diabetes patients compared to controls. The high RBP4 plasma levels in type 2 diabetes subjects can be related to degree of obesity and IR. In agreement with our results, Derosa et al. [16] found that RBP-4 was significantly higher in obese subjects with high waist circumference compared to controls. Also, Eduardo et al. [17] found significant increase of RBP4 level in the obese group and viscerally obese groups when compared to the normal weight group.

In visceral obese group, there was significant negative correlation between RBP4 and body weight, while there was non-significant correlation with other anthropometric parameters. Similarly Scribner et al. [18] observed a significant increase of RBP4 proportional to the increase of body weight, BMI and percentage of body fat in viscerally obese patients. On contrary, Ulgen et al. [19] who found no significant correlation of serum RBP4 with BMI and waist-to-hip-ratio in viscerally obese patients.

In the current study, there was significant positive correlation between Rbp4 and IR markers (FI, HOMA-IR) in visceral obese group, while no correlations with FBG, 2 hpp blood glucose, HbA1c and HOMA-B%. These results are in agreement with Derosa et al. [16] who found significant positive correlation between RBP4 and HOMA-IR in viscerally obese patients.

On contrary Ulgen et al. [19] found no significant association of RBP4 levels with fasting glucose, 2hr-pp blood glucose, HOMA-IR, or HOMA-B in viscerally obese patients.

In the current study, there was significant negative correlation between RBP4 and HDL in viscerally obese group while no correlation with cholesterol, TG and LDL .The same results were reported by Ulgen et al. [19] who found no correlation as regard cholesterol and TG in visceral obese patients. Awad et al. [13] found significant positive correlations between plasma RBP4 concentration and LDL and on the other hand a negative correlation with HDL in obese subjects with or without impaired glucose metabolism. It is postulated that RBP4 raise lipid concentrations, especially triglycerides, which mediated through regulation of the expression of genes involved in lipid metabolism and its effect on liver fatty acid metabolism [20].

There was non-significant correlation between RBP4 and (anthropometric parameters, lipid profile, FBG, 2HPP, HBA1C, FI, HOMA-IR, HOMA-B) in the diabetic group.

In the present study, visceral (area 2) and subcutaneous fat (area 6) at the level of L1 & L5 were significantly higher in diabetic and viscerally obese groups compared to controls. Scheuer et al. [21] found that diabetics had higher visceral fat compared to visceral obese and

control groups, but regarding subcutaneous fat, it was higher in visceral obese group followed by controls than the diabetic group (by use of ultrasound not CT scan). Choi et al. [22] found significant higher visceral and subcutaneous fat at level of L5 in viscerally obese patients with high WC and BMI compared to controls.

In the current study, there was negative correlation between RBP4 and visceral fat at level of L5 in diabetic group. Also there was non-significant correlation between RBP4 and both visceral and subcutaneous fat in ml at level of L1 and L5 in viscerally obese group.

Conclusion

The current study demonstrated the value of RBP4 as an indicator of insulin resistance in type 2 diabetes and viscerally obese subjects as it was high in viscerally obese group as well as diabetics than control group. Also, RBP4 had significant positive correlation with FI & HOMA-IR in the viscerally obese group, so it may be a risk factor for type 2 diabetes in this group. RBP4 had significant negative correlation with HDL in the viscerally obese group, so it may act as a risk factor for cardiovascular disease. RBP4 had significant negative correlation with visceral fat at L5 in the diabetic group. Viscerally obese subjects should be monitored by HOMA-B% for early detection of impaired glucose tolerance aiming to delay the onset or prevent development of type 2 diabetes. Viscerally obese subjects should be assessed for serum Rbp4 as it is a good predictor for occurrence of type 2 diabetes and CVD. Weight reduction is recommended in viscerally obese and diabetic subjects to decrease amount of visceral fat and abnormal adipokines level as Rbp4 is implicated in the pathogenesis of type 2 diabetes and CVD.

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