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Serum Retinol Binding Protein 4 and Nonalcoholic Fatty Liver Disease in Some Egyptian Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Retinol binding protein 4 (RBP4) is a novel adipokine that closely associated with insulin resistance. **Objective:** Our aim was to investigate the association between RBP4 and nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM). **Study design:** 90 subjects were included in the study and divided into 3 groups: Group I; included 30 patients with T2DM who had NAFLD. Group II; included 30 patients with T2DM without NAFLD. Group III; included 30 healthy subjects matched for age and gender. Laboratory and anthropometric measurements including serum RBP4 levels were assessed. **Results**: RBP4 levels were highest in group I; 53.03±10.04 mg/l versus 46.9±9.85 mg/l in group II (p=0.02), while the least levels were in the control group; 35.06 ± 7.06 mg/l. RBP4 levels were negatively correlated with HDL cholesterol, while positively correlated with; fasting plasma glucose, 2-hour post prandial plasma glucose, HbA1c, fasting insulin, HOMA-IR, total cholesterol, triglycerides, LDL cholesterol, alanine aminotransferase and aspartate aminotransferase. **Conclusion:** Significant elevation of serum RBP4 in patients with T2DM and NAFLD demonstrates that it might contribute to the pathogenesis of NAFLD as well as it can be considered as a non-invasive biomarker of intrahepatic lipid content.

Keywords: T2DM, NAFLD, RBP4.

Introduction

The global epidemic of type 2 diabetes mellitus (T2DM) has become a major public health concern with serious social and economic consequences. Although major driving factors behind the epidemic are poor nutrition and lifestyle transitions, growing evidence supports a role of multiple adipokines in the pathogenesis of T2DM **(Sun et al., 2014)**.

Retinol-binding protein 4 (RBP4) was originally considered to be a retinol transport protein synthesized mainly by the liver **(Blaner et al., 1989)** until its expression in adipocytes was first discovered in 1992 **(Tsutsumi et al., 1992)**. More recently, RBP4 has been recognized as a novel adipokine that is elevated in the mouse model of insulin resistance (IR), as well as in patients with obesity and/or T2DM **(Yang et al., 2005)**.

However, in humans the link between RBP4 and IR is less clear. It was found that serum RBP4 correlated positively with presence of insulin resistance in individuals with obesity, impaired glucose tolerance, or T2DM, and was even increased in healthy individuals with a strong family history of T2DM **(Graham et al., 2006)**. Other reports have found no relationship between circulating RBP4 and IR **(Lewis et al., 2008)**.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western populations

and it has come to be recognized as the hepatic manifestation of the metabolic syndrome **(Alkhouri et al., 2009)**. IR is the pathophysiological hallmark of NAFLD. Although hepatocytes are regarded the principal source of circulating RBP4 under normal conditions, adipose tissue has the second highest expression level **(Tsutsumi et al., 1992)**. Changes in adipocyte derived RBP4 can have systemic effects on insulin sensitivity and glucose homeostasis. In the past decade, attention has been addressed to the role of RBP4 in patients with clinical or histological diagnosis of NAFLD **(Seo et al., 2008)**.

Aim of work:

The aim of this study was to investigate the association between RBP4 and nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM).

Subjects and Methods

Study population: This case control study was conducted at endocrinology outpatient clinic, faculty of medicine, Ain Shams University Hospitals. 90 subjects were included in the study. Subjects were divided into the following three groups: Group I; included 30 patients with T2DM who had NAFLD according to the ultrasonography criteria for the diagnosis of fatty liver (see later). Group II; included 30 patients with T2DM, matched for age and gender without any clinical features of liver diseases that had normal liver ultrasonic appearance and normal liver functions. Group III; included 30 healthy subjects matched for age and gender representing control group.

Subjects were excluded if they had known hepatitis B or C, as well as other liver diseases. Also, subjects with excessive alcohol consumption (≥30 g/d in men and ≥20 g/d in women) were excluded from the study. Other exclusion factors were diseases affecting the metabolic state or not suitable to participate in this study, such as endocrine disorders, neoplasm and any other chronic illness.

Anthropometrical measurements: Body height and weight were measured with the patient standing in light clothes and without shoes. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. Waist-to-hip ratio (cm/cm) was determined by measurement of the circumference of waist and hip in the standing position. Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the mid axillary line. Hip circumference was measured at the level of the anterior superior iliac spine. Blood pressure was measured in the supine position on the right arm after 10 min of rest. A standard sphygmomanometer of appropriate cuff size was used, and the first and fifth phases were recorded. Values used in the analysis are the average of three readings taken at 5- min intervals. The same physician performed all examination.

Biochemical measurements: Blood samples were drawn from each subject, 7 ml of venous blood was collected by venipuncture under complete aseptic conditions after an overnight fasting period of 8 hours for the measurement of fasting plasma glucose (FPG), fasting serum insulin and fasting serum RBP 4 levels. After completing 14 hours of fasting, another 3 ml of venous blood sample was collected for the measurement of lipid profile (total cholesterol, HDL-c and tiglycerides). Then a 75- gram glucose load was performed for the measurement of 2-hour post load plasma glucose (2-hour PPG).

Serum was centrifugated at 4.000 g for 10 min, immediately divided into aliquots, and frozen at -20°C until analysis. The serum glucose, lipid profile parameters and liver enzymes were determined using standard clinical biochemistry methods. The level of low-density lipoprotein (LDL)-cholesterol was estimated using the formula: total cholesterol-HDL-cholesterol-(Triglyceride/5). HbA1C was measured by high-performance liquid chromatography by means of a fully automated glycated hemoglobin analyzer system (Hitachi L- 9100). Fasting serum insulin concentrations were measured in duplicate by a monoclonal immuno-radiometric assay (the bio source INS-EASIA). Insulin resistance was estimated by homeostasis model assessment of IR (HOMA-IR). HOMA-IR was calculated using fasting glucose and insulin with the formula: HOMA-IR = glucose (mg/dl) x insulin (U/ml)/405.

Measurement of RBP4 was done by enzyme linked immunodorbent assay (ELISA). Retinol-binding protein (rbp) / rbp4 ELISA kit, Immundiagnostik AG, Stubenwald-Allee 8a, D-64625 Bensheim. This ELISA was used for quantitative determination of retinol-binding protein (RBP)/RBP4 in serum. In a first incubation step, RBP/RBP4 in the samples is bound to polyclonal rabbit anti RBP/RBP4 antibodies, immobilized on the microtitre plate. A peroxidase-conjugated anti RBP/RBP4 antibody is used for detection and quantification, and tetramethylbenzidine

(TMB) as a peroxidase substrate. Samples are quantified by referring their optical density to a lot-dependant master calibration curve and the use of a calibrator that is run with each test.

Abdominal ultrasonography: A fatty liver was diagnosed on ultrasonography by a single experienced radiologist who was blinded to the laboratory data. Of the four known criteria used for the diagnosis of fatty liver (hepatorenal echo contrast, liver brightness, deep attenuation and vascular blurring), the participants were required to have hepatorenal echo contrast and liver brightness for the diagnosis of fatty liver.

Statistical Analysis: All collected data were first assessed before taken for analysis. The normality test of Kosmogorov-Smirnov was done to assess whether the data were normally distributed or not. Unless otherwise stated, data represent the means±SD. Differences between parameters were tested using ANOVA or student's t-test, post hoc tests (least significant of difference) were performed for multiple comparisons between groups. Correlation between variables of interest was performed using Pearson's correlation. The significance of the test was determined according to the P value to be: non-significant (NS) if $P > 0.05$, significant (Sig) if $P < 0.05$, highly significant (HS) if $P < 0.01$.

Results

The characteristics of the study subjects are summarized in Table 1. The distribution of age and gender between the study groups was not different. And as expected, there was a highly significant difference regarding; BMI, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, 2-hour post prandial plasma glucose, HbA1c, fasting insulin, HOMA-IR, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and RBP4 levels between the three groups.

However, diabetic subjects with NAFLD in group I had a significantly greater BMI, waist-to-hip ratio, total cholesterol, triglycerides, LDL cholesterol, HbA1c, and RBP4 levels than diabetic subjects without NAFLD in group II. RBP4 levels were highest in group I; 53.03±10.04 mg/l versus 46.9±9.85 mg/l in group II (p=0.02), while the least levels were in the control group; 35.06 ± 7.06 mg/l (Fig. 1).

We also found a highly significant positive correlation between RBP4 levels and all of the following; BMI, waist-to-hip ratio systolic blood pressure, diastolic blood pressure, fasting plasma glucose, 2-hour post prandial plasma glucose, HbA1c, fasting insulin, HOMA-IR, total cholesterol, triglycerides, LDL cholesterol, ALT and AST. While there was a highly significant negative correlation between fasting RBP4 levels and HDL-C, data described in Table 2, (Fig. 2-5).

Discussion

RBP4 has been known as the retinol carrier in blood since the 1960s **(Kanai et al., 1968)**. Its emerging role as an ‘‘adipocyte-derived signal’’ of type 2 diabetes was first revealed by the work of Yang et al. when their animal model experiments suggested a close relation between RBP4 and systemic insulin resistance **(Yang et al., 2005)**. However, Mercader et al. showed that RBP4 concentration decreased in insulin-resistant fa/fa Zucker rats or remained unchanged in diet-induced obese rats when compared with lean controls **(Mercader et al., 2008)**.

Meanwhile, the relation between RBP4 and T2DM remains controversial in human studies. Results from previous studies were basically cross-sectional in nature and had relatively small sample sizes. For instance, Graham et al. found that circulating RBP4 was higher in 40 individuals with type 2 diabetes or impaired glucose tolerance than in 20 controls of normal glucose tolerance **(Graham et al., 2008)**, whereas Erikstrup et al. observed that RBP4 concentration was lower in patients with diabetes compared with those with normal glucose tolerance **(Erikstrup et al., 2006)**.

However, Meisinger et al. reported an independent association between RBP4 and prevalence of prediabetes in the Cooperative Health Research in the Region of Augsburg (KORA) F4 Study **(Meisinger et al., 2011)**. Also, Awad et al. showed that serum RBP4 levels are elevated in obese IGT and T2DM subjects**,** compared with lean subject and are associated with metabolic parameters of IR in agreement with our results **(Awad et al., 2013)**.

Luft et al. suggested that higher RBP4 levels predict type 2 diabetes in a long-term prospective study testing the hypothesis that higher plasma RBP4 con-centrations predict incident diabetes **(Luft et al. 2013)**.

And more recently, Sun et al. revealed that plasma RBP4 was positively correlated with BMI, waist circumference, blood pressure, total and LDL

Table 1. Anthropometric and metabolic characteristics of the study subjects

Variables		Group I (T2DM & NAFLD)	Group II (T2DM)	Group III (Control)	ANOVA	Tukey's test	
		Mean ± SD	Mean ± SD	Mean ± SD	P-value	Comp.	P-value
Age (years)		51.56 ±4.00	50.73±4.57	49.73 ± 3.58	0.224	-----	-----
Sex n(%)	**Male**	15 (50%)	15 (50%)	15 (50%)	1.000	-----	-----
	Female	15 (50%)	15 (50%)	15 (50%)			
SBP (mmHg)		139.83±6.62	137.5 ± 7.62	120.00 ± 3.93	<0.001*	I&II	**0.21**
						I&III	<0.001*
						II&III	<0.001*
DBP (mmHg)		91.50±3.51	89.66±5.07	75.50 ± 4.79	<0.001*	I&II	**0.109**
						I&III	<0.001*
						II&III	<0.001*
BMI (kg/m²)		32.13±3.70	29.73±2.28	23.55± 2.65	<0.001*	I&II	**0.003**
						I&III	<0.001*
						II&III	<0.001*
WHR		0.97±0.01	0.93±0.04	0.74± 0.02	<0.001*	I&II	<0.001*
						I&III	<0.001*
						II&III	<0.001*
FPG (mg/dl)		154.3±22.45	148.86±25.1	82.73± 6.37	<0.001*	I&II	**0.78**
						I&III	<0.001*
						II&III	<0.001*
2hPP.PG (mg/dl)		214.93±39.58	203.4±37.12	123.2±7.47	<0.001*	I&II	**0.24**
						I&III	<0.001*
						II&III	<0.001*
HbA1c (%)		10.15±1.09	8.46±1.51	5.3 ± 0.58	<0.001*	I&II	<0.001*
						I&III	<0.001*
						II&III	<0.001*
Fasting Insulin (mU/ml)		22.76±6.79	20.8±7.28	5.81± 0.57	<0.001*	I&II	**0.28**
						I&III	<0.001*
						II&III	<0.001*
HOMA IR		8.94±3.69	7.95±3.92	1.19± 0.20	<0.001*	I&II	**0.318**
						I&III	<0.001*
						II&III	<0.001*
Total Cholesterol (mg/dl)		219.13±30.34	190.86±27.9	153.73±16.05	<0.001*	I&II	<0.001*
						I&III	<0.001*
						II&III	<0.001*
Triglycerides (mg/dl)		196.53±47.92	164.43±51.5	108.4±15.46	<0.001*	I&II	**0.015**
						I&III	<0.001*
						II&III	<0.001*
Chol.HDL (mg/dl)		34.10±8.13	39.73±5.74	57.20±6.76	<0.001*	I&II	**0.003**
						I&III	<0.001*
						II&III	<0.001*
Chol.LDL (mg/dl)		172.82±23.51	150.03±19.08	120.61±14.35	<0.001*	I&II	**0.001**
						I&III	<0.001*
						II&III	<0.001*
ALT (IU/L)		38.13±8.34	18.8±3.26	17.33± 1.80	<0.001*	I&II	<0.001*
						I&III	<0.001*
						II&III	0.035
AST (IU/L)		26.23±4.40	21.46±3.39	19.43± 2.25	<0.001*	I&II	<0.001*
						I&III	<0.001*
						II&III	0.008
RBP4 (mg/L)		53.03±10.04	46.9±9.85	35.06 ± 7.06	<0.001*	I&II	**0.02**
						I&III	<0.001*
						II&III	<0.001*

*highly significant difference.

Table 2. Correlation analyses between RBP4 levels and various parameters in all subjects

Correlations		
Variables	**RBP4 (mg/L)**	
	r	**P-value**
Age (years)	0.14	0.188
SBP (mmHg)	0.54	<0.001*
DBP (mmHg)	0.53	<0.001*
BMI (kg/m²)	0.59	<0.001*
WHR	0.61	<0.001*
FPG (mg/dl)	0.60	<0.001*
2hPP.PG (mg/dl)	0.57	<0.001*
HbA1c (%)	0.57	<0.001*
Fasting insulin (mU/ml)	0.64	<0.001*
HOMA IR	0.61	<0.001*
Total Cholest (mg/dl)	0.56	<0.001*
Triglycerides (mg/dl)	0.50	<0.001*
Chol.HDL (mg/dl)	-0.62	<0.001*
Chol.LDL (mg/dl)	0.58	<0.001*
ALT (U/L)	0.57	<0.001*
AST (U/L)	0.46	<0.001*

***** highly significant difference.

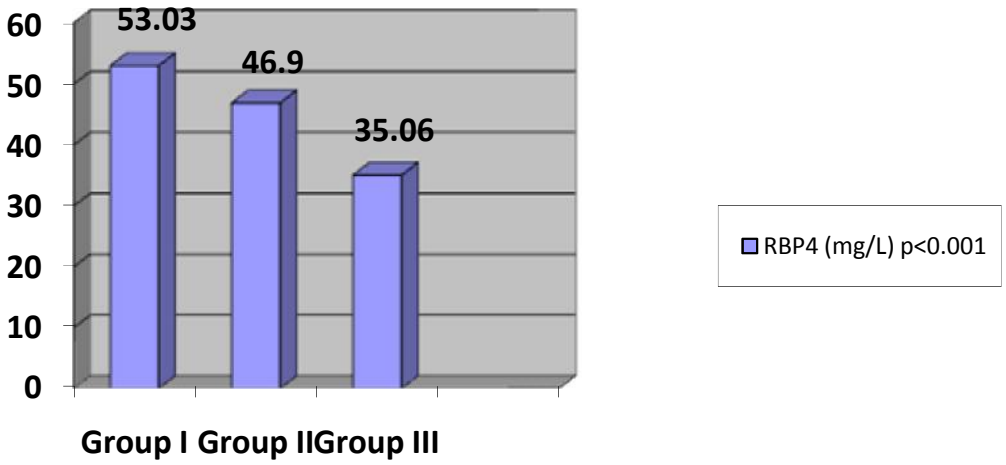

Figure 1: comparison between the studied groups regarding RBP 4 levels

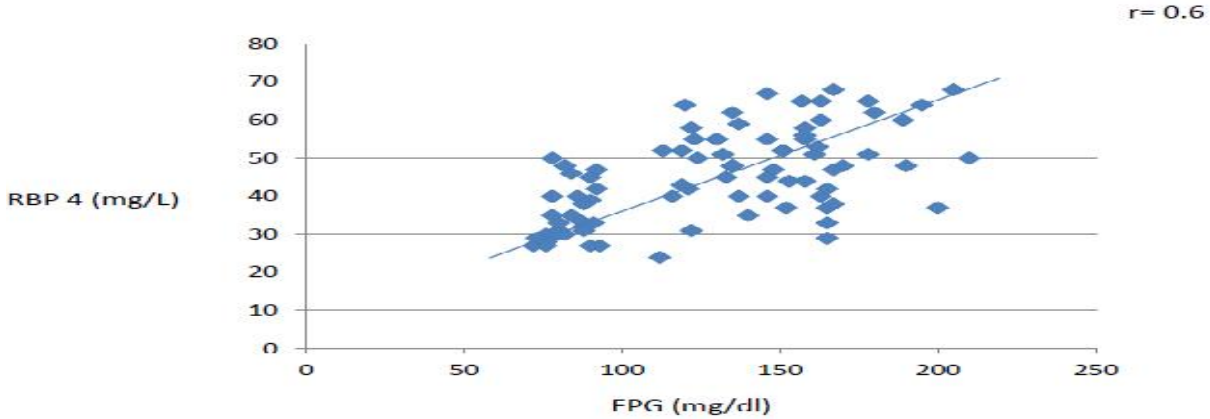

Figure 2: Correlation between serum RBP 4 and FPG

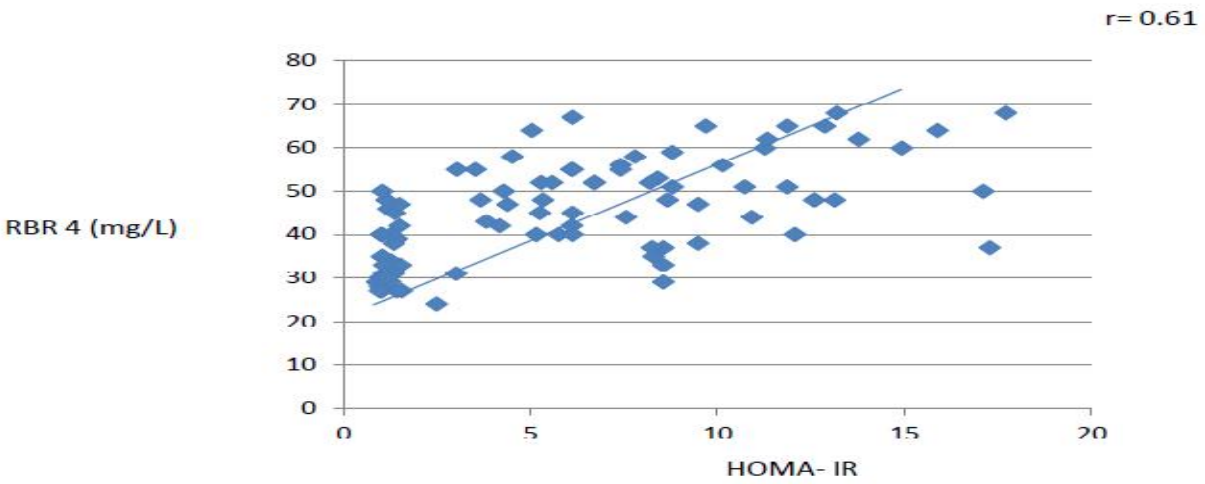

Figure 3: Correlation between serum RBP 4 and HOMA-IR

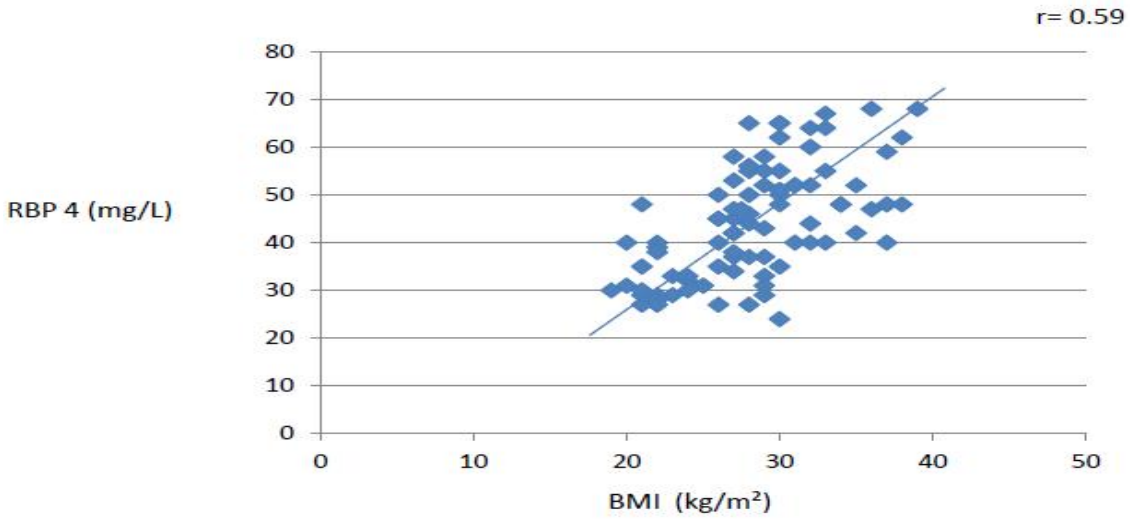

Figure 4: Correlation between serum RBP 4 and BMI

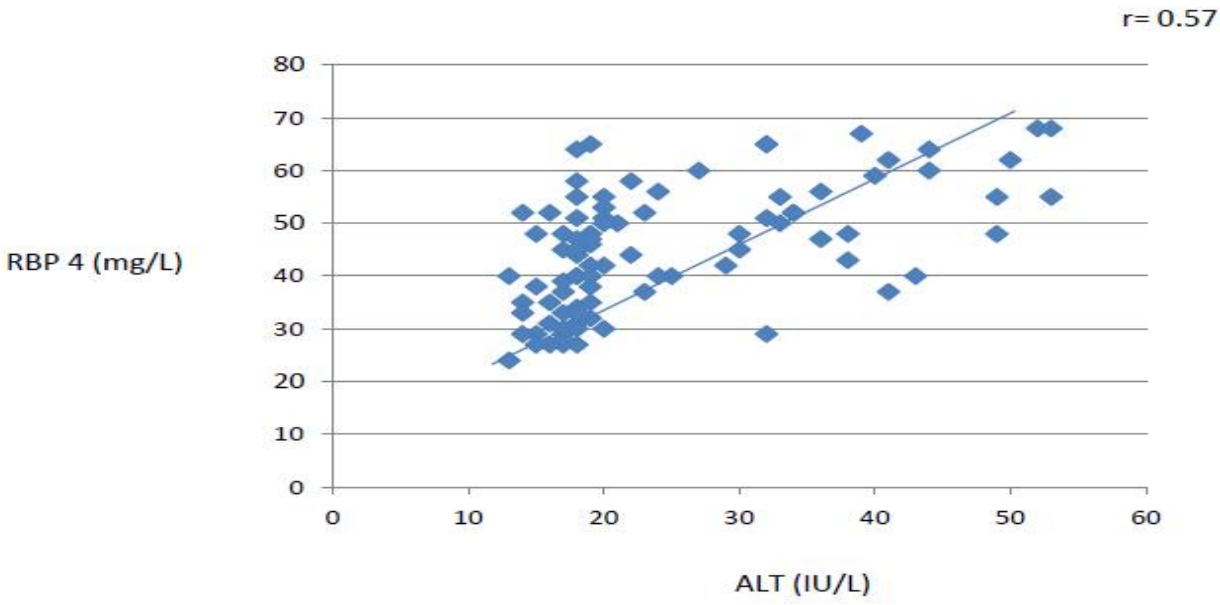

Figure 5: Correlation between serum RBP 4 and ALT

cholesterol, TGs, glycohemoglobin, insulin and HOMA-IR, but inversely correlated with HDL cholesterol, which is matched with our results in the current study. They also found a significant positive association between plasma RBP4 concentrations and risk of developing type 2 diabetes in a Chinese population after 6-y follow-up **(Sun et al., 2014)**.

However, in contrary to our results, previous studies in different populations failed to observe any association between circulating RBP4 levels, insulin sensitivity and type 2DM (**Lewis et al., 2008, Tajtakova et al., 2010)**. Also, Broch et al. showed no association between circulating RBP4 concentration and parameters of IR, they concluded that RBP4 could be one signal from insulin-resistant tissues that impacts on β-cell secretion and this mechanism could be behind the association between increased circulating RBP4 and type 2 DM **(Broch et al., 2007)**.

The discrepancies among different studies could be related to variations in study design and sample size, or characteristics of study populations (different ethnic populations in the studies, RBP4 genetic variation, and sex-specific dimorphism of RBP4). Notably, although ELISA methods have been used in most of the existing studies, the influence of inter-laboratory variations on the methodology cannot be completely ruled out.

Several mechanisms link RBP4 to IR and T2DM. Increasing serum RBP4 induces hepatic expression of the glyconeogenic enzyme phosphoenol-pyruvate carboxykinase and impairs insulin signaling in skeletal muscle **(Yang et al., 2005).** Insulin signaling in primary human adiocytes was affected by RBP4 through blocking the insulin-stimulated phosphorylation of insulin receptor-1 at serine in position 307**(Ost et al., 2007)**. Also, RBP4 may induce insulin resistance by stimulating inflammatory state in adipose tissue **(Norseen et al., 2012)**. Meanwhile, other researchers also revealed the underlying role of stimulated by retinoic acid 6, which could activate the Janus kinase/signal transducer and activator of transcription signaling cascade, in the link between RBP4 and insulin resistance **(Muenzner et al., 2013)**.

Increased serum RBP4 levels have been reported in subjects with other insulin-resistant states**.** It was reported that serum RBP4 levels associated negatively with insulin sensitivity (determined by a hyperinsulinemic euglycemic clamp) in non-diabetic **(Gavi et al., 2007)** or impaired glucose metabolism participants **(Yang et al., 2012)** and in women with polycystic ovary syndrome **(Weiping et al., 2006)** or in women with normal glucose tolerance with different obesity **(Kowalska et al., 2008)**.

However, there are some controversies among the previously published studies on the relationship between RBP4 and NAFLD. For instance, Seo et al. demonstrated that serum RBP4 concentrations are elevated in nondiabetic subjects with NAFLD compared to normal healthy controls, and that circulating RBP4 was an independent factor associated with NAFLD. RBP4 was found to be positively correlated with body mass index, waist circumference, waist-to-hip ratio, systolic and diastolic blood pressure, total cholesterol, triglycerides, LDL cholesterol, fasting glucose, HOMA as well as liver enzymes; AST and ALT **(Seo et al., 2008)**.

Also, Wu et al. demonstrated that serum RBP4 levels were elevated in diabetic patients with NAFLD. They found that increasing concentrations of RBP4 were independently and significantly associated with NAFLD in diabetic patients, which is matched with our results. Their results suggested that RBP 4 might contribute to the pathogenesis of nonalcoholic fatty liver disease **(Wu et al. 2008)**.

On the other hand, Milner et al. displayed no differences between the controls and the NAFLD adults (**Milner et al., 2009**). Furthermore, Schina et al. reported even lower serum RBP4 levels among the NAFLD individuals compared to the control group (**Schina et al., 2009**).

These findings suggest the existence of substantial differences in characteristics of study populations, and different methodologies of RBP4 examination and fatty liver grading.

RBP4 may influence the transactivation of retinoic acid-sensitive transcription factors such as retinoic acid receptor (RAR) and retinoic acid-X receptor (RXR) in NAFLD. RXRs bind to DNA as obligate heterodimers with peroxisome-proliferator activated receptors (PPARs) that regulate the transcription of genes involved in fatty acid metabolism **(Ferre, 2004)**. Another possible mechanism explaining the link between RBP4 and NAFLD is that changes in retinoid metabolism induced by RBP4 might alter the tissue level of retinol. A previous study reported that normalization of circulating RBP4 by synthetic retinoid improves insulin resistance **(Yang et al., 2005)**.

Conclusion

Our study investigated the association between RBP4 and NAFLD in patients with T2DM, we found that serum RBP4 levels were significantly elevated in diabetic patients with NAFLD. These findings suggest that RBP 4 might be related to pathogenesis of NAFLD. Additional researches are needed to confirm our results and elucidate potential biologic mechanisms underlying this association. RBP4 can also be considered as a currently available non-invasive biomarker of intrahepatic lipid content in obese individuals, in whom the sensitivity of a sonography is decreased due to an increase of abdominal wall thickness by fat deposits. Nonetheless, these findings need to be confirmed in larger studies with biopsy proven NAFLD in order to introduce RBP4 as an alternative diagnostic method of NAFLD.

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