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ROLE OF RETINOL-BINDING PROTEIN 4 IN OBESE ASIAN INDIANS WITH METABOLIC SYNDROME

ULOGA RETINOL-VEZUJUĆEG PROTEINA 4 KOD GOJAZNIH INDIJACA SA METABOLIČKIM SINDROMOM

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Summary: Retinol-binding protein 4 is an adipocytokine separately implicated in the development of obesity-related insulin resistance and proatherogenic lipid profile, however, its role in humans is unclear. This study was carried out to assess the role of retinol-binding protein 4 as a potential marker of metabolic syndrome in obese Asian Indians (a high-risk population for diabetes). 52 obese (BMI >23 kg/m^2) Asian Indians were grouped into those with and without metabolic syndrome based on IDF criteria and compared with healthy controls. The anthropometric and biochemical parameters (fasting blood sugar, lipid profile, serum insulin, high-sensitivity C-reactive protein, and retinol-binding protein 4) were estimated. The obese groups had significantly altered adiposity indices, insulin resistance parameters (fasting blood sugar (only in the metabolic syndrome group), serum insulin, HOMA-IR and QUICKI), index of inflammation (C-reactive protein) and proatherogenic dyslipidemic profile (serum triglycerides, VLDL-cholesterol, and triglyceride/HDL-cholesterol ratio). Retinol-binding protein 4 levels were elevated in the obese groups, but were not significant. Retinol-binding protein 4 levels were correlated with anthropometric parameters and atherogenic lipids, while C-reactive protein was correlated with anthropometric and insulin resistance parameters in the entire group of subjects. Although these correlations were not observed in the obese groups, in the control group, retinol-binding protein 4 was

Kratak sadržaj: Retinol-vezujući protein 4 je adipocitokin koji ima zasebnu ulogu u razvoju insulinske rezistencije u gojaznosti i proaterogenog lipidskog profila, međutim, ona kod ljudi nije razjašnjena. Ova studija izvedena je kako bi se utvrdila uloga retinol-vezujućeg proteina 4 kao potencijalnog markera metaboličkog sindroma kod gojaznih Indijaca (populacije sa visokim rizikom za šećernu bolest). Pedeset dvoje gojaznih ispitanika (indeks telesne mase > 23 kg/m^2) podeljeni su na one sa i bez metaboličkog sindroma na osnovu kriterijuma IDF i upoređeni sa zdravim kontrolnim subjektima. Određeni su antropometrijski i biohemijski parametri (šećer u krvi, lipidski profil, insulin u serumu, visokoosetljivi C-reaktivni protein i retinol-vezujući protein 4). U gojaznim grupama značajno su bili izmenjeni adipozni indeksi, parametri insulinske rezistencije (šećer u krvi (samo u grupi sa metaboličkim sindromom), insulin u serumu, HOMA-IR i QUICKI), indeks inflamacije (C-reaktivni protein) i proaterogeni dislipidemijski profil (trigliceridi, VLDL-holesterol i odnos trigliceridi/HDL-holesterol u serumu). Nivoi retinol-vezujućeg proteina 4 bili su u korelaciji sa antropometrijskim parametrima i aterogenim lipidima, dok je C-reaktivni protein korelisao sa antropometrijskim kao i parametrima insulinske rezistencije kod svih ispitanika obuhvaćenih studijom. Iako ove korelacije nisu uočene u gojaznim grupama, retinol-vezujući protein 4 bio je u korelaciji sa lipidskim parametrima a C-reaktivni protein sa adipoz-

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List of abbreviations: BMI = body mass index; CVD = cardiovascular disorders; DBP = diastolic blood pressure; FBS = fasting blood sugar; HDL-C = HDL-cholesterol; HC = hip circumference; HOMA-IR = homeostasis model assessment of insulin resistance; Hs-CRP = high sensitivity C-reactive protein; ICO = index of central obesity; IDF = International Diabetes Federation; IR = insulin resistance; MS = metabolic syndrome; QUICKI = quantitative insulin sensitivity check index; RBP4 = retinol binding protein 4; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; VLDL-C = VLDL-cholesterol; WC = waist circumference; WHR = waist: hip ratio.

correlated to the lipid parameters and C-reactive protein to adiposity indices. Thus, the role of retinol-binding protein 4 as a potential marker of metabolic syndrome is limited to the prediction of proatherogenic risk among Asian Indians.

Keywords: retinol-binding protein 4, obesity, metabolic syndrome, Asian Indians, insulin resistance

nim indeksima. Stoga je uloga retinol-vezujućeg proteina 4 kao potencijalnog markera metaboličkog sindroma ograničena na predviđanje proaterogenog rizika kod Indijaca.

Ključne reči: retinol-vezujući protein 4, gojaznost, metabolički sindrom, Indijci, insulinska rezistencija

Introduction

The impact of lifestyle modifications and socioeconomic transitions on the population of developing countries has led to the growing prevalence of obesity and MS (1). In spite of several definitions with disparities in their criteria and cut-off limits, the diagnosis of MS in different populations is still difficult and poses severe social, economic and health problems to the community (2). Several approaches to identify potential markers of MS like Hs-CRP (3), oxidative stress (4) and IR parameters (including the adipocytokines) (5) have been made.

Genetic predisposition, nutritional and environmental transitions result in obesity (6). Obesity is linked IR, which in turn promotes the development of type 2 diabetes mellitus, dyslipidemia and related cardiovascular disorders (7). IR is a major cause of impaired insulin action in adipose tissue, skeletal muscle and liver (8). The adipose tissue produces and secretes a variety of adipocytokines: alterations in the expression or secretion of these adipokines probably contribute to the development of obesity and related disorders (5, 9).

Retinol-binding protein 4 (RBP4), a specific carrier of retinal in the blood, is secreted by the liver and adipose tissue (5). RBP4 has been shown to be a modulator of insulin sensitivity in animal models – an overexpression of RBP4 generates IR in mice (10). However, the role of RBP4 in humans is controversial. While some reports have associated elevated RBP4 with IR (11), other studies have not demonstrated any role for RBP4 in IR (12, 13); on the other hand, RBP4 levels have been implicated with markers of inflammation and lipid profile (12).

A recent study on the prevalence of MS in a rural population of South India from our Department has indicated that although 17.8% and 20.5% of the subjects exhibited MS using modified NCEP-ATP III (14) and IDF criteria (15), respectively, only a small minority of 38.5% of those diagnosed as MS were common to both definitions (unpublished data). Thus, a large majority of the cases of metabolic syndrome will go undiagnosed if only one definition is applied. This suggests the need for better markers to delineate the MS population. Hence, a comparative study of the anthropometric and biochemical parameters including the levels of RBP4, Hs-CRP, fasting insulin and lipid profile in obese subjects with and without metabolic syndrome from a semi-urban population (residing adjacent to the above mentioned rural population) has been made to elucidate the role of RBP4 as a marker of MS.

Materials and Methods

Adult subjects attending the Endocrine Clinic at the M.S. Ramaiah Hospitals, Bangalore, South India, were recruited after informed consent. The study protocol was approved by the Ethics Review Board of the Institution.

The subjects of either sex aged between 25 and 50 years were divided into 3 groups: Group I (controls): 26 adult non-obese healthy volunteers with BMI < 23 kg/m^2; Group II (obesity): 26 adult normotensive, normoglycemic obese subjects with BMI > 23 kg/m^2 as cut off for obesity as per WHO standards for Asians (16); Group III (metabolic syndrome): 26 adults with BMI ≥ 23 kg/m^2 and metabolic syndrome (IDF criteria (15)) (hyperglycemia and hypertension/dyslipidemia).

The inclusion criteria were: subjects between 25 and 50 years of age of either sex diagnosed as simple obesity without metabolic syndrome (Group II) and with obesity and metabolic syndrome (hyperglycemia and hypertension/dyslipidemia) (Group III). The exclusion criteria included: subjects with diabetes mellitus and other endocrine disorders, systemic disorders like hypertension, ischemic heart disease, asthma (Group II); subjects with secondary endocrine disorders (Group III). Smokers, tobacco users, alcoholics, those on other medication like vitamins, steroids and antioxidants and subjects with acute illness or chronic inflammatory conditions were excluded from the study.

A detailed clinical examination and family history were taken of all the subjects.

Anthropometric measurements including height, weight, waist (WC) and hip circumferences (HC) were measured as per standard procedures. BMI (Body mass index), waist: hip ratio (WHR) and the index of central obesity (ICO) (WC/height) (17) were calculated.

Analytical Methods

Blood samples were drawn, after a 12-hour overnight fast, for the determination of fasting blood glucose (FBS) (Enzymatic kit, BioSystems, S.A. Barcelona, Spain), triglycerides (TG) (Enzymatic kit, BioSystems, S.A. Barcelona, Spain), total cholesterol (TC) (Enzy-

matic kit, BioSystems, S.A. Barcelona, Spain) and HDL-cholesterol (HDL-C) (Enzymatic kit, BioSystems, S.A. Barcelona, Spain). VLDL-cholesterol (VLDL-C) and LDL-cholesterol (LDL-C) were calculated using Friedwald's equation.

Hs-CRP was estimated using the Latex-high sensitivity immunoturbidimetric kit method (BioSystems, Barcelona, Spain). The intra-assay and inter-assay coefficient of variation were 1.8 and 3.6%, respectively. Serum fasting insulin levels were estimated by immunoradiometric assay (Immunotech a.s., Prague, Czech Republic). The intra-assay and inter-assay coefficient of variation were 4.3 and 3.4%, respectively. RBP4 was assayed by a quantitative sandwich enzyme immunoassay technique (Quantikine Human RBP4 Immunoassay, R & D Systems, Inc., Minneapolis, USA). The intra-assay and inter-assay coefficient of variation were 5.7 and 5.8%, respectively. Homeostasis model assessment of insulin resistance (HOMA–IR) [insulin (μU/mL) × glucose (mmol/L) /22.5] (18) and the Quantitative insulin sensitivity check index [QUICKI = 1/[log (fasting insulin (mU/L) + log (fasting glucose (mg/dL)] (19) were calculated.

Statistical Analysis

The data are presented as mean ± SD. Statistical analysis was done using SPSS version 13 software. Analysis of variance (ANOVA) was used for the comparison of the three groups. Multiple comparisons were made by Bonferroni test and chi-square test. Pearson's correlation coefficient was calculated. $P<0.05$ was taken as significant.

Results

The anthropometric characteristics of the three groups of subjects are presented in *Table I*. The BMI was significantly increased in both the obese groups (II and III). The WC and ICO were also elevated in Group II and further increased in Group III suggesting the presence of visceral obesity. However, the WHR did not show any significant change. The blood pressure was significantly increased only in Group III.

In *Table II*, the biochemical parameters of the three groups are presented. While there was no significant increase in fasting blood sugar in Group II, a significant increase was observed in Group III. Fasting serum insulin levels were elevated significantly in both Groups II ($P<0.0001$) and III ($P=0.012$) in comparison to Group I. HOMA-IR also showed a similar pattern to fasting insulin while QUICKI (insulin sensitivity) concomitantly decreased in both the obese groups.

The TG ($P=0.005$) and VLDL-cholesterol ($P=0.004$) levels were significantly increased only in Group III in comparison to Group I. The other lipid

Table I Anthropometric parameters of Group I (controls), Group II (obese without metabolic syndrome) and Group III (obese with metabolic syndrome) subjects. [Mean ±SD]

Parameter	Group I n = 26	P value I vs. II	Group II n = 26	P value II vs. III	Group III n = 26	P value III vs. I
Age, years	39.27 ± 6.84	–	39.27±6.36	–	41.81±5.96	–
Sex, Male/Female	7/19	–	9/17	–	9/17	–
Weight, kg	52.69±5.86	<0.0001	67.73±8.74	–	72.54±10.93	<0.0001
Height, cm	158.58±6.80	–	159.12±9.21	–	159.88±9.03	–
BMI, kg/m^2	20.94±1.81	<0.0001	26.79±3.20	–	28.44±4.32	<0.0001
WC, cm	76.19±6.93	<0.0001	87.27±7.76	0.002	95.77±10.96	<0.0001
HC, cm	87.04±7.02	<0.0001	96.85±8.40	0.007	104.38±9.99	<0.0001
WHR	0.87±0.06	–	0.90±0.07	–	0.91±0.06	–
ICO	0.48±0.04	0.001	0.55±0.06	0.015	0.60±0.08	<0.0001
Systolic BP, mm Hg	120.69±7.24	–	125.62±7.78	<0.0001	141.46±14.70	<0.0001
Diastolic BP, mm Hg	77.38±4.07	–	81.85±5.36	<0.0001	90.85±11.19	<0.0001

P values of < 0.05 are considered as significant and are indicated.

Table II Biochemical parameters of Group I (controls), Group II (obese without metabolic syndrome) and Group III (obese with metabolic syndrome) subjects. [Mean ±SD]

Parameter	Group I n = 26	P value I vs. II	Group II n = 26	P value II vs. III	Group III n = 26	P value I vs. III
FBS, mmol/L	5.08±0.55	–	5.17±0.59	<0.0001	8.40±3.21	<0.0001
Serum insulin, pmol/L	29.45±13.82	<0.0001	61.74±36.04	–	52.64±29.79	0.012
Hs-CRP, mg/L	1.12±1.07	0.028	2.49±2.30	–	3.16±1.96	<0.0001
RBP4, mg/L	26.80±12.68	–	30.60±13.77	–	36.13±15.84	–
TG, mmol/L	1.44±0.75	–	2.03±1.01	–	2.42±1.39	0.005
TC, mmol/L	5.28±1.36	–	5.48±1.04	–	6.27±2.46	–
HDL-C, mmol/L	0.76±0.26	–	0.64±0.21	–	0.63±0.17	–
LDL-C, mmol/L	3.86±1.35	–	3.91±1.18	–	4.53±2.41	–
VLDL-C, mmol/L	0.65±0.34	–	0.93±0.47	–	1.11±0.64	0.004
TG/HDL-C	4.78±2.79	0.039	8.45±6.16	–	9.34±5.95	0.007
HOMA-IR	0.97±0.48	0.007	2.04±1.20	–	2.71±1.68	<0.0001
QUICKI	0.40±0.06	0.008	0.36±0.05	–	0.34±0.03	<0.0001

P< 0.05 is taken as significant and has been indicated.

Table III Correlations of Hs-CRP with selected anthropometric and biochemical variables in the entire group of subjects. [Groups I+II+III; n=78.] Pearson's correlation coefficient (r) and P values are shown.

Variable	r	P
BMI	0.513	0.000
WC	0.456	0.000
HC	0.467	0.000
ICO	0.538	0.000
Systolic BP	0.280	0.013
Diastolic BP	0.310	0.006
Serum insulin	0.235	0.038
HOMA-IR	0.246	0.030
QUICKI	-0.276	0.014

Table IV Correlations of RBP4 with selected anthropometric and biochemical variables in the entire group of subjects. [Groups I+II+III; n=78.] Pearson's correlation coefficient (r) and P values are shown.

Variable	r	P
WC	0.318	0.005
HC	0.315	0.006
Systolic BP	0.255	0.026
Diastolic BP	0.260	0.023
FBS	0.247	0.032
TG	0.413	0.000
TC	0.300	0.008
VLDL-C	0.414	0.000
TG/HDL-C	0.318	0.005

parameters did not show any significant alteration in any of the groups (*Table II*).

Hs-CRP levels were significantly elevated in Groups II (P=0.028) and III (P<0.0001) when compared with the control group I. However, RBP4 levels showed a slight increase in Groups II and III which was not significant (*Table II*).

The Pearson's correlation analysis for the entire group of subjects (Groups I+II+III) for Hs-CRP and significant adiposity indices and biochemical parameters is presented in *Table III*. Hs-CRP is significantly correlated with BMI, WC, ICO (indices of obesity – mainly visceral), blood pressure and IR parameters (insulin levels, HOMA-IR and QUICKI (negative correlation)). The correlation analysis for RBP4 and significant

anthropometric and biochemical parameters for the entire group of subjects (Groups I+II+III) is given in *Table IV*. There was a positive correlation between RBP4 and WC, HC, blood pressure, fasting blood sugar and lipid parameters (TG, TC, VLDL-cholesterol and TG/HDL-C ratio). In Group I there was also a significant correlation between CRP and the parameters of adiposity (BMI, WC, HC, WHR and ICO), but not with IR (data not shown). There were no such correlations observed in the individual Groups II and III. Similarly, only in Group I, RBP4 was correlated to systolic blood pressure and lipid parameters (TG, TC, and VLDL-C and TG/HDL-C ratio); however, there were no such correlations in Groups II and III when considered individually.

Discussion

The study group belonged to a semi-urban area of South India, where there is a significant rise in obesity and MS due to nutritional transitions and lifestyle modifications (2, unpublished data of Dharmalingam et al.). The subjects were grouped into obese with and without MS based on the BMI of > 23 kg/m^2 for obese as per Asian Standards (16). While an increase in BMI indicates the presence of abnormalities (20), the risk associated with overweight/obesity is further dependent on the location of the excess fat (21). Hence, the inclusion of parameters like WC could augment the identification of high-risk abdominally obese patients with increased BMI (20). The obese subjects in this study had increased WC and ICO in comparison with controls indicating the presence of visceral obesity.

Adipose tissue dysfunction is known to be related to the development of metabolic diseases linked to obesity: MS, type 2 diabetes mellitus and CVD (22). Inflammation is an important manifestation of the adipose tissue dysfunction and is closely related to IR. The significant elevation of Hs-CRP levels in the obese group, which is further enhanced in the MS group, shows the presence of low-grade inflammation. There was a positive correlation of Hs-CRP with BMI, WC, ICO and the parameters of IR (HOMA-IR, QUICKI and fasting insulin levels) in the entire group of subjects (Groups I+II+III); however, this correlation with IR parameters was not apparent in the three groups when considered individually.

The adipose tissue produces various adipocytokines and alterations in the expression or secretion of these molecules probably contribute to the development of obesity and related disorders like MS, type 2 diabetes mellitus and CVD (9). RBP4, an adipocytokine, expressed both in the visceral and subcutaneous fat of humans, is proposed to be involved in the regulation of systemic glucose metabolism and in the pathogenesis of IR (23). In this study, the serum RBP4 levels showed an increase, which was not significant, in the obese groups as also observed by Shim et al. (24). Further, there was no correlation, in any of the groups, between RBP4 and the parameters of inflammation, like Hs-CRP, as also reported by Broch et al. (25). Balagopal et al. (26) have reported a positive correlation between RBP4 and Hs-CRP in a small group of adolescents, whereas Takebayashi et al. (27) did not observe any correlation in the two parameters in hospitalised type 2 diabetes patients. RBP4, secreted from the liver, is bound to transthyretin, which is a negative acute phase reactant (28); hence, RBP4 levels may decrease during acute inflammation. In the positive acute phase response, Baeten et al. (29) have observed a decrease in the serum RBP4 levels. However, in this study there was a slight increase in RBP4 levels and a significant increase in the Hs-CRP levels in the obese groups, suggesting that subclinical inflammation did not affect RBP4 in these groups.

The significantly elevated levels of fasting insulin and HOMA-IR and decreased QUICKI indicate the presence of IR in both the obese groups. The increased Hs-CRP levels also corroborate the presence of IR in the obese groups (30). However, the role of RBP4 in IR seems controversial. Earlier studies (12, 13) have not found any correlation between RBP4 levels and IR, which is in contrast to other reports (31, 32) wherein an association of RBP4 levels and IR has been indicated. In this study also there was no correlation between RBP4 levels and IR in any of the groups. Genetic variants of RBP4 have been implicated in the susceptibility to type 2 diabetes and IR, possibly through the expression of RBP4 (33). Therefore, polymorphism in RBP4 may be responsible for the differences in RBP4 levels as also observed by Munkhtulga et al. (34) and in IR susceptibility (33). Further, a recent study on twins suggests that the association of RBP4 with IR is secondary and non-causal (35).

In the obese group with MS, there was a significant increase in TG and VLDL-C levels in comparison to control or obese without metabolic syndrome groups. There was a correlation between RBP4 and these lipid parameters when the entire group (Groups I+II+III) was considered and also individually with only the control group. The elevation in TG and VLDL-C levels were independent of RBP4 levels in the obese groups. The circulatory RBP4 levels are probably linked to the proatherogenic lipids (5). Serum RBP4 levels have been significantly and independently associated with hepatic lipase activity in patients with type 2 diabetes mellitus and coronary artery disease but not with controls (12). Hepatic lipase hydrolyses VLDL TG leading to the accumulation of proatherogenic small, dense LDL particles, which are accompanied by the presence of increased TG and decreased HDL in MS (36). The elevated TG/HDL-C ratio is also a marker of small, dense, proatherogenic LDL particles (37). The observed elevation in TG/HDL-C ratio indicates a greater population of small, dense, proatherogenic LDL particles and increased risk for the development of CVD.

Conclusions

The role of RBP4, as a marker for IR/MS, seems limited in this ethnic group probably due to the presence of genetic variants. However, the association of RBP4 with the TG/HDL-C ratio indicates its predictive nature for CVD, but does not contribute any further information over traditional risk factors for CVD.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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