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Influence of obesity on the serum concentration of retinol-binding protein 4 (RBP4) in young adults

Influência da obesidade sobre a concentração sérica da proteína ligadora do retinol 4 (RBP4) em adultos jovens

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ABSTRACT

Introduction: Obesity is a chronic low-grade inflammation, in which macrophages play an important role in the maintenance of inflammation by producing pre-inflammatory and inflammatory substances such as retinol-binding protein 4 (RBP4), which acts as a trigger for adipose tissue inflammation and associated with obesity co-morbidities. **Objective:** This study evaluated the serum concentration of RBP4 and biomarkers of insulin resistance (IR) in young adult patients with normal weight, overweight and obese. **Methods:** A cross sectional study was conducted involving 149 subjects: 54 healthy individuals (32 women and 22 men), 27 overweight (17 women and 10 men) and 68 obese (41 women and 27 men). The anthropometric measures and the concentrations of RBP4, insulin, HbA1c and glucose were determined, in addition to the calculations for homeostatic model assessment of insulin resistance (HOMA-IR) and insulin sensitivity (IS). **Results:** overweight and obese patients showed significantly higher levels of glucose, HbA1c, insulin, and HOMA-IR ($p < 0.0001$), and decreased IS ($p > 0.0001$) when compared with the normal weight group. There was an increase in RBP4 proportional to the increase in body mass index (BMI); the obese group showed significantly higher levels ($p < 0.05$). **Conclusion:** This study suggests that RBP4 may play a key role in the development of inflammation and IR in young obese individuals, as it may promote significant disturbances in insulin metabolism and may contribute to the development of obesity-related co-morbidities. This parameter can represent a hope in the identification of new inflammatory and IR markers to assist in the diagnosis and follow-up of overweight and obese patients.

Key words: retinol-binding proteins; obesity; insulin resistance; glucose.

INTRODUCTION

Obesity is characterized by the accumulation of regional or generalized adipose tissue, associated with chronic low-grade inflammatory process[1]. Annually the number of obese individuals increases about 1% among adults. This increase is related to food consumption and sedentary lifestyle. Its determinants are of genetic, nutritional, demographic, socioeconomic, epidemiological and cultural nature, as well as environmental issues, making obesity a multifactorial disease[2].

Brazilian society experienced a peculiar and rapid nutritional transition from a country that had high rates of malnutrition in the 1970s, to a country with more than half of the adult population overweight. According to the Risk Factors Surveillance System for Chronic Diseases Protection by Telephone Inquiry (Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico) from 2014, Brazil is the fifth country worldwide with overweight adult population (52.5%), however the survey conducted by the Brazilian Institute of Geography and Statistics [Instituto Brasileiro de Geografia e Estatística (IBGE)] showed, in 2015, an index that is close to 60%[3].

Obesity and overweight induce the development of numerous co-morbidities, among them insulin resistance (IR), which is presented as a mechanism of physiological adjustment that acts in order to increase the weight gain, influencing glucose and lipids metabolisms[4].

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Several markers are being investigated to evaluate IR, especially in obese patients, such as the retinol-binding protein 4 (RBP4). This protein is produced by the liver and macrophages and has the ability to increase IR in muscles and the hepatic gluconeogenesis, and may be a central mediator of IR in obesity, demonstrating a strong relationship with the development of type 2 diabetes *mellitus* (DM2)[5].

Recent studies have shown that RBP4 levels are increased in obese humans and animal models with IR. Moreover, the administration of RBP4 in normal mice promoted the onset of IR[6]. Some studies show a strong correlation between increased RBP4 serum levels and the severity of IR, obesity and components of the metabolic syndrome, including hypertension[7], dyslipidemia[8], waist-hip ratio[8], cardiovascular diseases[9] and amount of intra-abdominal fat[10], but others do not demonstrate these correlations[11, 12].

Cho *et al*. (2006)[13], investigated the relationship between RBP4 plasma concentration and several metabolic parameters in humans, they found that RBP4 was increased in subjects with glucose intolerance and DM2 when compared with subjects with normal glucose tolerance. Furthermore, they observed an association between increased levels of RBP4 and waist circumference and IR.

Other studies also demonstrate an association between increased waist circumference and waist-hip ratio with increased plasma levels of RBP4 and markers of systemic inflammation, evidencing that this protein is an important biomarker to be explored in overweight patients[14]. Therefore, the objective of this study was to evaluate the serum concentration of RBP4 in obese, overweight and normal weight young adult patients, correlating the concentrations of this biomarker with IR rates in the study population.

METHODS

Study population

This study was characterized as a cross-sectional study. Participants were recruited from March to August 2015, in the laboratory of Clinical Biochemistry of the Universidade do Oeste de Santa Catarina (Unoesc) in São Miguel do Oeste (SC). The study protocol was approved by the Ethics Committee of the Unoesc no. 219.091, and all participants signed the written informed consent.

The volunteers were classified according to criteria established by the World Health Organization (WHO), 2000, based on body mass index (BMI) and waist circumference (WC) – normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obesity (≥ 30 kg/m^2) –, and central obesity, defined as WC ≥ 102 cm for men and ≥ 88 cm for women.

The sample consisted of 149 young individuals paired by sex, age and BMI, of which 54 were normal weight (32 women and 22 men), 27 were overweight (17 women and 10 men) and 68 were obese (41 women and 27 men), all aged between 19 and 30 years. Participants were not smokers and were not taking any medication. We selected all obese, overweight and non-obese patients without previous diseases such as DM2, coronary diseases, neoplasia and other diseases or disorders that could influence the distribution in the obese genotype and biomarkers.

Anthropometric analysis

All measurements were taken at the Anthropometry Laboratory at Unoesc. The height (cm) was measured with 0.1 cm accuracy, using a wall-mounted stadiometer (Charder, model HM-210D); the weight (kg), with 0.1 kg of accuracy, was measured using a calibrated electronic scale (Toledo, model 2124); BMI was calculated as weight/(height)^2 (kg/m^2); WC and the neck circumference (NC) were measured in centimeters with a flexible tape of 0.1 cm accuracy. For WC, the tape was applied above the iliac crest with the abdomen relaxed, the arms at the side of the body and the feet together. For NC, the participant remained in the same position and the tape was placed over the middle of the throat on the hyoid bone. The anthropometric measurements were performed with all participants wearing light clothing and barefoot. The percentage of body fat and the body fat weight were determined by bioimpedance (Biodynamics Model 450). The anthropometric analysis was performed according to the methods established in the literature[15].

Laboratory tests

Blood samples with ethylenediamine tetraacetic acid (EDTA) and serum were obtained from participants after a 10-hour fasting. Serum glucose was measured enzymatically by GOD-Trinder methodology, using a commercial assay kit (LabtestDiagnostics®, Brazil), as recommended by the manufacturer in BIOPLUS 2000 (BIOPLUS® SP, Brazil) device. Serum insulin was determined by electrochemiluminescence immunoassay, using an Elecsys 2010 analyzer (Roche

Diagnostics®, Switzerland). The IR index was calculated by the homeostatic model assessment of insulin resistance (HOMA-IR), which is (fasting insulin mIU/l) × (fasting glucose mg/dl)/22.5, and the evaluation of insulin sensitivity (IS) by the Quantitative Insulin Sensitivity Check Index (QUICKI). Glycated hemoglobin (HbA1c) was measured from EDTA whole blood samples by high performance liquid chromatography (HPLC) on Tosoh 2.2 Plus A1C device, Tosoh Corporation, Tokyo-Japan, and expressed as a percentage.

The RBP4 concentration was measured in duplicate, in serum samples using an enzyme-linked immunosorbent assay (ELISA), according to the manufacturer (EMD Millipore Corporation, Billerica, MA, EUA), in Luminex 100 IS Analyser System (LuminexCorp, Austin, TX, EUA). RBP4 showed a sensitivity of 0.78 ng/ml; accuracy of 76%-113%; accuracy of 3.8% inter-assay and 4.8% intra-assay, and curve range of 0.14-100 ng/ml.

Statistical analysis

Data were analyzed using Statistica 6.0 software (StatSoft, Tulsa, OK, USA) and are expressed as mean ± standard deviation (SD) or median (interquartile range). The Kolmogorov-Smirnov test was used to examine the distribution of variables. Data comparisons between the groups were performed using analysis of variance (Anova) followed by the Tukey or Kruskal Wallis test and the Dunn comparison test. The $p < 0.05$ values were considered significant.

RESULTS

As can be observed in **Table 1**, weight, BMI, the body fat percentage and the fat weight were significantly elevated in the overweight and obese groups when compared to the normal weight group ($p > 0.0001$). There were no significant differences in height and age between the groups studied. Significant increases in glucose, HbA1c, insulin and HOMA-IR were observed in obese and overweight groups when compared to the normal weight group ($p > 0.0001$), as well as a significant decrease in IS ($p > 0.0001$) (**Table 2**).

Regarding the serum concentration of RBP4, we found a progressive increase of this protein according to the increase of BMI. The results showed a significant increase of RBP4 in the obese group when compared to the normal weight group ($p < 0.05$). There was no significant difference among the other groups, as shown in **Figure**.

TABLE 1 – Baseline characteristics of study participants

Analyzed characteristics	Groups		
	Normal weight	Overweight	Obese
n	54	27	58
Male/female	22/32	10/17	27/41
Age (years)	21 (19.8-24)	24 (21-26)	25 (22-27)
Weight (kg)	60.1 ± 9.4	77.2 ± 7†	97.7 ± 16†¥
Height (cm)	167.8 ± 7.3	167 ± 8.3	166.8 ± 10.5
BMI (kg/m²)	20.9 (19.3-22.6)	28.1 (26.5-28.7)†	34.1 (32.4-37.5)†¥
NC (cm)	36 ± 4.3	36 ± 3.3	38.8 ± 3.5†¥
WC (cm)	72.3 ± 6.8	87.7 ± 6.3†	104.2 ± 13.7†¥
Body fat (%)	25.3 (18.9-28.9)	33.3 (27.4-36.8)†	38.7 (34.8-41.6)†¥
Weight in fat (kg)	14.9 (12.7-17.9)	24.2 (21-28.3)†	36.1 (31.1-40.7)

Data are expressed as mean ± SD or median (interquartile range) and were processed by One-way Anova, followed by Tukey's test or Kruskal Wallis test and Dunn's multiple comparison test.

†p < 0.0001 compared to the normal weight group; ¥p < 0.0001 compared to the overweight group.

BMI: body-mass index; NC: neck circumference; WC: waist circumference; SD: standard deviation; Anova: analysis of variance.

TABLE 2 – Biochemical characteristics related to insulin resistance

Biochemical characteristics	Groups		
	Normal weight	Overweight	Obese
Glucose (mg/dl)	79.6 ± 6.7	83.4 ± 7.2	87.1 ± 10.8*
HbA1c (%)	4.9 ± 0.3	5.1 ± 0.3	5.3 ± 0.4*¥
Insulin (µUI/ml)	9.5 (6.8-11.5)	11 (8.6-14.2)	13.8 (10.3-20)*¥
HOMA-IR index	1.8 (1.3-2.3)	2.2 (1.6-3)	3.1 (2-4.4)*¥
Insulin sensitivity	0.35 (0.34-0.37)	0.34 (0.32-0.36)	0.32 (0.3-0.35)*¥

Data are expressed as mean ± SD or median (interquartile range) and were processed by One-way Anova, followed by Tukey's test or Kruskal Wallis test and Dunn's multiple comparison test.

**p < 0.0001 0001 compared to the normal weight group; ¥p < 0.0001 compared to the overweight group.*

HOMAR-IR: homeostatic model assessment of insulin resistance; Anova: analysis of variance.

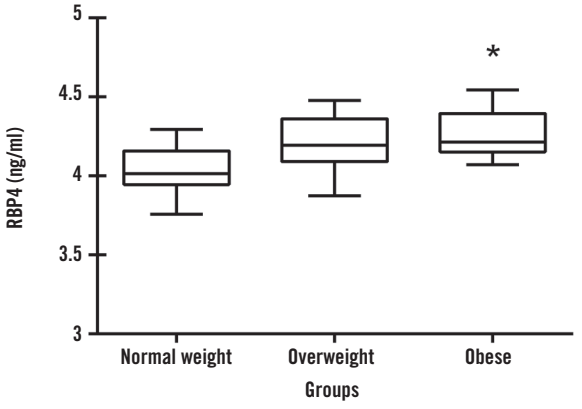

FIGURE – *Serum RBP4 levels in the study groups.*

Data are expressed as mean ± SD and were processed by One-way Anova followed by Tukey's test.

**p < 0.05 compared to the normal weight group.*

RBP4: retinol-binding protein 4; SD: standard deviation; Anova: analysis of variance.

DISCUSSION

RBP4 is an adipokine secreted in adipose tissue and liver; it belongs to the lipocalin family and is the sole specific retinol (vitamin A) transporter in blood. Its role as a mediator of IR was recognized through its interference in the glucose transporter (GLUT-4) and the decrease of IS to target tissues. It is an adiponectin with the role of increasing IR in muscle and hepatic gluconeogenesis, and it may be the central mediator of obesity-induced IR[16]. Therefore, this study aimed to evaluate the serum concentrations of RBP4 in obese and overweight young adult patients, comparing these results with a normal weight control group, as well as correlating the concentration of this biomarker with serum dosages and calculations related to the development of IR.

The results found in the present study show significantly elevated RBP4 levels in the obese group when compared to the normal weight group (Figure), as well as the IR-related biochemical parameters (Table 2), which leads us to consider the interference of cytokines produced by body fat, especially that of the abdominal region, as well as by macrophages infiltrated in this tissue, such as RBP4, which may interfere with insulin action.

Recently it was identified that the macrophage are novel expression site of RBP4[17], and thus it is considered a pre-inflammatory substance with important interference in insulin action. High levels of RBP4 contribute to increase IR by modification of the GLUT4 transporter, inhibition of insulin signaling at muscle tissue level, and increasing liver glucose release[16], as well as by inhibition of insulin receptors substrate 1 (IRS1) in adipose tissue[18]. In fact, the data from this study corroborate this hypothesis, since obese patients presented the highest concentrations of RBP4 and showed concomitantly the highest concentrations of glucose and IR markers (Figure, Table 2). The increased levels of this protein are correlated with insulin resistance in obese individuals with glucose intolerance and DM2, but also in non-obese, non-diabetic individuals with family history of DM2[19]. In patients undergoing bypass surgery, there was a marked reduction in RBP4 levels, which was correlated with the reduction of visceral fat[20].

A study investigating the association between serum RBP4 levels and IR observed that RBP4 values were higher among obese subjects. This protein was positively correlated with adiposity rates, glucose tolerance index and lipid profile[16]. The RBP4 concentration was positively and significantly associated with traditional cardiovascular risk factors and/or components of the metabolic syndrome. It has been suggested that visceral fat is related to the production of RBP4. Non-obese men with high visceral fat had higher values of glucose, fasting insulin, HOMA-IR and RBP4 when compared to volunteers with low visceral fat[21]. Obese with low visceral fat had lower RBP4 levels and consequently fewer factors associated with the metabolic syndrome[21, 22].

Researchers have suggested a link between serum levels of RBP4 and obesity and DM2[23]. RBP4 represents a central regulator of IS, in animal models. The overexpression of RBP4 genes or injections of recombinant RBP4 rapidly induced in animals, RBP4 knockout animal models increased IS[24]. It is also postulated that RBP4 can raise lipid concentrations, especially triglycerides, which can be mediated through its effect on liver fatty acid metabolism and the regulation of the expression of genes involved in lipid metabolism[25]. Unfortunately, one limitation of our study is that it does not show lipid values, especially triglycerides, precluding detailed observation and correlation at this point. However, our data corroborate those of other authors who have studied the correlation between increased levels of RBP4 with measures of adiposity, inflammatory factors and percentage of body fat[26]. This study observed a progressive increase of RBP4 proportional to the increase of BMI, body weight and percentage of body fat.

The condition of obesity and metabolic syndrome are accompanied by chronic low grade inflammation, which is characterized by an increase in the expression of inflammatory cytokines and infiltration of immune cells into adipocytes[27]. The inflammatory response promotes the activation of transcription factors and proinflammatory cytokines, which may lead to a persistent inflammatory response associated with inhibition of insulin signaling and high risk of cardiovascular events[28].

The results presented here assume that the determination of RBP4 in the blood can be an important indicator of IR and increase of abdominal fat in young and obese adults, and that in the future, the determination of serum levels of RBP4 may become simple, fast and efficient to predict metabolic risk factors related to IR and DM2, besides the cardiovascular risk factors, guiding the diagnosis, treatment and monitoring of this population.

CONCLUSION

The results of this study showed that obese patients presented significantly higher concentrations of RBP4 when compared to

normal weight patients, moreover, it suggests that this cytokine secreted by adipocytes, liver and macrophages could interfere in regulatory mechanisms of glycemia and insulin, contributing to the development of IR, especially in obese patients due to the higher stock of visceral fat. These data are in agreement with others already presented in the literature, suggesting that the dosage of this biomarker presents important clinical relevance and becomes a promising hope in the evaluation and monitoring of patients with increased body fat, especially to monitor the development of IR and the metabolic syndrome and thus, preventing future cardiometabolic problems in patients with increased body weight.

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CONFLICT OF INTEREST

No conflicts of interest.

RESUMO

Introdução: *Na obesidade, ocorre inflamação crônica de baixo grau, na qual os macrófagos desempenham um papel importante na manutenção desta inflamação por produzirem sustâncias pré-inflamatórias e inflamatórias, como a proteína transportadora de retinol (RBP4), que funciona como gatilho para a inflamação do tecido adiposo, aliando-se a comorbidades da obesidade.* ***Objetivo:*** *Este estudo avaliou a concentração sérica de RBP4 e biomarcadores de resistência insulínica (RI) em pacientes adultos jovens, com peso normal, sobrepeso e obesos.* ***Métodos:*** *Foi conduzido um estudo transversal que envolveu 149 indivíduos: 54 saudáveis (32 mulheres e 22 homens), 27 com sobrepeso (17 mulheres e 10 homens) e 68 obesos (41 mulheres e 27 homens). As medidas antropométricas e as concentrações de RBP4, insulina, HbA1c e glicose foram determinadas, além dos cálculos do modelo de avaliação da homeostase da resistência à insulina (HOMA-IR) e da sensibilidade insulínica (SI).* ***Resultados:*** *Pacientes obesos e com sobrepeso mostraram níveis significativos maiores de glicose, HbA1c, insulina e HOMA-IR* ($p > 0,0001$) *e diminuição da SI* ($p > 0,0001$), *quando comparados com o grupo de peso normal. Observou-se um aumento de RBP4 proporcional ao aumento do índice de massa corporal (IMC); o grupo obeso apresentou níveis significativamente superiores* ($p < 0,05$). ***Conclusão:*** *Este estudo sugere que a RBP4 pode ter papel-chave no desenvolvimento da inflamação e da RI em obesos jovens, uma vez que pode promover perturbações significativas no metabolismo da insulina, além de contribuir para o desenvolvimento de comorbidades relacionadas com obesidade. Este parâmetro pode representar uma esperança na identificação de novos marcadores inflamatórios e de RI que auxiliem o diagnóstico e o acompanhamento de pacientes com sobrepeso e obesos.*

Unitermos: *proteínas de ligação ao retinol; obesidade; resistência à insulina; glucose.*

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