v. 4, n. 64, 2024

International Journal of Health Science

RELATIONSHIP OF RBP4 PROTEIN WITH SPERM QUALITY IN MEN AND WITH BMI

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Abstract: Obesity is a chronic-degenerative disease, data from the World Health Organization shows that Obesity has doubled worldwide. Metabolic syndrome does not produce any symptoms, but some have been linked to obesity and an apparent decrease in fertility. Likewise, it has been related that Obesity is a pro-inflammatory state where adipokines contribute to the subclinical state of inflammation, such as the Retinol Binding Protein RBP4, which has reportedly been found at elevated levels in states of Obesity. The objective of this work was to evaluate the relationship of the RBP4 protein with DNA damage and sperm quality in men and with BMI. Anthropometric and biochemical measurements were performed, as well as the expression of RBP4 protein in serum, quality and damage to sperm DNA. The results obtained show that as the BMI increases, the expression of the RBP4 protein and the DFI% increase, in the same way Obesity was related to high levels of triglycerides, finally it was observed that for each increase in the RBP4 protein, there is a decrease of Liquefaction in patients with Normal weight and a decrease in Motility in patients with Overweight. These results show us that, if there is a slight relationship between the increased expression levels of the RBP4 protein and some Parameters of sperm quality, DNA damage% according to BMI.

Keywords: RBP4, Sperm quality, Sperm DNA damage, BMI

INTRODUCTION

Obesity is a chronic-degenerative disease of multifactorial origin that is characterized by the abnormal and excessive accumulation of adipose tissue in the body that can be harmful to health. Data from the World Health Organization indicate that since 1980 the frequency of Obesity has doubled worldwide. In 2008, 1.5 million adults were overweight. Within this group, more than 200 million men and nearly 300 million women were obese. The World Health Organization has declared Obesity and Overweight to be a global epidemic (Moreno., 2012; Pich., 2020; Wu and Ballantyne., 2020). In Mexico, an increase in the prevalence of subjects with Overweight and Obesity has been reported. In 2018 alone, a frequency of Overweight and Obesity of 73% and 30.5% was reported in adults aged 20 years or older. (Shamah Levy., et al., 2020). Obesity can be treated in its initial phases with modifications in the patient's lifestyle that results in reversibility and control (García et al., 2008; Lara de la Calleja et al., 2016). The increase in the consumption of saturated fats and carbohydrates, with the decrease in the intake of vegetables and coupled with a sedentary lifestyle, are the most important causes in the development of this global health problem (Jiménez., 2012; Ibarra., 2016).

The term "metabolic syndrome" groups together several cardiovascular risk factors, among them insulin resistance stands out. However, the physiopathogenesis of metabolic syndrome, Obesity is one of the most important triggering factors; Other metabolic alterations that characterize metabolic syndrome are: altered fasting glucose, abdominal obesity, dyslipidemia and hypertension (García-García., et al., 2008; Wu, and Ballantyne., 2020; De Filippo., 2021). Metabolic syndrome consists of the association of a set of anthropometric and biochemical indicators that substantially increase the development of cardiovascular diseases (Burguete-García., et al., 2014; De Filippo., 2012).

Metabolic syndrome does not produce any symptoms. However, given the metabolic alterations that these patients present, they have a greatly increased risk of presenting the following complications: Coronary heart disease with the development of myocardial infarction and angina pectoris, Cerebrovascular disease with an increased risk of having a stroke or a TIA, Peripheral arterial disease, Diabetes mellitus, Hyperuricemia and gout attacks, Polycystic ovary syndrome, Non-alcoholic fatty liver, Sleep apnea syndrome (Conway., 2004; Yanai et al., 2021). Recently, the global prevalence of Obesity has occurred concomitantly with an apparent decline in fertility (Morrison, and Brannigan, 2015). Furthermore, experimental studies of animal and human models have demonstrated a direct relationship between Obesity and infertility in both men and women (Crujieras and Casanueva., 2015; Craig., et al., 2017; Venkatesh., et al., 2022). Recently, white adipose tissue has been recognized not only as an energy reservoir, but also as a secretory organ of bioactive molecules recognized as chemical messengers with local and systemic actions called adipokines. Nowadays, Obesity is considered a pro-inflammatory state and adipokines include a wide variety of pro-inflammatory peptides that contribute to the subclinical state of inflammation and promote a series of metabolic alterations (Nava-Santana., et al., 2013).

Adiponectin is an adipokine that improves insulin sensitivity in addition to having lipid-lowering and antiatherogenic functions. Unlike leptin, adiponectin has several protective effects and health benefits (Ramírez-Montesinos., 2008; Fang and Judd., 2018). Another adipokine secreted by adipose tissue is the Retinol Transport Protein RBP4, which, like leptin, its circulating levels in humans are elevated in states of Obesity (Nava-Santana, et al., 2013). This protein is encoded by the RBP4 gene located on chromosome 10q23 24 in humans. It is mainly synthesized in the liver and adipose tissue, and to a lesser extent in other organs, such as the lungs, kidneys, testes, brain and retina (Nono Nankam and Blüher., 2021). Retinoids regulate important cellular processes, including cell proliferation, differentiation, and apoptosis, and therefore play a role in many essential physiological processes, including the maintenance of immunity, barrier integrity, male and female reproduction, and embryonic development (Gudas., 2012). The retinol-RBP4 complex is secreted from the hepatocyte into the circulation to enable retinoid-dependent delivery of retinol to peripheral tissues bound to another protein, transthyretin (TTR), (Abumrad and Davidson, 2012; Kwanbujan, et al., 2018; Blaner.., et al., 2009). The retinol transporter protein is a poorly studied adipokine that is secreted from adipocytes and hepatocytes. High levels of this are largely related to Obesity and have been associated with various complications such as: Insulin resistance, Type Diabetes mellitus. 2, Dyslipidemia, Arterial hypertension, Liver disease, Effects on sex hormones and a positive correlation was found between elevated levels of TG in serum and RBP4 (Meisinger., et al., 2011; Rocha., et al., 2013; Chiba.., et al., 2010; Saki., et al., 2012; Yan., et al., 2013;

Obesity is capable of affecting sperm quality and/or fertility through multiple mechanisms. However, it is important to clarify that not all obese individuals suffer from sub/infertility and that the alterations that will be described occur more frequently in those individuals who present morbid obesity (BMI>4.0) (Giagulli., et al., 1994; Roth., et al., 2008; Ameratunga., et al., 2023). As reported by Jensen., et al., (2004), where 1558 Danish men with BMI>25 presented a reduction of 21.6% and 23.9% in sperm concentration and in the total number of gametes respectively, with respect to the candidates of normal BMI (20-25 kg/m2), however, did not observe alterations in other sperm Parameters such as Motility and morphology. On the other hand, Koloszar., et al., (2005) reported a significant reduction in sperm concentration in obese individuals compared to normospermic individuals. In fact, there is a study in which they reported a positive correlation between BMI and sperm morphology (Qin., et al., 2007). For its part, Eisenberg., et al. (2013) showed a positive correlation between body mass and the Volume and Concentration of abnormal semen. In this study, only 6% of men with BMI were oligospermic, and in the group of obese men it was 17% oligospermic. Sermondade., et al., (2013) published a meta-analysis, which added original data from 21 studies that included 13,077 men. In this meta-analysis, he found a significant J-shaped association revealed between BMI and abnormal sperm count, defined as less than 40 million sperm per ejaculate.

The odds ratio with a 95% confidence interval for oligozospermia or azoospermia in underweight men (BMI < 18.5) was 1.15 (0.93-1.43), in underweight men (BMI 25-29.9) it was 1.11 (1.01-1.21), in obese men (BMI 30–39.9) it was 1.28 (1.06–1.55), and in men with Morbid Obesity (BMI > 40) it was 2.04 (1.59–2.62). Kort, et al., 2006 were among the first to demonstrate a significant correlation between BMI and DFI in sperm chromatin structure assay tests among a population of 520 healthy men ages 26 to 45 who presented for semen analysis tests. The DFI of men with normal BMI, 19.9 ± 1.96%, was significantly lower than the DFI in the Overweight group, 25.8 ± 2.23%, and Obesity, 27.0 ± 3.16%. Also Fariello., et al., (2012) reported a relationship between BMI and sperm DNA fragmentation.

Currently there are no studies on the correlation of the RBP4 protein with sperm quality and DNA in men with Overweight and Obesity. However, Yan., et al., (2013), found that RBP4 could be a marker of Obesity related to cardiometabolic factors, such as systolic blood pressure, total cholesterol, triglycerides and LDL cholesterol negatively related to estrogens in women with Obesity. For their part, Valderrama., et al., (2019) mention that the RBP4 protein and leptin have a relationship in terms of their serum levels and that being at increased levels promotes Obesity; The increase in leptin is linked to Obesity, therefore it is known that in individuals with Obesity, the storage of fat at the scrotal level generates reactive oxygen species (ROS), which can oxidize lipids, proteins and carbohydrates, in addition to cause damage to the DNA of sperm stored in the caudal region of the epididymis and which in turn is associated with the induction of apoptosis in this organ. For all of the above, the objective of this work was to evaluate the relationship of the RBP4 protein with DNA damage and sperm quality in men and with BMI.

MATERIALS AND METHODS

A total of 40 voluntary participants aged 18 years, who met the established requirements regarding the manner of collection of the seminal sample. The participants were students from the Faculty of Nursing No.2 located in the City of Acapulco, Gro. All experiments were carried out in accordance with the established guidelines of the Helsinki Treaty with its ethical principles for medical research in humans and NOM-087-ECOL-SSA1-2002 for the protection and environmental health of infectious biological hazardous waste.

ANTHROPOMETRIC MEASURES

Weight measurement, height measurement, waist circumference, and hip circumference were taken.

BIOCHEMICAL ANALYSIS MEASUREMENT

A blood sample was obtained after 8 hours of fasting. 10 mL of blood was taken from each young person by venipuncture. Glucose, triglycerides, total cholesterol in whole blood, and RBP4 protein in serum were quantified. Glucose, total cholesterol and triglycerides tests were determined using the Accutrend Plus Manual equipment (Roche).

EVALUATION OF RBP4 PROTEIN

The serum obtained was stored in cryogenic vials at 4°C until use. For the quantification of RBP4, the RBP4 Elisa kit (human) was used according to the manufacturer's instructions and analyzed in an Elisa reader.

OBTAINING THE SEMEN SAMPLE

The donors were asked to have 3 to 7 days of sexual abstinence. The sample was obtained through masturbation and was placed in a sterile container, which was maintained at a temperature of 37 °C. It was transferred to the work area for analysis. processing within one hour of collection. The macroscopic and microscopic studies were based on what was established by the World Health Organization (2021) where sperm quality was evaluated, which was categorized into macroscopic and microscopic.

EVALUATION OF SPERM CHROMATIN STRUCTURE BY FLOW CYTOMETRY (SCSA)

This was performed using the flow cytometry technique: Sperm Chromatin Structure Assay, described by Evenson., et al., (1993). The SCSA technique evaluates the susceptibility of sperm chromatin to in situ denaturation, since the sperm are subjected to an acid treatment that potentially induces DNA denaturation. The sample is then incubated with the fluorochrome acridine orange (NA), which has metachromatic properties that allow it to intercalate between the bases of double-stranded DNA and emit a green fluorescence that represents undenatured DNA and when intercalated with DNA single chain emits a red fluorescence representing denatured DNA.

STATISTIC ANALYSIS

The distribution of continuous variables was evaluated using the Shapiro-Wilk test, variables with parametric distribution were represented as mean and standard deviation, while variables without normal distribution were represented as medians and interquartile range (p25 - p75). The comparison between the groups was carried out using the ANOVA or Kruskal-Wallis test, the relationship between the variables was evaluated using the Spearman or Pearson correlation coefficient; The association between the RBP4 protein level and the Parameters of interest was estimated using generalized linear models, in all cases values of $p < 0.05$ were considered statistically significant.

RESULTS

CATEGORIZATION OF PATIENTS ACCORDING TO THEIR BODY MASS INDEX (BMI)

Forty male student participants from the Faculty of Nursing No. 2 of the UAGro underwent anthropometric measurements (Table 1). The students were categorized by their body mass index (BMI), it was observed that the serum concentration of triglycerides was higher in the Obesity group.

PARAMETERS RELATED TO SPERM QUALITY, DNA DAMAGE AND RBP4 PROTEIN CONCENTRATION BY BMI

A directly proportional relationship was observed between BMI with RBP4 protein levels and the percentage of DNA fragmentation (DFI%) (Table 2).

CORRELATION COEFFICIENT BETWEEN THE RBP4 PROTEIN AND THE PARAMETERS OF QUALITY AND DAMAGE TO SPERM DNA

The correlation analysis between RBP4 levels and the Parameters of interest shows that there is an inversely proportional relationship with sperm concentration, this relationship is moderate. Furthermore, a directly proportional relationship was identified between the levels of RBP4 and DFI, this relationship is considered strong (Table 3).

CORRELATION BETWEEN RBP4 AND THE PARAMETERS OF INTEREST BASED ON BMI

No relationship was observed between RBP4 levels and the Parameters of interest based on BMI (Table 4).

CHANGES IN SPERM QUALITY PARAMETERS AS A FUNCTION OF RBP4 BY STUDY GROUP

The analysis revealed that for each increase in RBP4 (ng/mL), there is a -0.05 decrease in Liquefaction time in patients with Normal weight. Furthermore, it is observed that for each increase in RBP4 there is a 0.89% decrease in mobility in Overweight patients (Table 5).

DISCUSSION

In the present work, the anthropometric characteristics of the 40 subjects were obtained, who were categorized into normal weight, overweight and obesity according to their BMI as established by the World Health Organization. Studies have reported that a high BMI is an indication that the patient is at a high level of weight and obesity, and is closely related to the waist-hip ratio (World Health Organization, 2016). On the other hand, it has been reported that BMI correlates with high levels of cholesterol and triglycerides, knowing that subjects tend to have a greater risk of predisposing metabolic diseases such as diabetes mellitus, due to having excess adipose tissue and visceral fat in the body (Rocha., et al., 2013).

In this work it was shown that triglyceride levels increase when BMI increases. Studies have considered triglycerides and BMI as a parameter of insulin resistance (Lim., 2019). Additionally, triglycerides and BMI have been shown to be related to hypertension, hyperuricemia (Bala., 2019; Gu., 2020) and risk of suffering from pre-diabetes (Jiang., 2021). On the other hand, it has been reported that there is a significant correlation of the RBP4 protein with triglycerides and with chronic inflammation of adipose tissue (Aeberli., et al., 2007).

Parameters	Normal weight	Overweight	Obesity	p-value
Age	20 ± 1.7	21 ± 2.4	22 ± 2.7	0.72*
Weight (Kg)	65.9 ± 9.4	81.2 ± 9.0	105.5 ± 15.7	***0.02****
Size (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.6	0.97*
Hip circumference (cm)	88.2 ± 6.6	100.2 ± 5.1	110.7 ± 19.2	***0.03****
Waist circumference (cm)	79.7 ± 6.9	93.9 ± 6.7	109.7 ± 10.4	***0.03****
BMI (Kg/m²)	22.7±2	27.7±1.5	36±3.7	***<0.0001****
ICC	0.9(0.86-0.93)	0.93(0.91-0.94)	0.94(0.9-1.04)	0.11+
Glucose (mg/dL)	82.5(77-93)	85(76-93)	87(75-100)	0.91+
Cholesterol (mg/dL)	213.6±37.5	211.1±53.5	216.2±43.9	0.75*
Triglycerides (mg/dL)	140.5(127-171)	158(133-219)	165(135-219.5)	***0.02+***

Table 1: Biochemical and anthropometric parameters by study group

Data are represented as mean±standard deviation or median (p25-p75).

*P value estimated by ANOVA

+Kruskal-Wallis estimated p value

Parameters	Normal weight	Overweight	Obesity	p-value
Liquefaction	1.3(1.1-2.1)	0.5(0.4-1.2)	1.3(0.4-2.4)	0.09+
Volume	2.3(2-3)	2.3(1-3)	1.5(1-3)	0.49+
pH	7±0	7.2±0.4	7.1±0.3	0.24*
Motility	57.8±8.9	50.9±15.1	55.5±15.1	0.46*
Viability	72.5(66-79)	64(61-73)	67.2(60-69)	0.19+
Concentration	39(26.4-99.8)	29.8(19.5-48.6)	20.3(18.4-32)	0.05+
Morphology (Normal)	18.5(15-20)	17(14-27)	14(12-23)	0.25+
Morphology (Abnormal)	82(81-85)	83(73-86)	86(77-88)	0.26+
Protein RBP4	91.4(80.6-112.7)	119.5(106.3-129.3)	187.5(173.5-217.1)	***<0.001+***
DFI%	7.7±2.6	10.7±2.1	19.7±3.3	***<0.0001****
HDS	16(13-18)	28(14-39)	16(11-48)	0.31+

Table 2. Parameters related to sperm quality, DNA damage and RBP4 protein concentration by study group

Data are represented as mean±standard deviation or median (p25-p75).

*P value estimated by ANOVA

+Kruskal-Wallis estimated p value

Parameters	rho	p-value
Liquefaction	0.04	0.8+
Volume	-0.19	0.3+
pH	-0.09	0.6*
Motility	0.08	0.6*
Viability	-0.16	0.4*
Concentration	-0.32	***0.04+***
Morphology (Normal)	-0.30	0.06+
Morphology (Abnormal)	0.26	0.1+
DFI%	0.79	***<0.0001****
HDS	0.19	0.3+

Table 3. Correlation coefficient between the RBP4 protein and the Parameters of quality and damage to sperm DNA

* Pearson correlation coefficient

+Spearman correlation coefficient

Parameters	Normal weight	Overweight	Obesity
Liquefaction +	-0.58(0.08)	0.29(0.28)	-0.38(0.2)
Volume+	0.47(0.17)	0.19(0.48)	-0.10(0.74)
pH*	0.02(0.9)	0.26(0.35)	-0.45(0.09)
Motility*	0.35(0.32)	-0.51(0.06)	0.36(0.18)
Viability*	0.5(0.14)	0.19(0.53)	0.14(0.6)
Concentration+	0.4(0.25)	-0.06(0.82)	-0.18(0.55)
Morphology (Normal) +	-0.25(0.48)	-0.09(0.74)	-0.39(0.19)
Morphology (Abnormal) +	-0.003(0.99)	0.09(0.74)	0.39(0.19)
DFI%*	0.41(0.23)	-0.33(0.24)	0.05(0.84)
HDS+	0.14(0.69)	0.44(0.98)	-0.09(0.77)

Table 4. Correlation coefficients between RBP4 and parameter of interest by BMI

Data represents rho(p-value)

*Pearson correlation coefficient

+Spearman correlation coefficient

Parameters	Normal weight	Overweight	Obesity
Liquefaction	**-0.05(<0.001)**	0.015(0.22)	-0.012(0.05)
Volume	0.023(0.53)	0.002(0.89)	-0.007(0.42)
Motility	0.18(0.32)	**-0.89(0.03)**	0.23(0.17)
Viability	0.34(0.11)	0.14(0.49)	0.023(0.63)
Concentration	1.92(0.31)	0.74(0.33)	0.004(0.96)
Morphology (Normal)	-0.095(0.43)	-0.12(0.53)	-0.082(0.09)
Morphology (Abnormal)	0.06(0.69)	0.16(0.46)	0.068(0.29)
DFI%	0.057(0.29)	-0.05(0.25)	0.006(0.83)
HDS	0.1(0.43)	0.37(0.08)	-0.15(0.32)

Table 5. Changes in sperm quality parameters as a function of RBP4 by study group

Data represent β(p-value) estimated under a generalized linear model

On the other hand, in our work an inversely proportional relationship was observed between RBP4 levels and liquefaction, motility and sperm concentration and DNA damage (DFI%). Currently there are only works where BMI has been related to alterations in sperm quality parameters and DNA damage (Barbara Muciaccia., 2012).

Our study demonstrated that the data between the sperm quality parameters of each patient are within the lower reference limits, established by the World Health Organization, having slight significant variations in liquefaction, motility and sperm concentration related to the concentrations of the binding protein. to retinol 4 (RBP4).

THANKS

The authors thank the Male Reproductive Toxicology Laboratory of the Department of Toxicology of CINVESTAV-IPN for the support in the SCSA Technique and the Proteomics and Genomics Laboratory of the Faculty of Nursing No.2-UAGro for the support and space provided to the realization of this project.

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