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Original Article

Estimation of Serum Vaspin Levels in Humans as a Novel and Therapeutic Biomarker of Visceral Obesity

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Abstract

Background: Obesity is associated with metabolic complications and significantly increases the risk of developing insulin resistance. Visceral fat is potentially dangerous as it is the major player in the adverse metabolic consequences of obesity. In this context, one of the recently discovered and interesting adipokines that provide a new insight into the physiology, pathology, and treatment of obesity is vaspin. Vaspin is a visceral adipose tissue-derived serine protease inhibitor with insulin-sensitizing effects and its upregulation in obese individuals may be a defensive and a protective mechanism aimed to reduce insulin resistance in humans.

Aims and Objectives: This study aims to determine the circulating serum vaspin levels in humans with visceral obesity to assess its association and link to obesity-related metabolic alterations.

Materials and Methods: A cross-sectional study consisting of 120 obese subjects in the age group of 30–55 years having a body mass index (BMI) of ≥35 (Group I) and another 120 subjects of the same age group with a normal range BMI (Group II) was done with their measures of obesity and serum vaspin levels measured.

Results: The obese subjects (Group I) showed significant differences in the BMI, measures of obesity, and the serum vaspin levels ($P < 0.001$). Pearson's correlation revealed that the serum vaspin levels were positively correlated with the measures of obesity.

Conclusion: From this study, it can be demonstrated that vaspin may be used as a circulating biomarker for early identification of obesity-related metabolic alterations and vaspin also plays an important role in the pathogenesis of obesity and its related metabolic disorders.

Key words: Insulin resistance, Obesity, Vaspin

INTRODUCTION

Obesity is a chronic, multifactorial disease involving environmental, genetic, physiological, metabolic, behavioral, and psychological components. It has been increasing at an alarming rate throughout the world to the extent that it is now a pandemic, affecting millions of people globally. It has become the second leading and a preventable cause of death worldwide, with increasing rates in adults, especially in women and children. Globally, the prevalence of obesity is estimated to be 36.9% for men and 38.0% for women.[1] There have been substantial increases in the prevalence of obesity in the developing countries as well, which is estimated to be 23.8% for men and 22.6% for women.[1]

India is now following a trend of other developing countries that are slowly and steadily becoming more obese. Obesity in India has reached epidemic proportions in the 21st century, with morbid obesity affecting 5% of the country's population.

Obesity implies an excess storage of fat to an extent that it may have a negative impact on health. The serious impact

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of obesity on individuals and societies throughout the world in terms of health, social, and economic costs is a major concern.

The mortality rates rise as obesity increases, particularly when obesity is associated with an increased intra-abdominal or visceral fat. Visceral fat is body fat that is stored within the abdominal cavity around a number of important internal organs such as liver, pancreas, and intestines. Visceral fat is also known as "active fat" as it plays a unique and potentially dangerous role in affecting how our hormones function. Carrying a high amount of visceral fat is known to be associated with insulin resistance, which can lead to an increased risk of many health conditions such as type 2 diabetes mellitus, heart diseases, breast cancer, colorectal cancer, and Alzheimer's disease.[2] Furthermore, the hyperinsulinemia that accompanies insulin resistance would magnify and mediate the detrimental effects of visceral obesity. Thus, insulin resistance plays a crucial role in the pathogenesis of all these disorders.[3]

The various measures of visceral obesity include the estimation of the body mass index (BMI), waist and hip circumference, waist–hip ratio, percentage of body fat, and the skinfold thickness.

However, the waist circumference is globally used as a parameter and is a simplest way to quantify central obesity.[4] This is because it correlates well with excessive visceral fat, which appears to be the most metabolically active fat, which is responsible in causing insulin resistance. Measures of central obesity help refine the clinical evaluation of obesity-related risk.

Apart from this important function, the visceral adipocytes are involved in the energy metabolism and are the source of hormones, cytokines, and metabolites that play an important role in whole-body metabolism and insulin resistance. These cytokines or the bioactive mediators also called the cell signaling proteins secreted by the visceral adipose tissue are known as adipokines or adipocytokines. These adipokines send signals to organs of metabolic importance including brain, liver, skeletal muscle, and the immune system – thereby regulating the blood pressure, homeostasis, lipid and glucose metabolism, inflammation, hemostasis, angiogenesis, and atherosclerosis.[5]

Obesity is strongly associated with alterations in the physiological functions of the visceral adipose tissue, leading to insulin resistance, chronic inflammation, and altered secretion of adipokines.[6] An excessive accumulation of visceral fat can cause a dysregulation of the function of the adipocytes, thus causing an over secretion of the deleterious adipokines and a hyposecretion of the advantageous ones. An adipose tissue dysfunction or adisopathy plays a crucial role in the different obesity-linked diseases, including inflammation, insulin resistance, and cancer.

The visceral adipose tissue that is diseased and does not function properly is called as sick fat or adisopathy, which results in endocrine and immune responses that would cause metabolic abnormalities and directly promote cardiovascular disease.[7,8]

The harmful effects of visceral fat are due to lipotoxicity. Unlike subcutaneous fat, visceral fat cells release their metabolic products directly into the portal circulation, which is, in turn, carried to the liver. These visceral fat cells that are enlarged with an excess of triglycerides pour the free fatty acids into the liver causing them to accumulate in the pancreas, heart, and other vital organs. These free fatty acids accumulate in cells, in various locations of the body resulting in an organ dysfunction, which produces impaired regulation of insulin, blood sugar, and cholesterol, as well as abnormal heart functions.

One of the newly discovered adipocytokines is vaspin (visceral adipose tissue-derived serine) which was found to have insulin-sensitizing effects. It is a member of serine protease inhibitor family which was first isolated from visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, a model of abdominal obesity and type 2 diabetes.[9]

In the diet-induced obese OLETF rats, serum vaspin levels were found to be very high at the age when obesity and the plasma insulin levels reached a peak, and the administration of vaspin to these obese rats was found to significantly improve their glucose tolerance and insulin sensitivity.[9]

Expression of vaspin gene in visceral adipose tissue of humans and an increased circulating levels in the serum was found to be positively associated with parameters of obesity, obesity-related diseases, insulin resistance, and glucose metabolism. It is also indicated that vaspin plays a role in the adipoinsular axis and is associated with insulin resistance in obese subjects.[10]

Thus, this study aims at estimating the serum vaspin levels as a novel, circulating, and therapeutic biomarker in obese subjects and to study its association and link to obesity-related metabolic alterations.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, a cross-sectional study was conducted during the period of June 2016–May 2017 at the Institute of

Physiology and Experimental Medicine, Madras Medical College. The study subjects were recruited from the Institute of Internal Medicine and The Medical Endocrine Clinic, Rajiv Gandhi Government General Hospital, Chennai.

A total of 120 obese subjects in the age group of 30–55 years having a BMI of ≥35 (who were categorized as Group I) and another 120 subjects of the same age group with a normal range BMI (who were categorized as Group II) were selected for the study. Subjects with Type I and Type II diabetes, renal and hepatic diseases, hypertension, thyroid dysfunction, polycystic ovary syndrome, Cushing's disease, alcohol or drug abuse, smoking, cancer, hormonal therapies, chronic medication therapies (such as on antidepressants, anticonvulsants, hypoglycemic drugs, antihypertensives, lipid-lowering agents, oral contraceptives, and corticosteroids), pregnancy, and any other chronic medical or psychiatric illness were excluded from the study.

After obtaining an informed consent, a detailed history was obtained from all the study subjects and they underwent a careful and thorough physical examination and laboratory investigations to exclude any condition that might interfere with the study parameters.

The following were obtained and measured for all the study subjects using standard protocols:

1. The anthropometric measurements, i.e., the standing height and weight in light clothing without shoes were obtained using a stretch-resistant measuring tape and the BMI was calculated using the formula: wt (kg)/Ht (m^2)
2. The measures of obesity, i.e., the waist circumference and the hip circumference were obtained and the waist–hip ratio was calculated.
   According to the WHO Stepwise Approach to Surveillance protocol, the measurement for the waist circumference was made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest at the end of a normal expiration, and the measurement for the hip circumference was taken around the widest portion of the buttocks. The measurement was made with a stretch-resistant measuring tape that provides a constant 100 g of tension, with the tape parallel to the floor. It was ensured that the subject was standing erect with relaxed abdominal muscles, the arms by the side, feet positioned close together, and the weight evenly distributed across the feet and the clothing removed from the waistline. The measurement was made with a stretch-resistant measuring tape that provides a constant 100 g of tension, with the tape parallel to the floor.
3. After an overnight fast, between 8 and 10 am, a blood sample was taken and serum collected and stored at −80°C
4. Serum vaspin levels were assayed using the commercially available human vaspin ELISA kit using a human vaspin sandwich ELISA technique
5. The serum vaspin levels were correlated with the measures of obesity in the obese subjects.

The sample handling, storage, and preparation were done according to the manufacturer's instructions.

Statistical Analysis

The mean and standard deviation of the variables were determined for the two study groups.

Unpaired Student's *t*-test was employed as the test of significance at 95% confidence interval and Pearson's correlation was done using the SPSS software version 21.

- $*P < 0.05$ was considered as statistically significant
- $**P < 0.01$ was considered as highly statistically significant
- $***P < 0.001$ was considered as very highly statistically significant.

RESULTS AND DISCUSSION

In the current study, the purpose was to estimate and investigate the role of vaspin as a novel and a potential biomarker of visceral obesity. This was with the view that serum vaspin levels could be used as an early identification of visceral obesity and its related metabolic alterations, which would, in turn, enable us to make early interventions to protect oneself from its ruinous complications.

In this study, the BMI, measures of obesity, and the serum vaspin levels were estimated and compared in both the obese and the non-obese subjects.

Moreover, the serum vaspin levels also correlated with the BMI and the measures of obesity in the obese subjects.

In this study, the obese subjects showed an elevated BMI when compared to the non-obese subjects. The vaspin levels also showed a significant positive correlation with their BMI values.

This means that the vaspin concentration increases with an increase in BMI.

The results presented here are in line with Youn *et al.* and Alberti *et al.* who observed a significant BMI adjusted correlation with vaspin.[11]

Table 1: The mean values of the study parameters

Parameters	(Group I) Mean±SD	(Group II) Mean±SD	*P* value
Body mass index	40.59±3.98	22.87±1.81	0.0001
Waist circumference (cm)	115±9.13	83.23±1.54	0.0001
Hip circumference (cm)	127±10.75	104.60±3.45	0.0001
Waist/hip ratio	0.95±0.073	0.79±0.02	0.0001
Serum vaspin levels (ng/ml)	1.26 ± 1.18	0.73±0.59	0.03

Table 2: Correlation of serum vaspin levels with the waist circumference, hip circumference, waist–hip ratio, and BMI

Variable	WC (cm)	HC (cm)	Waist/hip ratio	BMI
Vaspin				
r	0.6140	0.5775	-0.0815	0.722
P	0.0003	0.0008	0.67	0.00001

BMI: Body mass index, WC: Waist circumference, HC: Hip circumference

Regarding the measures of obesity, the waist circumference, the hip circumference, and the waist–hip ratio were found to be elevated in the obese subjects when compared to the non-obese subjects with a normal range BMI.

Moreover, the waist circumference of the obese subjects showed a significant positive correlation with their serum vaspin levels. This result is in accordance with Alberti *et al.* (2009) who proposed that the waist circumference is a globally used parameter to quantify central obesity and is the key culprit in insulin resistance and its related complications.[12] Thus, it can be proposed that greater the waist circumference of an individual, greater would be the serum vaspin levels. This finding in this study is to be highlighted as it suggests that a higher serum vaspin levels in the obese individuals are an indicator of visceral obesity and its related complications.

These results suggest that the obese subjects with a high serum vaspin levels may be prone to develop the obesity-related metabolic complications in future.

It was postulated that an increase in the serum vaspin levels in the obese individuals was due to an increased secretion of the adipokine vaspin from the visceral adipose tissues and represented a compensatory mechanism or a response associated with obesity to antagonize the action of the other unknown proteases that are upregulated in obesity and in states of insulin resistance. Hence, this upregulation is said to be a defensive mechanism against insulin resistance [Tables 1 and 2].[13-15]

CONCLUSION

The conclusions derived from the present study are as follows:

1. Vaspin, a visceral adipose tissue-derived factor with potential antiprotease properties and insulin-sensitizing effects is increased in obesity
2. Vaspin levels are positively correlated and associated with the BMI and the measures of obesity
3. Vaspin could be used as a biomarker of visceral obesity and as an indicator of cardiovascular risk
4. Vaspin also plays an important role in the pathogenesis of obesity and its related metabolic disorders.
5. Hence, vaspin can also be used as a circulating biomarker for early identification of obesity-related metabolic alterations and thus can enable us to make interventions at the earliest.

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