

**OBESITY, INFLAMMATION AND METABOLIC SYNDROME****Saranya Mani^{1*} and Raskin Erusan²**

¹Dept of Pharmacology, Madras Medical Mission College of Health Sciences, Tamil Nadu, India.

²Dept of Genetics, Tirunelveli Medical College, Tamil Nadu, India.

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Corresponding Author*Saranya Mani**

Dept of Pharmacology,
Madras Medical Mission
College of Health Sciences,
Tamil Nadu, India.

ABSTRACT

Obesity is rapidly increasing in countries like India. Currently it is seen as a pro-inflammatory state with a risk in inflammatory parameters such as Tumour necrosis factor- α (TNF- α) along with the increase in the secretion of leptin. Evaluation of these parameters in 20 control and 20 cardiovascular disease(CVD) subjects of normal and overweight

BMI might enable us to understand the link between obesity, BMI, inflammation and CVD. In this connection, serum leptin, TNF- α were measured using ELISA methods and serum triglycerides, cholesterol and lipid profile in normal and overweight BMI subjects were analysed. Interestingly leptin level was found to be higher in normal & overweight BMI of CVD subject. A profound positive correlation has been observed between obesity, serum leptin and TNF- α suggesting a possible link between obesity, inflammation and metabolic syndrome.

KEYWORDS: obesity, inflammation, CVD, TNF- α , leptin.

INTRODUCTION

Obesity is the epidemic of 21st century and has become one of the most serious health problems in human population in both developed and developing countries. Obesity and insulin resistance are very frequent disorder and are described as the dominant risk factors for CVD.^[1]

According to World Health Report 2002, cardiovascular diseases (CVD) will be the largest cause of death and disability by 2020 in India. In 2020 AD, 2.6 million Indians are predicted to die due to coronary heart disease which constitutes 54.1 % of all CVD deaths.^[2] Given the increasing prevalence of obesity and the metabolic syndrome worldwide, there is an urgent need for a better understanding of the molecular mechanisms linking these conditions to atherosclerotic disease.^[3] The release of atherogenic and inflammatory cytokines from visceral fat also may contribute to cardiovascular complications.^[1]

Leptin, an adipocyte-derived nonglycosylated polypeptide hormone, promotes the onset of CVD in its ability to modulate the immune response.^[4] Also, leptin stimulates the production of proinflammatory cytokines from cultures of monocytes and enhances the production of T helper 1 (Th1) type cytokines such as interferon (IFN)- γ and tumor necrosis factor (TNF)- α from stimulated lymphocytes.^[5]

Though leptin plays a physiological role, leptin resistance may be pathophysiological for metabolic and cardiovascular dysfunction under inflammatory conditions. While the role of leptin has been determined in the elevation of sympathetic nervous system activity, many of its action on cardiovascular events such as inflammation has not been carefully studied.

Therefore, the present study was undertaken to assess the correlation between leptin and inflammation in control & CVD subjects. The aim and objectives of this study to compare the serum leptin & the biochemical parameters such as the serum levels of glucose, lipid profiles and inflammatory cytokines such as TNF- α in control & CVD subjects.

MATERIALS AND METHODS

The study was carried out on a total of 40 subjects, from Chennai based population, India. Out of 40 subjects 20 were newly diagnosed CVD patients and 20 were normal healthy subjects(control). All the individuals were subjected to a complete evaluation by a physician including a full medical history and physical examination. Informed written consent was obtained from all the subjects. Both males and females between 30-75 years of age were included in study. Individuals with severe systemic illness of history of kidney, liver, cancers, GITs and CNS were excluded from the study.

Anthropometric measurements

Height (cm), waist and hip circumference (cm) were noted using a measuring tape (to the nearest 0.1 cm). Waist circumference were measured at the mid point between the lower border of rib cage and the iliac crest and hip circumference were measured at the level of trochanter, the widest part of the hip region. weight (kg) were measured to the nearest 0.1 kg using a portable Stadiometer simultaneously. Obesity was defined as BMI > 30 kg/m³.

Blood collection

The blood samples (5ml) were collected from control and CVD subjects. The blood was allowed to clot and retract, then the serum was separated by centrifugation at 3500 rpm for 10 minutes. The separated serum was transported in ice cold box and stored at -80°C until use.

Elisa methods for measuring leptin and TNF- α concentration

Serum leptin level was measured using the sandwich leptin ELISA kit (Diagnostic Biochem Canada Inc kit, Canada) Normal serum leptin : 0-20 ng/ml. TNF- α level was measured using Avibion Human TNF- α ELISA kit (Orgenium Laboratories Business Unit, Finland) Normal serum TNF- α :0-500 pg/ml. All the analyses are performed according to the manufacturer's instruction.

Serum biochemical analysis

Serum glucose was estimated using glucose oxidase - peroxidase method. Cholesterol measured by the cholesterol oxidase – peroxidise method. HDL was measured by the direct method, triglyceride was measured using glycerol – 3 phosphate oxidase – peroxidise – N – ethyl methylanilin propan sulphonate sodic method using autoanalyzer (Bayer RA 50 ; Bayer copany India, Gunidy, Chennai, India.)^[6-9]

STATISTICAL ANALYSIS

For each experimental series, data are presented as Mean \pm SD.

RESULTS

Anthropometric measurements including BMI and biochemical Parameters including serum triglycerides, cholesterol, HDL, LDL, VLDL and inflammatory parameters such as leptin & TNF- α are analysed in 40 subjects from Chennai based population. The results thus obtained are tabulated (table 1).

A profound Positive correlation was observed between serum leptin and BMI in the subjects. The serum Leptin was elevated in normal BMI CVD and also in overweight control and CVD subject. It can be noted that subject especially overweight have higher value of leptin suggesting that this could be a risk factor for the incidence of metabolic disorders.

The mean waist to hip ratio in females was higher in normal & overweight CVD patients; and also in overweight non CVD subjects, on comparing with normal BMI non CVD subjects. In male, the waist to hip ratio was higher in normal & overweight CVD patients and also in overweight non CVD subjects, on comparing with normal BMI non CVD subjects.

Serum triglycerides level and LDL levels were found to be normal in control subjects 114.1 ± 35.9 & 116.4 ± 36.4 respectively. Overweight & Normal CVD subjects are found to exhibit high serum triglycerides. Further, more serum HDL level is found to be significantly high in normal control subjects when compared to that of other subject in study.

Elevated triglycerides level is one of the symptoms with triglycerides acting as a main form of storage of excess calories in fat. Therefore, increased triglycerides and low HDL observed in overweight subject with an elevated level of leptin suggest their increased risk for the incidence of CVD.

TNF- α identified as a key regulators of the inflammatory responses and reports suggest that leptin could be involved in synthesis of TNF- α in obesity. Serum TNF - α is found to be 480 ± 28.28 in normal BMI control subjects but elevated in normal BMI CVD & overweight BMI control and CVD subjects and this correlates with serum leptin levels.

DISCUSSION

Leptin is hormone which is involved in the maintaining of normal BMI. Elevated plasma leptin levels or hyperleptinemia have been demonstrated to correlate with hyperphagia, insulin resistance and other markers of metabolic syndromes including obesity, hyperlipidemia and hypertension, independent of total adiposity. Elevated plasma leptin levels was associated with an increase in the inflammatory markers (TNF- α and IL-6) which may be an independent risk factor for the development of CVD.

Hence this study was conducted to evaluate the relationship between leptin and CVD risks, which were assessed by the following parameters - BMI, serum leptin, TNF- α .

Leptin values are expected to be higher in thin subjects and lesser in obese subjects since it is known to correlate with the energy expenditure. But leptin are much higher in obese subjects and less in thin subjects indicating leptin resistance. Thus the amount of circulating leptin might be higher in obese subjects when compared to thin subjects. The increase in leptin values in CVD subjects when compared to that of control subjects clearly suggests that leptin can act as a pro-inflammatory cytokine.

In this study the serum leptin was elevated in both normal BMI & overweight patients with CVD. In overweight control subjects also it was elevated (21.25 ± 16.9) on comparing with normal BMI subject. This correlates with the study conducted by Jequier,(2002) where the leptin levels were higher in obese subjects.

Obesity is considered to be a pro-inflammatory state as the adipose tissue is known to secrete a number of cytokines including leptin, TNF- α and IL- 6 etc. These cytokines especially leptin is considered to be an important link between obesity and cardiovascular disease. In normal BMI CVD patients, overweight CVD patients and overweight control BMI individuals it was elevated on comparing with normal BMI control subject.

The values of TNF- α show a distinct variation with BMI values. The serum TNF- α showed the minimal increases in normal BMI control individuals, but in overweight control individuals it was elevated. In normal BMI CVD patients and overweight CVD patients TNF- α was also elevated.

This was similar to the study conducted by Kershaw, E.E. et al where it was observed that TNF- α levels correlated with serum leptin levels, in normal BMI and overweight CVD patients; and overweight control individuals.

The waist to hip ratio in normal BMI CVD and overweight CVD and overweight control male and female subject were greater than normal waist to hip ratio of (0.95) in males and (0.81) in females. In normal BMI male and female subject were within normal range. In this study, waist to hip ratio did not correlate with the BMI of the subjects. This was similar to the study conducted in Netherlands, where the relation of BMI, waist circumference and waist- to – hip ratio was evaluated, showed that waist circumference and not BMI may prove useful in the elderly patients. (Visscher *et al.*, 2001).

Many reports have shown that abdominal or central obesity is equally important as total adiposity and may be a better indicator of CVD risk. Waist circumference, used as a surrogate of abdominal obesity, is highly correlated with visceral adipose tissue.

In CVD patients with normal BMI and overweight BMI, the lipid profile showed an increase in the serum cholesterol, LDL, VLDL, TGL and a decrease in HDL levels. In control subjects with normal BMI and overweight BMI, the lipid profile (cholesterol, LDL, VLDL, TGL and HDL levels) was within normal reference range. This shows that elevated serum cholesterol, LDL and decrease HDL is associated with increased coronary heart disease risk.

Correlation between leptin and BMI among CVD and control

Table 1: Anthropometric measurements.

Profile	Normal BMI		Overweight BMI	
	Control	CVD	Control	CVD
Glucose mg/dl	121.±44.1	167.2±46.01	106.4±32.4	181.6±82.5
Triglycerides mg/ml	114.1±35.9	152.8±62.2	130.5±57.1	158.1±62.2
Cholesterol mg/ml	175.9±47.1	211.6±43.6	173.2±57.9	236.5±64.9
HDL mg/ml	41.6±6.3	36.6±9.1	39±9.0	32±9.1
LDL mg/ml	116.4±36.4	159±47.4	107.5±34.4	158.8±50.7
VLDL mg/ml	22.9±7.2	29.5±6.1	32±12.4	34.1±22.2
Leptin ng/ml	10.07±10.2	26.34±4.4	21.25±1.9	34.37±57
TNF -α pg/ml	480±28.28	719±228.89	910±410.12	1040±404.75

CONCLUSION

The results of our study suggest that TNF -α is an important mediator in the pathogenesis of obesity. Also TNF-α level observed in different BMI of CVD might be due to increased triglycerides level, low HDL and Leptin resistant.

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