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Original Article

Biochemistry Section

Correlation of Serum Adiponectin Level with Insulin Resistance in Healthy Obese Individuals: A Case-control Study

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ABSTRACT

Introduction: Obesity, emerging as a worldwide health burden having potential risk for development of atherosclerosis, diabetes, coagulopathy, arthritis and metabolic syndrome. Obesity is classified in terms of various anthropometric modalities like Body Mass Index (BMI), Waist Circumference (WC) and Waist Hip Ratio (WHR) etc. Adipocyte secretes adiponectin that has an important role in energy homeostasis and lipid metabolism. Adiponectin level reduces in obesity and its deficiency results in higher incidence of insulin resistance. Adiponectin has insulin sensitising, antiatherogenic and anti inflammatory properties.

Aim: To compare the level of serum adiponectin, fasting plasma insulin and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in healthy obese individuals with healthy non obese controls and also to find out the correlation of serum adiponectin with fasting plasma insulin level and HOMA-IR in healthy obese cases.

Materials and Methods: This case-control study was conducted in Department of Biochemistry, MKCG MCH, Berhampur, Odisha, India, during the period of October 2019 to October 2020 which included 86 subjects. Of which 43 were healthy obese individuals and 43 were age and sex-matched healthy non obese volunteers, in the age group of 20-45 years were taken as controls. About 4 mL of whole blood was collected to measure fasting plasma glucose, fasting plasma insulin and serum adiponectin. Statistical Package for the Social Sciences (SPSS) version 16.0 was used to do the statistical analysis and for correlation Pearson correlation test was done.

Results: In present study, maximum cases and controls were within the range of 20-35 years. Out of 43 cases, 25 were males and 18 were females and out of 43 controls, 27 were males and 16 were females. Insulin resistance and Fasting Plasma Glucose were significantly higher in healthy obese cases as compared to controls. Serum adiponectin in cases (2.35±0.77) was found to be significantly lower than controls (8.10±2.98). Present study found statistically significant negative correlation of serum adiponectin with fasting plasma insulin ($r=-0.918$, $p<0.001$) and HOMA-IR ($r=-0.934$, $p<0.001$).

Conclusion: Negative correlation of adiponectin and positive correlation of insulin resistance in obesity suggest inflammation which may lead to development of metabolic syndrome. So adiponectin is a target for future research to reduce morbidity and mortality in relation to obesity.

Keywords: Adipokines, Body mass index, Coronary artery disease, Fasting plasma glucose

INTRODUCTION

Obesity is the leading preventable cause of death worldwide which is a serious public health concern of the 21st century. World Health Organisation (WHO) World Health Statistics Report 2016 data suggest that more than 1.9 billion adults, 18 years and older, were overweight, out of these over 650 million were obese [1]. As per WHO, obesity though one of the most common, yet the most neglected, public health problems in both developed and developing countries [2]. A recent study demonstrated that India has raced to third place, after the United States of America and China in the highest number of obese people worldwide. The USA accounting for 13% of obese people globally and India with China accounting for 15% of the world's obese [3]. BMI scale is the most common metric used for assessing the prevalence of obesity. The WHO defines BMI as: "a simple index of weight-for-height that is commonly used to classify underweight, overweight and obese in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2) [4,5]. Highly active endocrine organ, adipose tissue produces a number of hormones and other substances such as Tumour Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), leptin, and adiponectin [6]. Adiponectin has a special role because of its antidiabetic and antiatherogenic effects. Plasma levels of adiponectin were significantly lower in obese subjects, type 2 diabetic patients, and with coronary artery disease [7].

Insulin resistance is a pathological condition where the cells/tissues lose their sensitivity to insulin resulting in impairment of glucose uptake and utilisation. Obesity being a chronic inflammatory condition can induce insulin resistance, recent evidence suggests that the opposite is also true, i.e., insulin resistance by itself can also induce inflammation [8]. Adiponectin enhances insulin's effects in the liver by stimulating phosphorylation of Acetyl CoA Carboxylase (ACC) and reduction of Phophoenolpyruvate Carboxykinase (PEPCK) and glucose 6 phosphatase activity and it also promotes glucose uptake in skeletal muscles. Thus reduced level of adiponectin in obese individuals results in insulin resistance [9]. Studies conducted by Diwan AG et al., and Aleidi S et al., showed negative correlation of adiponectin with obesity and insulin resistance in Type 2 diabetes patients [10,11]. Aguilar-Salinas CA et al., has shown in their study that high level of adiponectin are associated with metabolically healthy obese individuals [12]. Hence, present study was conducted to analyse serum adiponectin, fasting plasma insulin and HOMA-IR in healthy obese cases and healthy non obese controls and to correlate serum adiponectin with fasting plasma glucose and insulin resistance in cases.

MATERIALS AND METHODS

The present case-control study was carried out in the Department of Biochemistry, MKCG Medical College, Brahmapur, Odisha, India from October 2019 to October 2020. The Institutional Ethical

Committee (IEC) [reference number: 671] of MKCG Medical College, Brahmapur, Odisha, India gave approval for the study. Informed written consents from each individual prior to the study was taken.

Inclusion criteria: Healthy obese individuals in the age group of 20-45 years and equal number of age and sex matched non obese controls were included in this study. Obese individuals were identified by considering either BMI >30 Kg/m^2 or WC >90 cms in men and >80 cms in women and WHR >1.0 in men and >0.85 in women were identified as obese as per WHO [13].

Exclusion criteria: Patients having chronic disease like thyroid disease, type 2 diabetes mellitus, hypertension, liver disorder, renal disorder, hormonal disorders causing obesity, alcoholics, smokers and those taking any medications which can alter the biochemical parameters are excluded from the study.

Sample size calculation: According to a study conducted by Liu W et al., the median adiponectin concentration was lower in the obese group (1.03 (0.75-2.36) vs 3.38 (0.59-7.63) µg/L, p=0.03) as compared to the non obese group [14]. Assuming 50% of the controls having a higher proportion of adiponectin and odds ratio of 3.4, the sample size calculated by Epitools software at 95% confidence interval and a power of 80% was 86; 43 each in the case and control arms.

Study Procedure

About 4 mL of fasting venous blood was collected in a dry, sterile disposable syringe under aseptic conditions. Two mL of blood was kept for fasting plasma glucose estimation in vials containing fluoride as glycolytic inhibitor and fasting plasma insulin. The separated serum sample was analysed for serum adiponectin. Fasting plasma glucose was quantitated in TOSHIBA TBA 120 FR and its normal plasma level ranges from 70-110 mg/dL [15]. The estimation of fasting plasma insulin was done using commercially available kit of Roche cobas e411 diagnostics and its normal plasma level ranges from 2.6-24.9 µU/mL [16]. Serum human adiponectin was estimated using commercially available Enzyme Linked Immunosorbent Assay (ELISA) kit marketed by Assaypro LLC Catalog number: EA2500-1. Normal adiponectin plasma levels range from 3-14 µg/mL [17].

Estimation of HOMA-IR was used to quantify insulin resistance and beta cell function. Optimal insulin sensitivity- if HOMA-IR is less than 1. Levels above 1.9 signal early insulin resistance, while levels above 2.9 signal significant insulin resistance [18].

Calculation of HOMA-IR [18]:

$$\text{HOMA-IR} = \text{glucose (mmol/L)} \times \text{insulin (µU/mL)} / 22.5$$

OR

$$\text{HOMA-IR} = \text{glucose (mg/dL)} \times \text{insulin (µU/mL)} / 405$$

STATISTICAL ANALYSIS

The statistical analysis was done using SPSS version 16.0. Pearson Correlation of various parameters with serum adiponectin was analysed and was represented in tabular form. Independent sample t-test was applied to estimate the special parameters between cases and controls. Chi-square test of significance was used to see any difference between the two groups of categorical parameters like gender. The p-value ≤0.05 was considered as statistically significant

RESULTS

The study included 43 healthy obese individuals and 43 age and sex matched healthy non obese volunteers as controls. Maximum cases and controls were within the range of 20-35 years. Out of 43 cases, 25 (58.1%) were males and 18 (41.9%) were females and out of 43 number of total number of controls, 27 (62.8%) were males and 16 (37.2%) were females [Table/Fig-1].

Age group (years)	Cases (n=43)		Controls (n=43)	
	Male (%)	Female (%)	Male (%)	Female (%)
20-35	17 (39.5)	12 (27.9)	15 (34.9)	09 (20.9)
36-45	08 (18.6)	06 (13.8)	12 (27.9)	07 (16.3)
Total	25 (58.1)	18 (41.9)	27 (62.8)	16 (37.2)

[Table/Fig-1]: Age and sex distribution in cases and controls.

The comparison of mean age in cases (31.9535±9.37) with controls (32.0930±7.20) was found to be non significant (p-value 0.938). A significant difference was found between cases and controls for BMI (p-value <0.001), WHR (p-value <0.001), WC (p-value <0.001) [Table/Fig-2].

Parameters	Cases (n=43) (Mean±SD)	Controls (n=43) (Mean±SD)	p-value
Age (years)	31.9535±9.37	32.0930±7.20	0.938
Males n (%)	25 (58.1%)	27 (62.8%)	0.1946
Females n (%)	18 (41.9%)	16 (37.2%)	0.6591
BMI (kg/m^2)	33.19±6.17	24.01±0.49	<0.001*
WC (cms)	91.06±5.59	77.46±7.61	<0.001*
WHR	0.78±0.11	0.71±0.18	<0.001*

[Table/Fig-2]: Comparison of mean of various parameters between cases and controls.
*p-value <0.05 was statistically significant calculated by independent sample t-test; BMI: Body mass index; WC: Waist circumference; WHR: Waist to hip ratio

The mean serum adiponectin level in controls (8.10±2.98) µg/mL were higher than cases (2.35±0.77) µg/mL, which was found to be statistically significant (p<0.001). The mean fasting plasma insulin (p-value <0.001), fasting plasma glucose (p-value <0.001) and HOMA-IR (p-value <0.001) were significantly higher in cases as compared to controls [Table/Fig-3].

Parameters	Cases (n=43) (Mean±SD)	Controls (n=43) (Mean±SD)	t-value	p-value
Adiponectin (µg/mL)	2.35±0.77	8.10±2.98	12.208	<0.001*
FPG (mg/dL)	104.04±12.20	92.34±6.82	5.487	<0.001*
Insulin (µIU/mL)	19.71±4.02	6.53±2.27	6.082	<0.001*
HOMA-IR	5.54±4.12	1.32±0.29	12.263	<0.001*

[Table/Fig-3]: Comparison of mean of serum adiponectin, fasting plasma glucose, fasting plasma insulin and HOMA-IR level in cases and controls.
*p-value <0.05 is significant calculated by independent sample t-test

Serum adiponectin had a significant negative correlation with both fasting plasma insulin (r-value -0.918, p-value=0.001) and HOMA-IR (r-value -0.934, p-value=0.001). This signifies that lower serum adiponectin value is associated with increase in fasting serum insulin and HOMA-IR [Table/Fig-4].

Parameters	Adiponectin	
	r-value	p-value
FPG	-0.464	0.001*
Fasting plasma insulin	-0.918	0.001*
HOMA-IR	-0.934	0.001*

[Table/Fig-4]: Pearson correlation of serum adiponectin with FPG, fasting plasma insulin and HOMA-IR in healthy obese cases.
*p-value <0.05 is significant calculated by pearson correlation method

DISCUSSION

Obesity and overweight are defined as a systemic disease that shows excessive and abnormal accumulation of body fat leading to adverse health effects [19]. Obesity has reached epidemic proportions and is a major contributor to the global burden of chronic diseases and disability [20] and morbidity/mortality [21,22]. In the present study, maximum obese cases and controls were in the age group of 20-35 years and were mostly males. Demographic parameters like BMI (kg/m^2), WC (cms) and WHR in healthy obese

cases was significantly higher as compared to healthy non obese controls. The causes of increased BMI, WC and WHR might be due to sedentary lifestyle, proinflammatory state and genetic predisposition in obese individuals. Mallick AK et al., conducted a study on 200 participants of Rohilakhand, Uttar Pradesh, India found that the mean±SD of BMI, WC and WHR in cases were higher than controls which was statistically significant, $p<0.05$ [23].

Obesity is a state of low-grade inflammation, that results from enlargement of adipocytes and increased macrophage infiltration into the adipose tissue. There is abnormal production and secretion of adipokines as well as activation of inflammatory signalling in adipocytes [24]. TNF-α activates the NF-κB pathway and suppresses the expression of Peroxisome Proliferator-Activated Receptor-γ (PPARγ), which is a strong transcriptional inducer of adiponectin [25]. The study explores that the mean adiponectin level in healthy obese cases was lower as compared to healthy non obese controls. Yosaee S et al., conducted a study on metabolically healthy, metabolically unhealthy and normal weight metabolically healthy groups and found significant higher values of serum adiponectin in controls as compared to healthy obese subjects [26].

Obesity is also characterised by toxic accumulation of lipids in non adipose tissue and increased levels of proinflammatory cytokines, which induces or exacerbate insulin resistance [27]. To compensate for reduced insulin sensitivity due to insulin resistance, insulin secretion is increased in order to maintain euglycaemia [28]. Insulin increases the synthesis of fatty acids from glucose and facilitates the entry of glucose into adipocytes and inhibits the breakdown of fat in adipocytes [29]. Insulin resistance is a pathological state in which insulin action is impaired in target tissues including liver, skeletal muscle, and adipose tissue.

In the present study, the mean fasting plasma glucose, mean fasting plasma insulin and mean HOMA-IR for healthy obese cases was significantly increased as compared to healthy non obese controls, p-value <0.001. Gonzalez-Cantero J et al., conducted a cross-sectional study on 113 obese and non obese subjects, de Cassia da Silva C et al., conducted a study on homeostatic model of adiponectin and found that the mean value of fasting plasma insulin and HOMA-IR in obese cases is more as compared to non obese controls [30,31].

Adiponectin improves insulin resistance by inhibiting inducible Nitric Oxide Synthase (iNOS) resulting in suppression of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) [32]. Adiponectin activates adenosine Monophosphate activated Protein Kinase (AMPK) and peroxisome proliferator-activated receptor-α (PPAR-α) receptor in liver and skeletal muscles resulting in improvement of insulin resistance [33].

In present study a significant negative association between serum adiponectin and HOMA-IR level was observed, which was statistically significant, $p<0.001$. Since adiponectin increases insulin sensitivity, people who experience insulin resistance typically have low levels of adiponectin. Insulin resistance happens when cells in ones body don't respond to insulin as they should, which results in excess insulin release (hyperinsulinaemia) [34]. Xydakis AM et al., carried a study on Adiponectin, Inflammation in Metabolic syndrome in obese individuals, Gonullu G et al., had conducted a study on association between adiponectin, insulin resistance in colorectal tumour and found a significant negative association between serum adiponectin and HOMA-IR [35,36].

Limitation(s)

Though in the present study association was assessed, still the effect of individual variables cannot be predicted. So there is a need for prospective study to assess whether low adiponectin levels can be used to predict the development of T2DM and obesity in a population. The study can also be used to prevent its complications.

CONCLUSION(S)

The study demonstrated that fasting plasma glucose, fasting plasma insulin and HOMA-IR were higher in obese cases whereas serum adiponectin was lower in obese individuals. Serum adiponectin shows significant negative correlation with fasting plasma glucose, fasting plasma insulin and HOMA-IR. Further genetic analysis in those group of people with its correlation with adiponectin level may find a way to therapeutic plan. Finding the root cause in those group of people and advising preventive measures with proper therapeutic plan may reduce the morbidity and mortality in obese individuals. Future studies with large sample size could add on the treatment of metabolic diseases in association with obesity.

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