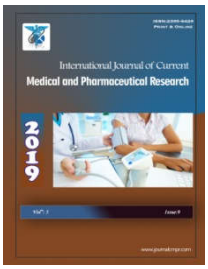
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 09(A); September 2019; Page No. 4553-4557
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201909744



Research Article

TO STUDY LEPTIN LEVELS IN OVERWEIGHT AND OBESE INDIVIDUALS AND CORRELATE WITH AMBULATORY BLOOD PRESSURE ABNORMALITIES

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ARTICLE INFO

Article History:
Received 4th June, 2019
Received in revised form 25th July, 2019
Accepted 23rd August, 2019
Published online 28th September, 2019

Key words:
Ambulatory blood pressure monitoring, Leptin, Overweight, Obesity

ABSTRACT

Objective: Various studies have suggested contradictory association between leptin and systolic or diastolic blood pressure in hypertensive individuals. Thus, the current study was conducted to assess the ambulatory blood pressure pattern and leptin levels in overweight and obese individuals and correlate leptin level with ambulatory blood pressure monitoring (ABPM) abnormalities.

Methods: This cross sectional study was conducted in the Department of Medicine, King George's Medical University, Lucknow over a period of 1 year. It involved patients of either gender, aged 20-60 years, with body mass index (BMI) more than 25 and less than 40 Kg/m^2. Eligible subjects were subjected to anthropometric measurements, leptin measurement, ABPM monitoring, and baseline investigations like random blood sugar and lipid profile.

Results: A total of 95 patients were enrolled and grouped according to BMI into normal, overweight, and obese. Various ABPM parameters were correlated with BMI. There was a significant correlation ($p < 0.05$) of increased leptin levels with total cholesterol, triglycerides, and LDL, but not with HDL. A weak correlation between leptin levels and various ABPM parameters, but not with diastolic day and night load blood pressure(BP) was noted. Although leptin showed a weak correlation with BP values, but these were significant ($p < 0.05$), especially systolic BP.

Conclusion: From this study it can be concluded that leptin plays a significant contributory role in causing obesity related hypertension.

INTRODUCTION

Incidence of obesity is reported to be increased three fold since 1975, culminating in raised prevalence of hypertension, diabetes, and heart diseases.[1-3]As per the WHO (2016) estimates, global adult overweight population was approximately 1.9 billion and obese adults contributed more than 650 million to this figure.[1] Moreover, the World Health Statistics reports that non-communicable diseases (NCDs) account for 41 million deaths annually, and cardiovascular diseases are the biggest contributor. In terms of attributable deaths, raised blood pressure is one of the leading risk factors.[4] The current literature reveals that adipose tissue is the link between hypertension and obesity. Adipose tissue, one of the endocrine organ, is involved in the regulation of a variety of biological functions including the secretion of hormones known as adipokines or adipocytokines such as leptin.[5]Leptin has pleiotropic actions on various organs.[6,7]Leptin plays an important role in the activation of neural pathways that boosts the sympathetic nervous system (SNS) activity, including renal SNS, resulting in raised plasma aldosterone, sodium retention, volume expansion, and raised blood pressure via stimulation of angiotensin-aldosterone system. Significant association have been noted between leptin and other factors (metabolic, inflammatory, and hemostatic factors) in the development of hypertension and cardiovascular disease.[8]

On the other hand, few authors reported no statistical association between leptin and systolic or diastolic blood pressure in hypertensive individuals.[9] Some of the recent studies in human and animal studies explain the involvement of leptin in hypertension.[10-12] Hence, this study was conducted with objectives to assess leptin levels in overweight and obese patients, and to correlate leptin level with ambulatory blood pressure monitoring (ABPM) abnormalities.

MATERIALS AND METHODS

This cross-sectional study is an additional analysis of the data from our original study.[13]It was performed in the Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India. It involved 95 patients, who attended the study site over a period of 1 year. The study commenced after approval of the study protocol by the Institutional Ethics Committee (IEC).

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The study involved the patients of either gender, aged 20-60 years, with body mass index (BMI) of more than 25 to less than 40 Kg/m^2, and willing to participate in the study. Whereas, subjects on medication such as antihypertensive agents, lipid lowering agents, those raising the blood pressure levels [amphetamines, corticosteroids, erythropoietin, tricyclic antidepressants, anti-migraine medication(triptans and ergot derivatives), estrogens (in contraceptive pills)], drugs of abuse (cocaine); with any pre-existing endocrine disorders, neurological disease with autonomic dysfunction, obstructive sleep apnoea, morbid obesity (BMI more than 40 Kg/m^2); and pregnant women were excluded from the study.

The patients were screened and those fulfilling the eligibility criteria were enrolled in the study. After obtaining the written informed consent, detailed history was obtained and general examination including anthropometric measurements was performed. The demographic profile of the patients was recorded. Anthropometric measurements including height, weight, and waist circumference (WC) were noted and BMI was calculated. On the basis of BMI, patients were divided into three groups: normal (18.5-24.9 kg/m^2), overweight (25-29 kg/m^2), and obese (30 kg/m^{2}or more).[1]

For the baseline investigations such as random blood sugar and lipid profile, 10 ml of venous blood was obtained from antecubital vein.

Leptin measurement

A fasting venous sample was withdrawn, between 8:00 - 10:00 am, in seated position. These samples were then centrifuged and refrigerated at -20 ^{0}C until analysis. A sandwich type enzyme immunoassay, utilizing highly specific monoclonal antibodies, was used for quantitative estimation of leptin levels. Quantitative estimation of leptin was done by leptin ELISA Cat No. CAN-L4260 (Version 8.1).

Ambulatory blood pressure monitoring (ABPM)

Procedure and precautions explained to the subjects

The CONTEC 06 C oscillometric device was used for the measurement of ambulatory BP. ABPM device was programmed to take readings at set intervals i.e., every 15 minutes during day-time and every 30 minutes during night-time. The entire procedure followed and the precautions taken have been described in detail in our previous publication.[13]

Circadian parameters

The BP values recorded between 6 am to 10 pm were used to estimate the mean day-time systolic blood pressure (SBP) and diastolic blood pressure (DBP) values, the BP values recorded between 10 pm to 6 am were used to estimate the mean night-time SBP and DBP values, and finally, the night-time dipping (ND) was calculated as: [(day-time mean SBP night - time-mean SBP)/day-time mean SBP] × 100.[14]The circadian BP patterns, based on the ND, were categorized into three groups: the dipper (a positive day-night ratio from 10 to 20%), the non-dipper (ratio of < 10%), and the inverse dipper (a negative day-night ratio).[15]

What did the results mean?

- 24-hour mean BP less than 115/75 mm of Hg (hypertension threshold 130/80mm of Hg)
- Day-time BP less than 120/80 mm of Hg (hypertension threshold 135/85 mm of Hg)
- Night-time BP less than 105/65 mm of Hg (hypertension threshold 120/75 mm of Hg)

Ambulatory BP values higher than 'normal' and less than thresholds for hypertension were considered as 'high normal'. BP was estimated in both the arms and if difference in SBP was found to be less than 10 mm of Hg, the non-dominant arm was used. However, if difference in SBP was more than 10 mm of Hg, arm with higher BP was used. By using a calibrated sphygmomanometer connected to ABPM device with help of a Y connector, a minimum of three readings were recorded simultaneously and this ensured the validity of ABPM device. The ABPM device was used, only if the average readings for ABPM device and sphygmomanometer were not found to be differing by more than 5 mm of Hg.

Statistical analysis

Demographic and biochemical parameters were compared with BMI by using analysis of variance (ANOVA). Chi-square test was used to find out the association of BMI with SBP, DBP, and pulse pressure (PP). Correlation analysis was performed using Pearson's bivariate correlation. The correlation was graded as r < 0.3: weak or negligible correlation; r = 0.3-0.5: mild correlation; r = 0.5-0.7: moderate correlation; and r > 0.7: strong correlation. SPSS version 19.0 (IBM SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.A probability value of less than 0.05 signified the statistical significance.

RESULTS

A total of 95 subjects were enrolled in the study and on the basis of BMI were grouped in three categories i.e. normal, overweight and obese. Table 1 demonstrates the demographic parameters of patients on the basis of BMI. Majority of the enrolled patients were overweight (i.e., 52.6%). With increase in BMI, the mean age of the patients increased, but did not attain significance level. However, compared to males, significantly higher number of females were obese (p-value = 0.020).

Table 1 Comparison of demographic parameters with body mass index

Characteristic	Group I (Normal BMI) (n=20)	Group II (Overweight) (n=50)	Group III (Obese) (n=25)	p-value
Age	37.80 (9.28)	38.48 (10.86)	41.72 (10.37)	0.361#
		Gender		
Female	10 (50)	21 (42)	19 (76)	0.020*
Male	10 (50)	29 (58)	6 (24)	

Data for age expressed as mean (S.D.) and for gender no (%); # -ANOVA;* - chi square test; p-value < 0.05 was considered as statistically significant.

The biochemical parameters were compared between the three groups and are shown in Table 2. With increase in BMI, levels of various parameters such as leptin (p-value <0.001), RBS (p-value = 0.005), and lipid parameters [TC (value = 0.001), TG (p-value = 0.014), HDL (p-value = 0.015), LDL (p-value <0.001)] were found to be significantly elevated. Moreover, the leptin levels were found to be raised in 85.4% of overweight and 100% of obese patients, thus showing a significant association between BMI and derangement of leptin levels (p-value <0.001).

Table 2 Comparison of biochemical parameters with body mass index

Characteristic	Group I (n=20)		Group II (n=50)		Group III (n=25)		Statistical significance (ANOVA)
	Mean	SD	Mean	SD	Mean	SD	P
Leptin	3.08	0.98	74.45	75.51	98.70	54.08	<0.001
RBS	101.60	15.29	112.88	12.96	106.00	13.41	0.005
TC	136.95	13.60	141.56	23.56	160.00	23.06	0.001
Triglycerides	115.85	13.34	121.66	24.27	135.12	25.60	0.014
HDL	44.05	7.63	44.64	8.47	51.24	13.42	0.015
LDL	66.40	6.14	72.82	19.10	91.76	18.98	<0.001

SD: standard deviation; RBS: random blood sugar; TC: Total cholesterol; HDL: high density lipoproteins; LDL: low density lipoproteins; p-value < 0.05 was considered as statistically significant.

The strength of correlation of leptin levels with demographic and biochemical parameters was assessed and is shown in Table 3. A mildly positive and significant correlation of leptin levels was observed with weight, total cholesterol, and LDL levels. Moreover, a moderately positive and significant correlation of leptin was also observed with waist circumference and BMI.

Table 3 Strength of Correlation of Leptin Levels with demographic and biochemical parameters (Pearson's bivariate correlation)

Parameter	"r"	"p-value"	Strength of correlation	Significance
Age	0.107	0.308	Weak	NS
Weight	0.410	0.000	Mild	S
Ht	-0.026	0.801	Weak	NS
WC	0.609	0.000	Moderate	S
BMI	0.538	0.000	Moderate	S
RBS	0.130	0.216	Weak	NS
Total Cholesterol	0.311	0.002	Mild	S
Triglycerides	0.298	0.004	Weak	S
HDL	0.110	0.293	Weak	NS
LDL	0.361	0.000	Mild	S

BMI: body mass index; Ht: height; WC: waist circumference; RBS: random blood sugar; HDL: high density lipoproteins; LDL: low density lipoproteins; NS: non-significant; S: significant; p-value < 0.05 was considered as statistically significant.

The strength of correlation of leptin levels with ABPM parameters was assessed and is shown in Table 4. The leptin levels did not show a considerable relationship with ambulatory BP measurements. The leptin levels were weakly correlated with all the ABPM parameters and in more than 50% of the parameters, this correlation was found to be statistically significant.

Table 4 Strength of Correlation of Leptin Levels with ABPM parameters (Pearson's bivariate correlation)

Parameter	"r"	"p-value"	Strength of correlation	Significance
SBP AVG	0.273	0.008	Weak	S
DBP AVG	0.244	0.018	Weak	S
Day SBP	0.281	0.006	Weak	S
Night SBP	0.265	0.010	Weak	S
Day DBP	0.246	0.018	Weak	S
Night DBP	0.232	0.025	Weak	S
%SBP Change	-0.097	0.357	Weak	NS
%DBP Change	-0.059	0.575	Weak	NS
BPLV Systolic Day	0.223	0.032	Weak	S
BPLV Diastolic Day	0.106	0.310	Weak	NS
BPLV Systolic Night	0.259	0.012	Weak	S
BPLV Diastolic Night	0.192	0.065	Weak	NS
Circadian SBP	-0.066	0.532	Weak	NS
Circadian DBP	-0.061	0.564	Weak	NS

r< 0.3: Weak or negligible correlation; r=0.3-0.5: Mild correlation; r=0.5-0.7: Moderate correlation; r>0.7: Strong correlation; "-" sign indicates a negative correlation; NS:not significant; S: significant; p-value < 0.05 was considered as statistically significant

DISCUSSION

In human beings, the obesity is reported to be linked with increased serum leptin levels and this indicates a state of leptin resistance, marked by impaired leptinaction and signaling. This results in disturbed physiological relationship between leptin and β-cell function and increases the chances of development of insulin resistance and Type 2 diabetes mellitus.[16]Various studies have demonstrated the association of leptin with various diseases such as obesity, hypertension, and metabolic syndrome.[17-21] Changes in the content and distribution of fat in the body describes variation in nearly 50% of the circulating leptin level.[22] The findings of the current study suggesting a significant correlation of increased leptin levels with TC and LDL, but not with TG and HDL is supported by some previous studies.[23,24]

In the current study, as compared to the normal patients, the leptin levels were found to be significantly higher in overweight and obese patients. In the past studies patients with ischemic heart disease, leptin levels in obese patients were reported to be higher than that seen in normal patients.[25,26]Moreover, in the present study, on correlating BMI with baseline investigations, it was found that BMI related significantly with TC, LDL, TG, and HDL. These findings are supported by study done by Patil *et al*.[27] and Ekmen *et al.*[25]

According to a study by Hu *et al.* involving a rural Chinese population, the association between BP and leptin was heavily influenced by body fat mass and distribution.[28]Contrary to this, a study conducted by Suter *et al.* reported no association between leptin and BP.[29] However, Lindgarde *et al.* reported the occurrence of high leptin levels in Swedish overweight women with high BP and low leptin in overweight Peruvian women with low BP.[30]According to Uckaya*etal.* plasma leptin was higher in hypertensive patients, but a continuous relationship between leptin and BP was not detected.[31] Moreover, several studies involving hypertensive patients reported the finding of high plasma leptin levels,but the confounding influence of overweight could not be ruled out.

In the present study, there was only a weak correlation between leptin levels and various ABPM parameters including 24 hour SBP, 24 hour DBP, day and night SBP, day and night DBP, and day and night systolic load values but not with day and night diastolic load BP. Although leptin showed a weak correlation with blood pressure values, these were statistically significant (p-value <0.05), particularly SBP. Similarly, Guagnano *et al.* evaluated the correlation of leptin levels with ABPM parameters in normotensive android obese women and reported strong positive correlations (p-value<0.001) between leptin levels and 24-hour SBP, daytime SBP, nighttime SBP,24-hour DBP, and daytime DBP in android obese women. Thus, they concluded that serum leptin levels contribute to the BP variation and are directly related to 24-hour BP values.[32]

Limitations

In this study, distribution of patients in overweight and obese group was unequal, thus affecting the precision of results. Same BP cuff size was used for all subjects irrespective of arm circumference, thus influencing the BP readings. Sample size was small, so generalizability of our results is difficult.

CONCLUSION

The results of the current study demonstrate a positive, though weak, correlation between leptin levels and majority of ABPM parameters, independently of BMI. However, the percentage change in SBP and DBP, and circadian SBP and DBP were negatively correlated with the leptin levels. These findings supports the association between leptin levels and obesity-related hypertension and thus, suggests that raised leptin levels already exists in normotensive obese patients. Moreover, the prior elevated leptin levels can play a critical role in the development of hypertension.

Funding source

None declared.

Conflict of interest

All authors have none to declare.

Acknowledgements

The authors would like to thank Dr. Vikas S. Sharma, MD for his medical writing services.

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How to cite this article:

Akash C Lohakare and Shuchi Singh (2019) 'To study leptin levels in overweight and obese individuals and Correlate with ambulatory blood pressure abnormalities', *International Journal of Current Medical and Pharmaceutical Research,* 05(09), pp 4553-4557.

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