Leptin Levels, Lipid Profiles, and Central Fat Distribution in Atherosclerosis: Implications for Cardiovascular Disease Risk

Mathangi R[1], Selvaraj J[2], Reji M[3], Jaideep M[4], Ponnulakshmi R5, Nalini D[4]*, Samyuktha. P[5], Pugazharasan[6]

Abstract

Background: Leptin, an adipocyte-derived hormone, is overexpressed in atherosclerotic lesions and implicated in promoting thrombosis and atherosclerosis through pro-inflammatory signaling. Despite its known role in obesity-related cardiovascular diseases (CVDs), the precise relationship between leptin levels and various metabolic and anthropometric factors in atherosclerosis remains underexplored. Methods: This study aimed to investigate the role of leptin in the pathogenesis of atherosclerosis by measuring serum leptin levels in atherosclerosis patients and analyzing their correlation with anthropometric variables (waist-to-hip ratio, body mass index) and biochemical parameters (lipids, glucose). Participants included both atherosclerosis patients and non-CVD controls. Serum leptin, glucose, triglycerides, cholesterol, HDL, and LDL levels were measured, and anthropometric measurements were taken. Results: Serum leptin levels were significantly higher in atherosclerosis patients compared to non-CVD controls across all weight categories: normal weight (23.1 ± 5.1 ng/mL vs. 5.7 ± 3.8 ng/mL, $p < 0.0001$), overweight (30.2 ± 3.7 ng/mL vs. 10.5 ± 4.2 ng/mL, $p < 0.0001$), and obese (42.8 ± 4.5 ng/mL vs. 29.3 ± 9.1 ng/mL, $p < 0.0001$). Leptin levels positively correlated with BMI ($r = 0.57$, $p < 0.0001$) and were higher in normal weight atherosclerosis patients than in overweight controls, indicating possible leptin resistance. Additionally, atherosclerosis subjects exhibited elevated serum glucose, triglycerides, cholesterol, HDL, and LDL levels compared to controls, with significant differences noted in overweight subjects. Both systolic and diastolic blood pressures were higher in overweight atherosclerosis patients. Waist-to-hip ratio positively correlated with triglycerides ($r = 0.42$, $p = 0.0001$) and VLDL ($r = 0.45$, $p < 0.0001$) in atherosclerosis patients. Conclusion: Elevated leptin levels in atherosclerosis patients, alongside increased triglycerides and altered lipid profiles, suggest a role for leptin in the pathogenesis of atherosclerosis and associated cardiovascular risk. The positive correlation between waist-to-hip ratio and lipid parameters underscores the significance of central fat distribution in cardiovascular health.

Keywords: leptin, atherosclerosis, triglycerides, central fat distribution, cardiovascular disease

Significance | Understanding leptin's role in atherosclerosis and its link with metabolic and anthropometric factors can aid in cardiovascular risk management.

*Correspondence. Nalini D, Central Research Laboratory, Meenakshi Ammal Dental College, Meenakshi Academy of Higher Education and Research, Chennai, India
E-mail: drnalini.crl@madch.edu.in

Editor Aman Shah Bin Abdul Majid, Ph.D., and accepted by the Editorial Board 18 December 2021 (received for review 23 November 2021)

Introduction

Cardiovascular diseases (CVDs) such as heart disease, vascular disease, and atherosclerosis represent a major global health crisis,

Author Affiliation.
[1] Department of Biochemistry, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India
[2]Department of Biochemistry, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India.
[3]Chengalpattu Medical College and Hospital, Chengalpattu, Chennai, India.
[4]Central Research Laboratory, Meenakshi Ammal Dental College, Meenakshi Academy of Higher Education and Research, Chennai, India
[5]Central Research Laboratory, Meenakshi Academy of Higher Education and Research, Chennai, India
[6]Department of General Surgery, Sree Balaji Medical College and Hospital, Bharath Institute of Higher Education and Research (BIHER), Chennai, Tamil Nadu, India

Please Cite This:
Mathangi R, Selvaraj J et al. (2021). Leptin Levels, Lipid Profiles, and Central Fat Distribution in Atherosclerosis: Implications for Cardiovascular Disease Risk, Journal of Angiotherapy, 5(2), 1-6, 2151

accounting for over one-third of the world's morbidity (Agha & Agha, 2017). These conditions are often rooted in in atherosclerosis, a process previously understood primarily as a lipid-storage disorder. Today, obesity is recognized as a significant underlying risk factor for CVD (Babu et al., 2020). Epidemiological studies and metabolic research have consistently shown that the accumulation of excess visceral fat is linked to an elevated risk of CVD, as well as various metabolic and inflammatory disturbances (Beaumont et al., 1972; Chandrasekaran et al., 2020; Cole et al., 1997).

Excess visceral fat, also known as ectopic fat, is associated with several key metabolic abnormalities including insulin resistance, atherogenic dyslipidemia, hypertension, impaired fibrinolysis (increased risk of thrombosis), and systemic inflammation (Kannan et al., 2018). These features collectively characterize metabolic syndrome, a condition frequently observed in individuals with visceral obesity.

Adipose tissue plays a crucial role in the development of obesity-related cardiovascular diseases. Adipocytes, or fat cells, secrete a variety of hormones, peptides, and other bioactive molecules that influence cardiovascular function through endocrine, autocrine, and paracrine mechanisms. This secretion can lead to cytokine-driven inflammatory changes in the liver, systemic inflammation, and atherosclerosis. Among these bioactive substances, leptin has emerged as a key player. Discovered in 1994, leptin is a hormone that regulates food intake and is now recognized for its broader implications in obesity and cardiovascular diseases (Dardeno et al., 2010; Devarajan et al., 2021; Haouari et al., 2019; Elsayed et al., 2008).

This study aimed to investigate the role of leptin in the interplay between obesity and atherosclerosis. Additionally, it will propose effective strategies for managing obesity and its associated comorbidities (Golia et al., 2015; Gomez-Delgado et al., 2021; Hema et al., 2019; Jayaraman et al., 2021).

Materials and methods

Selection of Participants

CVD and Non-CVD Subjects

The study included two groups: CVD patients and non-CVD controls. The non-CVD control group consisted of individuals aged 35-75 years with no history of cardiovascular disease (CVD), diabetes, thyroid disorders, or arthritis. None of the controls were on medications known to influence insulin action or plasma lipoprotein-lipid levels, nor were they taking anti-inflammatory drugs. Individuals on chronic aspirin therapy were excluded from the study. All participants were required to be free from any medication affecting the variables of interest for at least three months prior to the study.

Written informed consent was obtained from all participants. Trained interviewers administered structured questionnaires to collect data on participants' demographic information, including date of birth, occupation, smoking and alcohol consumption habits. Blood samples (5 mL) were drawn from each participant, allowed to clot, and then centrifuged at 3500 rpm for 10 minutes. The serum was separated and stored at -80°C for subsequent analysis. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Approval for the research protocol, including the selection of participants and procedures, was obtained from the Institutional Review Board (IRB) of Meenakshi Academy of Higher Education and Research. Written informed consent was obtained from all participants before their enrollment in the study. Participants were provided with detailed information about the purpose of the study, the procedures involved, potential risks, and their rights to withdraw at any time without any consequences. Data collection was carried out with strict adherence to confidentiality, and participants' personal information was anonymized before analysis.

Anthropometric Measurements

Anthropometric data were collected using standardized procedures. Participants' height and weight were measured with a precision scale (0.1 kg accuracy) and a vertical stadiometer, respectively. Body mass index (BMI) was calculated using the following formula:

BMI was calculated from height and weight as follows:

$$\mathrm{BMI} = \frac{\mathrm{Weight}\ (\mathrm{Kg})}{\mathrm{Height}(\mathrm{m}^2)}$$

Waist and hip circumferences were measured with the participant standing upright, abdomen relaxed, arms at the sides, and feet together. Waist circumference was measured at the narrowest part of the torso, and hip circumference was measured at the widest part of the buttocks. These measurements were recorded to the nearest 0.1 cm. The waist-to-hip ratio (WHR) was calculated as:

$$\mathrm{WHR} = \frac{\mathrm{Waist\ circumference}\ (\mathrm{inches})}{\mathrm{Hip\ circumference}\ (\mathrm{inches})}$$

Blood pressure was measured by trained nurses using a mercury sphygmomanometer.

Serum Biochemical Analysis.

Serum glucose was estimated using GOD-POD method (Kim et al., 2020), Serum triglyceride was measured using GPO-POD-ESPT method (Ku et al., 2010), Serum cholesterol was measured using CHOD-POD method (Lovren et al., 2015), Serum HDL-cholesterol was measured using direct method (Shanthi et al., 2016); VLDL and LDL were measured by indirect method.

Statistical analysis

Data from the study were analyzed using SPSS software version 17.0. Results are presented as mean ± standard deviation (SD). Given that the data were not normally distributed, the Mann-

Table 1. Values Of Serum Triglycerides In Atherosclerosis And Control Subjects

Bmi class (kg/m^2)	Subjects	N	Triglycerides (mg/dl)
Normal Weight	Control subjects	21	124.6±14.3
	Atherosclerosis subjects	22	145.46±25.1
	P value#		0.23
Over Weight	Control subjects	46	144.13±21.3
	Atherosclerosis subjects	45	173.9±18.9
	P value#		0.005**
Obese	Control subjects	33	167.9±25.8
	Atherosclerosis subjects	33	149.1±18.8
	P value#		0.644

Table 2. Values Of Serum Glucose In Atherosclerosis And Control Subjects

Bmi class (kg/m^2)	Subjects	N	Glucose (mg/dl)
Normal Weight	Control subjects	21	113.9±15.4
	Atherosclerosis subjects	22	138.9±22.3
	P value#		0.09
Over Weight	Control subjects	46	108.9±18.2
	Atherosclerosis subjects	45	148.4±17.6
	P value#		0.005**
Obese	Control subjects	33	114.9±11.9
	Atherosclerosis subjects	33	139.3±23.6
	P value#		0.1086

Whitney U test was employed for group comparisons. Spearman's rank correlation was used to assess relationships between continuous variables. Kruskal-Wallis analysis of variance by ranks was conducted as needed. A p-value of less than 0.05 was considered statistically significant.

Results

In our study, serum leptin levels were significantly higher in atherosclerosis subjects compared to control (non-CVD) subjects across all weight categories. For normal weight subjects, the mean serum leptin was 23.1 ± 5.1 ng/mL in atherosclerosis patients versus 5.7 ± 3.8 ng/mL in controls ($p < 0.0001$). In overweight subjects, leptin levels were 30.2 ± 3.7 ng/mL in those with atherosclerosis compared to 10.5 ± 4.2 ng/mL in controls ($p < 0.0001$). Obese atherosclerosis subjects had a mean leptin level of 42.8 ± 4.5 ng/mL, significantly higher than the 29.3 ± 9.1 ng/mL observed in obese controls ($p < 0.0001$). There was a notable positive correlation between serum leptin and BMI ($r = 0.57$, $p < 0.0001$), and leptin levels in normal weight atherosclerosis subjects were higher than in overweight controls, suggesting possible leptin resistance in the pathological state.

Additionally, serum glucose, triglycerides, cholesterol, HDL, and LDL levels were significantly elevated in overweight atherosclerosis subjects compared to controls (Table 1, Table 2). Specifically, serum glucose was 148.4 ± 17.6 mg/dL in atherosclerosis subjects versus 108.9 ± 18.2 mg/dL in controls ($p = 0.005$). Serum triglycerides were 173.9 ± 18.9 mg/dL versus 144.13 ± 21.3 mg/dL ($p = 0.005$), cholesterol levels were 233.2 ± 25.1 mg/dL compared to 174.4 ± 23.4 mg/dL ($p < 0.0001$), HDL was 41.4 ± 9.1 mg/dL versus 35.1 ± 9.8 mg/dL ($p = 0.008$), and LDL was 148.6 ± 53.1 mg/dL versus 112.02 ± 12.4 mg/dL ($p = 0.0005$). In the obese category, lipid profiles were similarly elevated in both control and atherosclerosis subjects, resulting in no significant differences between the groups.

Furthermore, both systolic and diastolic blood pressures were significantly higher in overweight atherosclerosis subjects compared to controls, with systolic blood pressure at 134.4 ± 16.6 mm Hg versus 122.8 ± 20.5 mm Hg ($p = 0.003$) and diastolic blood pressure at 90 ± 12.6 mm Hg versus 84.3 ± 15.5 mm Hg ($p < 0.0001$). The waist-to-hip ratio also positively correlated with triglycerides ($r = 0.42$, $p = 0.0001$) and VLDL ($r = 0.45$, $p < 0.0001$) in atherosclerosis subjects. Overall, these findings in atherosclerosis subjects are consistent with patterns observed in AMI subjects.

Discussion

The relationship between triglycerides and cardiovascular disease (CVD) has been well-established, with triglyceride-rich lipoproteins playing a direct role in atherogenesis. Our study supports this, as elevated triglyceride levels were observed in both atherosclerosis and acute myocardial infarction (AMI) subjects compared to control groups. This finding aligns with previous research indicating that triglycerides are crucial in the development of atherosclerotic plaques, further corroborated by the presence of triglyceride-rich lipoproteins in human atheromas (Nalini et al., 2015). Notably, our data reveal a significant positive correlation between serum leptin levels and triglycerides in atherosclerosis subjects, underscoring the potential interplay between adipokines and lipid metabolism in CVD.

In addition to triglycerides, we found higher levels of serum cholesterol, HDL, LDL, and VLDL in overweight AMI and atherosclerosis subjects compared to controls. Elevated VLDL levels can lead to increased cholesterol transfer to LDL and HDL particles, potentially exacerbating cardiovascular risk (Nordestgaard & Varbo, 2015). Experimental studies suggest that hypertriglyceridemic HDL may become dysfunctional, small, dense LDL particles are more prone to oxidative modification, and a higher number of atherogenic particles could further contribute to CVD risk. These mechanisms collectively highlight how elevated triglycerides, particularly in the context of obesity, may significantly impact cardiovascular health.

The distribution of adipose tissue, rather than total fat mass, is increasingly recognized as a critical factor in the risk of diabetes, hyperlipidemia, and coronary artery disease (CAD) (Ponnulakshmi et al., 2019; Raskin Erusan et al., 2008). Studies have shown that a more centralized pattern of fat distribution is associated with a substantially higher risk of mortality (Rajagopal et al., 2012). Waist-to-hip ratio (WHR) is a widely used metric for assessing central fat distribution and has been shown to predict CVD and coronary heart disease (CHD) mortality more accurately than waist circumference or body mass index (Rajendran et al., 2012; Redinger, 2007). In our study, WHR exhibited a significant positive correlation with triglycerides and VLDL specifically in atherosclerosis subjects, highlighting its relevance in identifying individuals at higher risk for CVD.

Overall, our findings suggest that increased visceral fat, as indicated by higher levels of leptin, triglycerides, and VLDL, may contribute synergistically to the elevated risk of CVD. Addressing obesity through interventions such as antioxidants, hypolipidemic agents, and nutraceuticals could be a promising strategy for preventing CVD and other related diseases (Rocha et al., 2009; Trinder, 1959; Young, 2000). This approach could potentially mitigate the adverse effects associated with increased visceral fat and improve cardiovascular health outcomes.

Author contributions

M.R., S.J., and R.M. conceived the study and developed the research framework. J.M., P.R., N.D., Samyuktha P., and Pugazharasan provided valuable guidance and supervision throughout the study.

All authors contributed to the interpretation of the results and participated in the drafting and revision of the final manuscript.

Acknowledgment

Author was grateful to their department.

Competing financial interests

The authors have no conflict of interest.

References

Agha, M., & Agha, R. (2017). The rising prevalence of obesity: Part A: Impact on public health. International Journal of Surgical Oncology (N Y), 2(7), e17. https://doi.org/10.1097/IJ9.0000000000000017

Babu, S., Krishnan, M., Rajagopal, P., Periyasamy, V., Veeraraghavan, V., Govindan, R., Jayaraman, S. (2020). Beta-sitosterol attenuates insulin resistance in adipose tissue via IRS-1/Akt mediated insulin signaling in high fat diet and sucrose induced type-2 diabetic rats. European Journal of Pharmacology, 873, 173004. https://doi.org/10.1016/j.ejphar.2020.173004

Beamount, J. L., Crison, L. A., Coope, G. R., Feifar, Z., Frederickson, D. S., & Strasser, T. (1972). Classification of hyperlipidemias and hyperlipoproteinemias. In Standard Methods of Clinical Chemistry (Vol. 9, pp. 123-135). Academic Press.

Chandrasekaran, K., Jayaraman, S., Umapathy, V. R., Veeraraghavan, V., Venkatachalam, S., Mathayan, M., Devarajan, N., Periyasamy, V., Vijayalakshmi, M., Manikkam, R., & Rajagopal, P. (2020). Molecular docking analysis of Bcl-2 with phytocompounds. Bioinformation, 16(6), 468-473. https://doi.org/10.6026/97320630016468

Cole, T. G., Klotzsch, S. G., & McNamara, J. (1997). Measurement of triglyceride concentration. In Handbook of Lipoprotein Testing. AACC Press.

D. Kannan, L. Pari, E. Paari, T. Gunaseelan, B. Tulsi, Deepak Singh, J. Selvaraj, V. Vishnupriya, R. Ponnulakshmi, B. Shyamaladevi, & K. Madhan. (2018). Changes in glycoprotein components in high-fat diet induced type 2 diabetes: Influence of cuminaldehyde. Drug Invention Today, 10(5), 3740-3745.

Dardeno, T. A., Chou, S. H., Moon, H. S., Chamberland, J. P., Fiorenza, C. G., & Mantzoros, C. S. (2010). Leptin in human physiology and therapeutics. Frontiers in Neuroendocrinology, 31(3), 377-393. https://doi.org/10.1016/j.yfrne.2010.06.002

Devarajan, N., Jayaraman, S., Mahendra, J., Venkatratnam, P., Rajagopal, P., Palaniappan, H., & Ganesan, S. K. (2021). Berberine—A potent chemosensitizer and chemoprotector to conventional cancer therapies. Phytotherapy Research. https://doi.org/10.1002/ptr.7032

El Haouari, M., & Rosado, J. A. (2019). Phytochemical, anti-diabetic and cardiovascular properties of Urtica dioica L. (Urticaceae): A review. Mini Reviews in Medicinal Chemistry, 19(1), 63-71. https://doi.org/10.2174/1389557518666180924121528

Elsayed, E. F., Tighiouart, H., Weiner, D. E., Griffith, J., Salem, D., Levey, A. S., & Sarnak, M. J. (2008). Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. American Journal of Kidney Diseases, 52(1), 49-57. https://doi.org/10.1053/j.ajkd.2008.04.002

Golia, E., Limongelli, G., Natale, F., Fimiani, F., Maddaloni, V., Russo, P. E., Riegler, L., Bianchi, R., Crisci, M., Palma, G. D., Golino, P., Russo, M. G., Calabrò, R., & Calabrò, P. (2014). Adipose tissue and vascular inflammation in coronary artery disease. World Journal of Cardiology, 6(7), 539-554.

Gomez-Delgado, F., Katsiki, N., Lopez-Miranda, J., & Perez-Martinez, P. (2021). Dietary habits, lipoprotein metabolism and cardiovascular disease: From individual foods to dietary patterns. Critical Reviews in Food Science and Nutrition, 61(10), 1651-1669. https://doi.org/10.1080/10408398.2020.1764487

Hema, P., Selvaraj, J., & Nalini, D. (2019). Hypolipidemic properties of Aloe vera in female Swiss albino mice. Drug Invention Today, 12, 2377-2380.

Jayaraman, S., Devarajan, N., & Rajagopal, P. (2021). β-Sitosterol circumvents obesity induced inflammation and insulin resistance by down-regulating IKKβ/NF-κB and JNK signaling pathways in adipocytes of type 2 diabetic rats. Molecules, 26(7), 2101. https://doi.org/10.3390/molecules26072101

Kim, H. W., Shi, H., Winkler, M. A., Lee, R., & Weintraub, N. L. (2020). Perivascular adipose tissue and vascular perturbation/atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology, 40(11), 2569-2576. https://doi.org/10.1161/ATVBAHA.120.312470

Ku, I. A., Farzaneh-Far, R., Vittinghoff, E., Zhang, M. H., Na, B., & Whooley, M. A. (2011). Association of low leptin with cardiovascular events and mortality in patients with stable coronary artery disease: The Heart and Soul Study. Atherosclerosis, 217(2), 503-508. https://doi.org/10.1016/j.atherosclerosis.2010.10.047

Lovren, F., Teoh, H., & Verma, S. (2015). Obesity and atherosclerosis: Mechanistic insights. Canadian Journal of Cardiology, 31(2), 177-183. https://doi.org/10.1016/j.cjca.2014.11.031

Nalini, D., Karthick, R., Shirin, V., Manohar, G., & Malathi, R. (2015). Leptin: A possible link between obesity, inflammation, and cardiovascular diseases. Thrombosis Journal, 13, 1-7. https://doi.org/10.1186/s12959-015-0042-4

Nordestgaard, B. G., & Varbo, A. (2014). Triglycerides and cardiovascular disease. The Lancet, 384(9943), 626-635. https://doi.org/10.1016/S0140-6736(14)61177-6

Ponnulakshmi, R., Shyamaladevi, B., Vijayalakshmi, P., & Selvaraj, J. (2019). In silico and in vivo analysis to identify the antidiabetic activity of beta-sitosterol in adipose tissue of high-fat diet and sucrose induced type-2 diabetic experimental rats. Toxicology Mechanisms and Methods, 29(4), 276-290. https://doi.org/10.1080/15376516.2018.1545815

Rajagopal, R., Devarajan, N., Ganesan, M., & Raghunathan, M. (2012). Correlation between obesity and inflammation in cardiovascular diseases: Evaluation of leptin and inflammatory cytokines. Open Journal of Endocrine and Metabolic Diseases, 2, 7-15. https://doi.org/10.4236/ojemd.2012.22002

Rajendran, K., Devarajan, N., Ganesan, M., & Ragunathan, M. (2012). Obesity, inflammation, and acute myocardial infarction: Expression of leptin, IL-6, and high sensitivity-CRP in Chennai based population. Thrombosis Journal, 10, 1-6. https://doi.org/10.1186/1477-9560-10-13

Raskin, E. R., Nalini, D., & Malathi, R. (2008). Obesity, inflammation, and metabolic disorders. Indian Journal of Science and Technology, 1(4), 1-5. https://doi.org/10.17485/ijst/2008/v1i4.8

Redinger, R. N. (2007). The pathophysiology of obesity and its clinical manifestations. Gastroenterology & Hepatology (N Y), 3(11), 856-863.

Rocha, V., & Libby, P. (2009). Obesity, inflammation, and atherosclerosis. Nature Reviews Cardiology, 6, 399-409. https://doi.org/10.1038/nrcardio.2009.55

Shanthi, N., Mani, R., Nalini, D., Hema, P., & Thiriveni, G. S. B. (2016). Leptin: An immunomodulator in peripheral blood mononuclear cells. IOSR Journal of Dental and Medical Sciences, 15(1), 52-57.

Trinder, P. (1959). Determination of blood glucose using 4-aminoantipyrine. Journal of Clinical Pathology, 22, 246. https://doi.org/10.1136/jcp.22.2.246-b

World Health Organization. (n.d.). Cardiovascular diseases (CVDs). Retrieved from https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

Young, D. S. (2000). Effects of drugs on clinical laboratory tests (5th ed.). AACC Press.