GMR
The Original

LEPTIN RECEPTOR GENE EXPRESSION AND ITS ASSOCIATION WITH CARDIOVASCULAR RISK MARKERS IN OBESE SUBJECTS: A CASE–CONTROL STUDY FROM SOUTH INDIA

Swathi Thoduvayil[1], Mohana Thiruchenduran[2], Dinesh Roy Divakaran[3], Jeyapal Viddhyadharan[4], Dhanavel Anandhi[5]

[1]Research scholar, Meenakshi academy of higher education and research (Deemed to be University), Chennai, Tamil Nadu, India.
Email: swathirajesh10@gmail.com
[2]Associate Professor, Department of Biochemistry, Meenakshi Ammal Dental College and Hospital, Meenakshi Academay of Higher Education and Research (Deemed to be University), Chennai, Tamil Nadu, India
[3]CEO&senior cytogeneticist, Genetika Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India
[4]Chairman and Senior consultant Cardiologist, Hridayalaya Heart and Robotics Research Centre Pvt.Ltd, Thiruvananthapuram, Kerala, India
[5]Assistant professor and scientist, Meenakshi Ammal Dental college and hospital, Meenakshi academy of higher education and research (Deemed to be University), Chennai, Tamil Nadu, India
*Corresponding Author: Email: swathirajesh10@gmail.com

ABSTRACT

Background: Obesity is a major global health concern associated with chronic inflammation, metabolic dysregulation, and an increased risk of cardiovascular disease (CVD). Altered leptin receptor (LEPR) signalling has been implicated in obesity-related cardiometabolic complications; however, evidence regarding LEPR gene expression and its relationship with cardiovascular risk markers in the South Indian population remains limited.

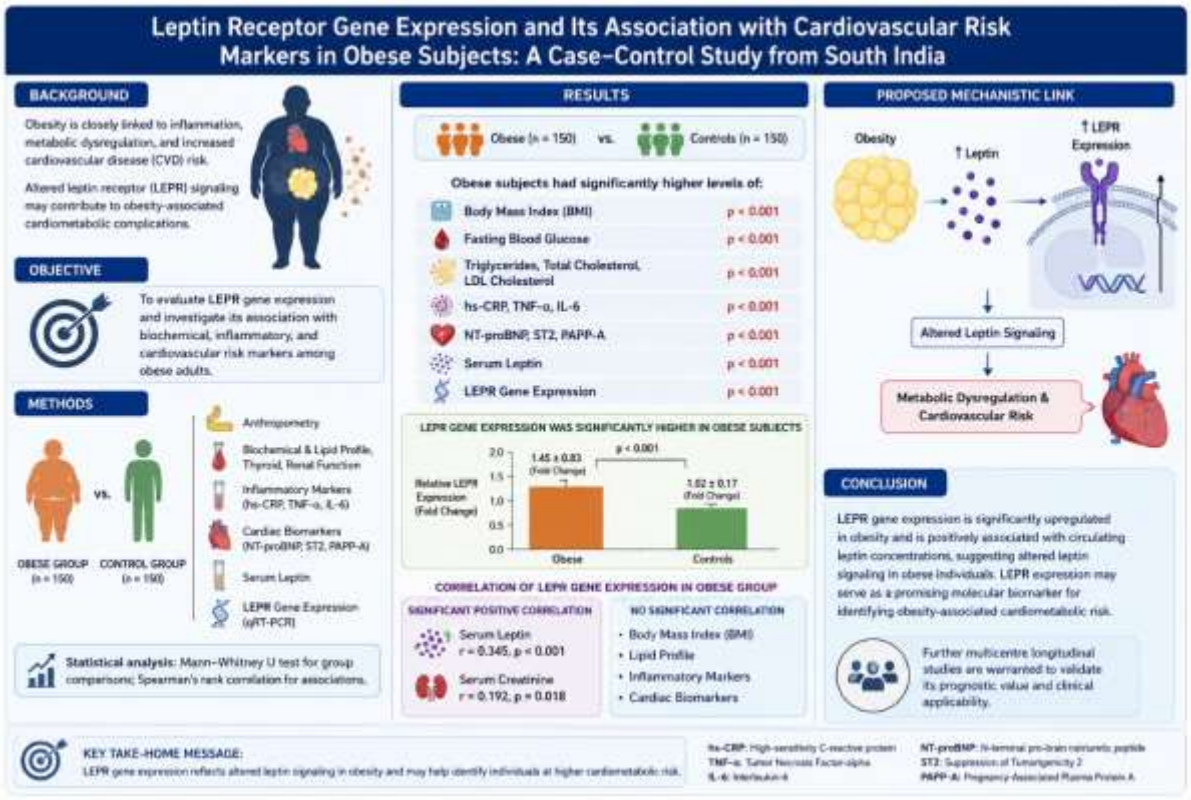
Objective: To evaluate LEPR gene expression and investigate its association with biochemical, inflammatory, and cardiovascular risk markers among obese adults.

Methods: A hospital-based case–control study was conducted involving 300 adults, including 150 obese subjects and 150 apparently healthy controls. Anthropometric measurements, fasting biochemical parameters, lipid profile, thyroid profile, renal function tests, inflammatory biomarkers (hs-CRP, TNF-α, IL-6), cardiac biomarkers (NT-proBNP, ST2, and PAPP-A), serum leptin concentrations, and LEPR gene expression were assessed. Relative LEPR expression was quantified using quantitative real-time polymerase chain reaction. Group comparisons were performed using the Mann–Whitney U test, while correlations between LEPR expression and clinical variables were analysed using Spearman's rank correlation.

Results: Obese participants demonstrated significantly higher body mass index, fasting blood glucose, triglycerides, total cholesterol, LDL cholesterol, hs-CRP, TNF-α, IL-6, NT-proBNP, ST2, PAPP-A, serum leptin concentrations, and LEPR gene expression than controls (all $p < 0.001$). LEPR gene expression was significantly elevated in obese subjects (1.45 ± 0.83 vs. 1.02 ± 0.17-fold change; $p < 0.001$). Within the obese group, LEPR expression showed a significant positive correlation with serum leptin ($r = 0.345$, $p < 0.001$) and serum creatinine ($r = 0.192$, $p = 0.018$), whereas no significant associations were observed with body mass index, lipid profile, inflammatory markers, or cardiac biomarkers.

Conclusion: LEPR gene expression is significantly upregulated in obesity and is positively associated with circulating leptin concentrations, suggesting altered leptin signaling in obese individuals. LEPR expression may serve as a promising molecular biomarker for identifying obesity-associated cardiometabolic risk. Further multicentre longitudinal studies are warranted to validate its prognostic value and clinical applicability.

KEYWORDS: Leptin receptor; Gene expression; Obesity; Cardiovascular risk; Biomarkers



1. INTRODUCTION

Obesity has become one of the most significant public health challenges worldwide and is a major contributor to the increasing burden of non-communicable diseases (NCDs). The World Health Organization estimates that more than one billion people are living with obesity, with prevalence continuing to rise because of rapid urbanization, unhealthy dietary patterns, reduced physical activity, and socioeconomic transitions. Obesity substantially increases the risk of type 2 diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, and cardiovascular disease (CVD), making it one of the leading causes of preventable morbidity and mortality globally [1,2]. South Asian populations, including Indians, exhibit greater visceral adiposity, insulin resistance, and cardiovascular risk at comparatively lower body mass indices than Western populations, highlighting the importance of identifying molecular determinants underlying obesity-related cardiovascular complications [3].

Adipose tissue is now recognized as a metabolically active endocrine organ that secretes several bioactive molecules known as adipokines, which regulate energy homeostasis, inflammation, and metabolic function. Among these, leptin is a 16-kDa peptide hormone predominantly produced by white adipocytes and plays a pivotal role in appetite regulation, energy expenditure, glucose metabolism, and neuroendocrine function [4]. Under physiological conditions, leptin binds to the leptin receptor (LEPR), a member of the class I cytokine receptor family encoded by the LEPR gene located on chromosome 1p31. The long receptor isoform (LEPRb) activates intracellular signaling pathways, including Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol-3 kinase (PI3K), and mitogen-activated protein kinase (MAPK), thereby regulating food intake, insulin sensitivity, lipid metabolism, and inflammatory responses [5].

Despite elevated circulating leptin concentrations in obese individuals, appetite suppression and energy regulation are often impaired because of leptin resistance, a condition characterized by defective leptin receptor signaling. Altered LEPR gene expression may contribute to impaired leptin responsiveness, leading to excessive adiposity, chronic low-grade inflammation, insulin resistance, and metabolic dysfunction [4,6]. Beyond its metabolic role, leptin has emerged as an important mediator linking obesity with cardiovascular disease. Experimental and clinical studies have demonstrated that hyperleptinemia and impaired leptin signaling promote sympathetic nervous system activation, endothelial dysfunction, oxidative stress, vascular smooth muscle proliferation, and chronic inflammation, all of which accelerate hypertension, atherosclerosis, and adverse cardiovascular remodeling [6,7,8].

Several conventional cardiovascular risk markers, including body mass index (BMI), waist circumference, blood pressure, fasting blood glucose, glycated hemoglobin (HbA1c), serum lipid profile, and inflammatory biomarkers, are routinely used to assess cardiometabolic risk in obese individuals. Emerging evidence suggests that abnormalities in leptin signaling may influence these markers through complex interactions between adipose tissue, vascular endothelium, and immune pathways [5,7]. However, most previous investigations have focused on circulating leptin concentrations or LEPR gene polymorphisms, while relatively few studies have evaluated LEPR gene expression and its association with cardiovascular risk factors. Furthermore, available evidence remains inconsistent across different ethnic populations, emphasizing the need for region-specific molecular studies.

Given the high prevalence of obesity and cardiovascular disease in India, understanding alterations in LEPR gene expression may improve early cardiovascular risk stratification and provide novel insights into the pathophysiology of

obesity. Therefore, the present case–control study aimed to evaluate LEPR gene expression and determine its association with cardiovascular risk markers among obese adults from South India. The findings may contribute to the identification of potential molecular biomarkers for early detection and personalized management of obesity-associated cardiovascular disease.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This hospital-based case–control study was conducted between April 2023 and April 2025 in collaboration with Hridayala Heart and Robotic Research Centre Pvt. Ltd. and Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India. The study protocol was approved by the Institutional Ethics Committee of Genetika (Ref. No. 08/2023/IECG; approved on 06 April 2023) and was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants before enrolment. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2 Study Population

A total of 300 adults were enrolled, including 150 obese individuals (case group) and 150 healthy non-obese individuals (control group). Cases were consecutively recruited from hospitals in Kerala and community-based screening programmes conducted during World Heart Day (29 September) and World Diabetes Day (14 November). Healthy controls were recruited from the same screening programmes and geographical region to minimise selection bias.

Eligible participants were adults aged > 23 years. Obesity was defined according to the World Health Organization (WHO) Asia–Pacific criteria as a body mass index (BMI) ≥25 kg/m², whereas controls had a BMI <25 kg/m² and no known history of obesity or major chronic illness [1].

Participants were excluded if they had acute or chronic inflammatory diseases, malignancy, autoimmune disorders, chronic liver or kidney disease, pregnancy, severe endocrine disorders other than obesity, or were receiving long-term corticosteroids, immunosuppressive agents, or medications known to significantly influence leptin metabolism. Individuals unwilling to provide written informed consent were also excluded.

2.3 Clinical Assessment and Sample Collection

Demographic characteristics, medical history, medication history, lifestyle habits, and anthropometric measurements were recorded using a standardized predesigned questionnaire. Body weight and height were measured using calibrated instruments, and BMI was calculated as weight (kg) divided by height squared (m²). Waist circumference was measured according to standard WHO recommendations using a non-elastic measuring tape.

Following an overnight fast of 8–12 hours, approximately 6–8 mL of peripheral venous blood was collected under aseptic conditions. Samples intended for biochemical analyses were collected in plain vacutainer tubes, whereas blood for molecular analysis was collected in EDTA tubes. Specimens were centrifuged at 3000 rpm for 10 minutes, serum was separated immediately, aliquoted, and stored at −20°C until laboratory analysis.

2.4 Biochemical, Inflammatory, and Cardiac Biomarker Analysis

Serum fasting blood glucose, lipid profile (triglycerides, total cholesterol, HDL-cholesterol, and LDL-cholesterol), thyroid profile (T3, T4, and TSH), renal function parameters (urea, creatinine, and uric acid), and serum leptin concentrations were analysed using standard automated laboratory methods following the manufacturers' instructions and routine quality-control procedures.

Inflammatory and cardiovascular biomarkers, including high-sensitivity C-reactive protein (hs-CRP), tumour necrosis factor-alpha (TNF-α), and N-terminal pro-B-type natriuretic peptide (NT-proBNP), were quantified using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits (Origin Diagnostics & Research, Clappana, Kerala, India; Cat. Nos. OPK8534, RK00030, and OPK1212) according to the manufacturer's instructions. Optical density was measured using a Thermo Scientific™ Multiskan™ FC Microplate Photometer, and biomarker concentrations were calculated from standard calibration curves. All assays were performed in duplicate under standardized laboratory conditions to ensure analytical accuracy, precision, and reproducibility.

2.5 LEPR Gene Expression Analysis

Peripheral blood samples collected in EDTA tubes were processed for total RNA extraction using standardized molecular biology protocols. RNA quality and concentration were assessed before complementary DNA (cDNA) synthesis. Relative leptin receptor (LEPR) gene expression was quantified using quantitative real-time polymerase chain reaction (qRT-PCR). Gene expression levels were normalized against an appropriate endogenous housekeeping gene, and relative expression was calculated using the comparative 2^−ΔΔCt method, with results expressed as fold change relative to the control group. All molecular analyses were performed under standardized laboratory conditions to ensure analytical consistency and reproducibility.

2.6 Sample Size Determination

The minimum sample size was estimated using the formula $n = Z^2pq/d^2$, assuming a 95% confidence level ($Z = 1.96$), an obesity prevalence of 16%, and a precision of 5%. Considering participant availability during the study period and the

exploratory nature of this molecular biomarker investigation, a total of 300 participants (150 cases and 150 controls) were enrolled, providing adequate statistical precision for comparative analyses.

2.7 Statistical Analysis

Statistical analyses were performed using Stata version 17.0 (StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages.

The normality of continuous variables was evaluated using the Shapiro–Wilk test. As most variables were not normally distributed, comparisons between obese subjects and healthy controls were performed using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate.

Associations between LEPR gene expression and biochemical, inflammatory, and cardiovascular biomarkers were evaluated using Spearman's rank correlation coefficient (ρ). All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

3. RESULTS

A total of 150 subjects were analysed in each group. Baseline demographic and anthropometric characteristics are summarised in Table 1.

Table 1. Demographic and anthropometric characteristics of the Test (obese/CVD) and Control groups

Characteristic	Test group (n = 150)	Control group (n = 150)	p-value
Age (years), mean ± SD	45.38 ± 10.16	41.51 ± 11.98	0.003
Female sex, n (%)	90 (60.0%)	87 (58.0%)	0.814
Body mass index (kg/m²), mean ± SD	31.08 ± 3.77	24.28 ± 3.57	<0.001

The case group had significantly higher BMI than the control group ($p < 0.001$). Sex distribution did not differ significantly between groups, while the cases group was on average approximately four years older than the Control group ($p = 0.003$).

3.1 Biochemical, inflammatory, and cardiac biomarker profile

All 19 biochemical, hormonal, inflammatory, and cardiac variables examined differed significantly between the case and control groups (Table 2). The case LDL cholesterol, TSH, hs-CRP, urea, creatinine, uric acid, leptin, NT-proBNP, TNF-α, IL-6, ST2, and PAPP-A, together with lower HDL cholesterol, T3, and T4 – consistent with the expected metabolic and inflammatory consequences of obesity and established cardiovascular disease. Of particular relevance to this study, LEPR gene expression was significantly higher in the obese group than in the control group (1.45 ± 0.83 vs. 1.02 ± 0.17 fold change; $p < 0.001$) (Figure 1).

Table 2. Comparison of biochemical, hormonal, inflammatory, and cardiac biomarkers between the Test and Control groups

Variable	Test group mean ± SD	Control group mean ± SD	p-value
Fasting blood sugar (mg/dL)	136.62 ± 40.88	94.06 ± 19.49	<0.001
Serum triglyceride (mg/dL)	164.61 ± 30.28	112.80 ± 17.99	<0.001
Serum total cholesterol (mg/dL)	241.73 ± 35.50	175.77 ± 20.33	<0.001
Serum HDL cholesterol (mg/dL)	47.75 ± 12.27	62.77 ± 14.53	<0.001
Serum LDL cholesterol (mg/dL)	161.05 ± 41.04	90.44 ± 24.50	<0.001
Tri-iodothyronine, T3	103.99 ± 32.51	124.17 ± 22.85	<0.001

Variable	Test group mean ± SD	Control group mean ± SD	p-value
Tetra-iodothyronine, T4	6.50 ± 2.52	7.84 ± 2.10	<0.001
Thyroid stimulating hormone, TSH	5.45 ± 3.61	3.11 ± 1.61	<0.001
hs-C-reactive protein, hsCRP (mg/L)	3.90 ± 3.06	0.94 ± 0.34	<0.001
Urea (mg/dL)	23.19 ± 7.46	21.58 ± 5.86	0.038
Enzymatic creatinine (mg/dL)	1.08 ± 0.40	0.86 ± 0.26	<0.001
Uric acid (mg/dL)	6.19 ± 1.69	4.86 ± 1.42	<0.001
Serum leptin (ng/mL)	16.11 ± 11.70	9.11 ± 4.79	<0.001
NT-proBNP (pg/mL)	127.22 ± 40.85	67.84 ± 34.34	<0.001
TNF-α (pg/mL)	28.59 ± 11.43	13.39 ± 5.00	<0.001
Interleukin-6, IL-6 (pg/mL)	7.31 ± 3.77	2.36 ± 1.79	<0.001
ST2 (ng/mL)	24.80 ± 9.03	12.48 ± 5.63	<0.001
PAPP-A (mIU/L)	30.91 ± 12.00	18.97 ± 6.46	<0.001
Leptin receptor (LEPR) gene expression (fold change)	1.45 ± 0.83	1.02 ± 0.17	<0.001

Of particular relevance to this study, LEPR gene expression was significantly higher, and considerably more variable, in the obese group than the control group (1.45 ± 0.83 vs 1.02 ± 0.17 fold-change; $p < 0.001$), indicating both a shift in central tendency and a wider spread of expression values among obese subjects with CVD.

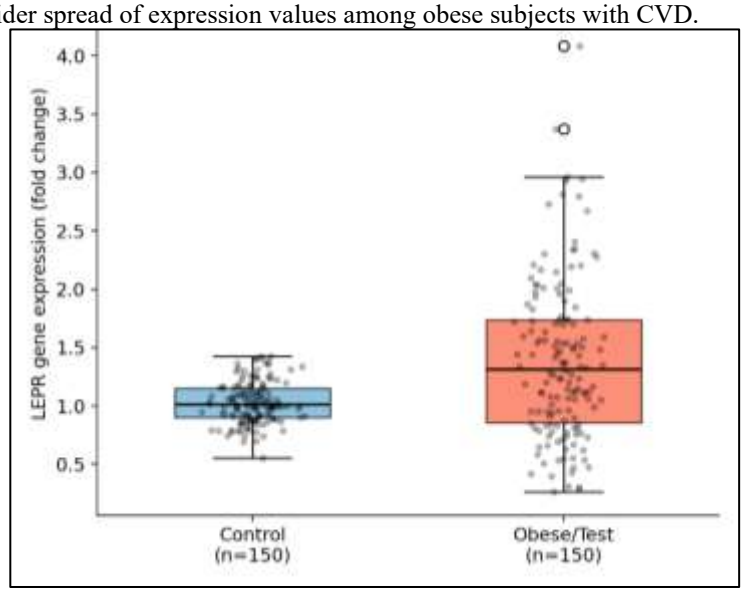


Figure 1. Comparison of relative LEPR gene expression between obese subjects and healthy controls.

3.2 Correlation of LEPR gene expression with clinical and biochemical variables within the case group.
To characterise what drives variation in LEPR expression among subjects who already share the obesity phenotype, Pearson correlations were calculated between LEPR expression and all other continuous variables within the Test group alone (Table 3). The overall correlation pattern between LEPR gene expression and the investigated biomarkers is illustrated in Figure 3. Within the obese group, LEPR gene expression correlated significantly and positively with serum leptin ($r = 0.345$, $p < 0.001$) (Figure 2).

Table 3. Correlation of LEPR gene expression with clinical and biochemical variables within the case group (n = 150)

Variable	Pearson r	p-value
Serum leptin	0.345	<0.001
Enzymatic creatinine	0.192	0.018
hsCRP	0.155	0.059
ST2	−0.153	0.063
Uric acid	−0.147	0.073
TNF-α	−0.136	0.098
Urea	−0.131	0.110
Total cholesterol	−0.126	0.125
Age	−0.092	0.265
LDL cholesterol	−0.087	0.291
PAPP-A	−0.067	0.418
HDL cholesterol	−0.059	0.471
T3	−0.054	0.510
IL-6	0.054	0.511
Fasting blood sugar	−0.037	0.653
BMI	0.031	0.711
Triglyceride	−0.030	0.716
T4	−0.020	0.810
NT-proBNP	−0.013	0.873
TSH	0.003	0.970

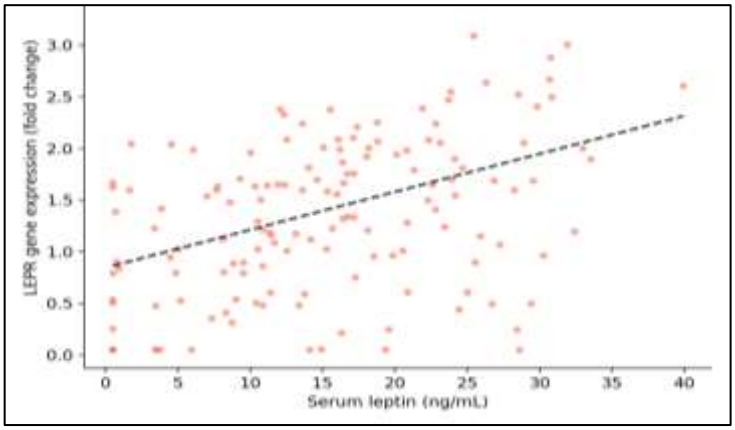


Figure 2. Correlation between LEPR gene expression and serum leptin concentrations among obese subjects.

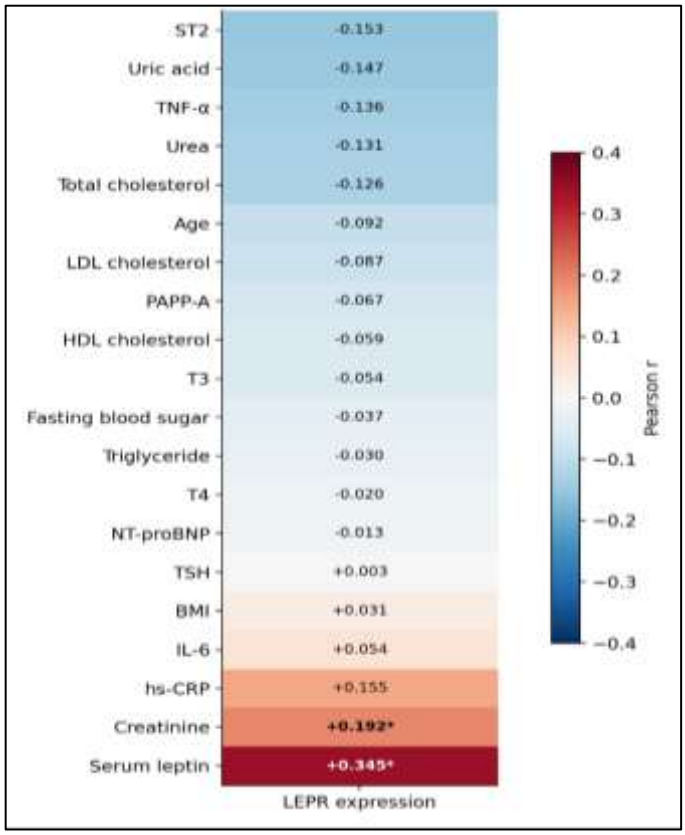


Figure 3. Heatmap showing correlations between LEPR gene expression and clinical biomarkers.

Within the obese group, LEPR gene expression correlated significantly and positively only with serum leptin ($r = 0.35$, $p < 0.001$) and, more weakly, with serum creatinine ($r = 0.19$, $p = 0.018$). hs-CRP showed a borderline positive association ($r = 0.15$, $p = 0.059$). No other biomarker – including BMI, fasting glucose, the lipid profile, TNF-α, IL-6, NT-proBNP, ST2, or PAPP-A – showed a statistically significant association with LEPR expression within this group.

When the analysis was repeated on the combined whole population data($n = 300$), LEPR expression correlated significantly with a much larger number of variables, including hs-CRP, IL-6, BMI, creatinine, triglycerides, NT-proBNP, HDL, LDL, total cholesterol, fasting glucose, T3, PAPP-A, TNF-α, T4, ST2, and TSH (all $p < 0.05$).

4. DISCUSSION

The present study demonstrated significantly higher LEPR gene expression in obese individuals than in healthy controls, accompanied by elevated serum leptin concentrations and adverse metabolic, inflammatory, and cardiovascular biomarker profiles. These findings support the growing evidence that dysregulated leptin signalling plays an important role in obesity-associated cardiometabolic dysfunction. Vilariño-García et al. [9] reported that obesity is characterized by chronic hyperleptinemia and impaired leptin receptor signalling, resulting in persistent inflammation, insulin resistance, endothelial dysfunction, and increased cardiovascular risk. Their review emphasized that altered leptin signalling contributes to metabolic abnormalities despite elevated circulating leptin concentrations. Our findings are consistent with their observations, as obese participants showed significantly higher serum leptin levels together with increased LEPR gene expression, suggesting that receptor upregulation may represent a compensatory response to leptin resistance rather than restoration of normal signaling.

Similarly, Flier and Ahima [10] highlighted that leptin resistance develops primarily because of defects in intracellular signalling pathways involving SOCS3 activation, PTP1B overexpression, hypothalamic inflammation, and impaired receptor trafficking rather than reduced receptor abundance. They proposed that receptor expression may remain unchanged or even increase despite impaired biological activity. The significantly elevated LEPR gene expression observed in our study strongly supports this concept and suggests that increased receptor transcription does not necessarily translate into effective leptin signaling in obese individuals.

A significant positive correlation between serum leptin concentration and LEPR gene expression was observed in the present study. Comparable findings were described by Gruzdeva et al. [11], who demonstrated that chronic hyperleptinemia induces adaptive alterations in LEPR expression while simultaneously activating inhibitory pathways that reduce downstream JAK2/STAT3 signaling. Their review concluded that elevated leptin and increased receptor expression frequently coexist in obese individuals because compensatory receptor upregulation cannot overcome post-receptor signalling defects. Our results closely parallel these observations, reinforcing the hypothesis that altered LEPR expression reflects compensation for chronic leptin resistance.

Our obese participants also exhibited significantly higher fasting blood glucose, triglycerides, total cholesterol, LDL cholesterol, and lower HDL cholesterol than controls, indicating marked metabolic dysfunction. Münzberg H et al. [12] described leptin as a central regulator of glucose homeostasis, lipid metabolism, and energy balance and reported that impaired leptin signaling contributes to insulin resistance and dyslipidemia. Although our study demonstrated substantial metabolic disturbances, LEPR gene expression was not significantly associated with fasting glucose or lipid parameters within the obese group. This discrepancy suggests that once obesity becomes established, metabolic abnormalities are influenced by multiple mechanisms beyond receptor expression alone, including insulin resistance, adipose tissue dysfunction, and genetic susceptibility.

Inflammatory biomarkers, including hs-CRP, TNF-α, and IL-6, were significantly elevated among obese individuals, confirming the presence of chronic low-grade inflammation. Christen T et al. [13] reported that leptin functions as a pro-inflammatory cytokine capable of stimulating macrophage activation, oxidative stress, endothelial dysfunction, and vascular inflammation, thereby promoting cardiovascular disease progression. While their review demonstrated strong mechanistic links between leptin signalling and inflammation, our study identified only a borderline association between LEPR gene expression and hs-CRP, with no significant correlation with TNF-α or IL-6 within obese subjects. These findings suggest that inflammatory activation during obesity may depend more on downstream signalling pathways and adipose tissue-derived cytokines than on LEPR gene expression itself.

The present study further demonstrated significantly elevated NT-proBNP, ST2, and PAPP-A concentrations among obese participants, indicating increased cardiovascular stress. Shin et al. [14] recently demonstrated that enhanced leptin receptor signalling contributes to obesity-associated sympathetic activation and hypertension through carotid body mechanisms independent of changes in body weight. Although we observed significant elevations in cardiovascular biomarkers among obese participants, LEPR gene expression was not significantly associated with NT-proBNP or ST2. This difference may reflect tissue-specific regulation of leptin receptors, where peripheral blood gene expression may not accurately represent receptor activity within cardiovascular tissues.

Interestingly, LEPR gene expression showed a weak but significant positive association with serum creatinine in our study. Gruzdeva et al. [11] suggested that excessive leptin signalling contributes to renal inflammation, oxidative stress, and glomerular fibrosis during obesity. Our findings partially support these observations and indicate that increased LEPR expression may also reflect early obesity-related renal involvement, although the relatively weak correlation suggests that additional molecular mechanisms contribute to renal dysfunction.

Overall, our findings are in agreement with most recent evidence demonstrating that obesity is associated with hyperleptinemia, altered LEPR expression, systemic inflammation, and increased cardiometabolic risk. Unlike several previous studies that primarily evaluated circulating leptin concentrations or LEPR polymorphisms, the present investigation assessed LEPR gene expression together with biochemical, inflammatory, and cardiovascular biomarkers in a South Indian population. This integrated molecular approach provides additional evidence that increased LEPR gene expression is more likely to represent a compensatory response to chronic leptin resistance than an indicator of preserved receptor function, supporting its potential utility as a biomarker for obesity-associated cardiometabolic risk.

5. CONCLUSION

The present study demonstrated significantly increased LEPR gene expression in obese individuals, accompanied by adverse metabolic, inflammatory, and cardiovascular biomarker profiles. LEPR expression was positively associated with circulating leptin concentrations, supporting the presence of altered leptin signaling in obesity. However, its limited correlation with conventional cardiovascular risk markers suggests that obesity-associated cardiometabolic dysfunction is mediated through complex molecular mechanisms beyond receptor expression alone. These findings highlight the potential utility of LEPR gene expression as a complementary biomarker for early cardiometabolic risk assessment. Future multicentre prospective studies incorporating mechanistic and functional analyses are required to validate its diagnostic and prognostic significance.

REFERENCES

1. Mendis S, Graham I, Branca F, Collins T, Tukuitonga C, Gunawardane A, Narula J. Alarming Rise of Obesity: The 4th United Nations High-Level Meeting on Noncommunicable Diseases and Mental Health Should Advance Action to Tackle Obesity. Glob Heart. 2025 Aug 28;20(1):70. doi: 10.5334/gh.1459. PMID: 40894082; PMCID: PMC12396183.

2. Collaborators G 2015 O. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. New England Journal of Medicine. 2017;377(1):13-27. doi:10.1056/nejmoa1614362
3. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab. 2008 Nov;93(11 Suppl 1):S9-30. doi: 10.1210/jc.2008-1595. PMID: 18987276.
4. Friedman JM. Leptin and the endocrine control of energy balance. Nat Metab. 2019 Aug;1(8):754-764. doi: 10.1038/s42255-019-0095-y. Epub 2019 Aug 12. PMID: 32694767.
5. Kang KW, Ok M, Lee SK. Leptin as a Key between Obesity and Cardiovascular Disease. J Obes Metab Syndr. 2020 Dec 30;29(4):248-259. doi: 10.7570/jomes20120. PMID: 33342767; PMCID: PMC7789022.
6. Sáinz N, Barrenetxe J, Moreno-Aliaga MJ, Martínez JA. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. Metabolism. 2015 Jan;64(1):35-46. doi: 10.1016/j.metabol.2014.10.015. Epub 2014 Oct 23. PMID: 25497342.
7. Correia ML, Haynes WG. Leptin, obesity and cardiovascular disease. Curr Opin Nephrol Hypertens. 2004 Mar;13(2):215-23. doi: 10.1097/00041552-200403000-00010. PMID: 15202616.
8. Landecho MF, Tuero C, Valentí V, Bilbao I, de la Higuera M, Frühbeck G. Relevance of Leptin and Other Adipokines in Obesity-Associated Cardiovascular Risk. Nutrients. 2019 Nov 5;11(11):2664. doi: 10.3390/nu11112664. PMID: 31694146; PMCID: PMC6893824.
9. Vilariño-García T, Polonio-González ML, Pérez-Pérez A, Ribalta J, Arrieta F, Aguilar M, Obaya JC, Gimeno-Orna JA, Iglesias P, Navarro J, Durán S, Pedro-Botet J, Sánchez-Margalet V. Role of Leptin in Obesity, Cardiovascular Disease, and Type 2 Diabetes. Int J Mol Sci. 2024 Feb 16;25(4):2338. doi: 10.3390/ijms25042338. PMID: 38397015; PMCID: PMC10888594.
10.Flier JS, Ahima RS. Leptin physiology and pathophysiology: knowns and unknowns 30 years after its discovery. J Clin Invest. 2024 Jan 2;134(1):e174595. doi: 10.1172/JCI174595. PMID: 38165042; PMCID: PMC10760948.
11.Gruzdeva, O., Gorbatovskaya, E., Dyleva, Y., Dolmatova, S., Romanova, A., Fanaskova, E., Tarasov, R., Stasev, A., & Barbarash, O. (2025). Systemic and Local Leptin Resistance in Patients with Cardiovascular Diseases. Diagnostics, 15(21), 2772. https://doi.org/10.3390/diagnostics15212772
12.Münzberg H, Heymsfield SB, Berthoud HR, Morrison CD. History and future of leptin: Discovery, regulation and signaling. Metabolism. 2024 Dec;161:156026. doi: 10.1016/j.metabol.2024.156026. Epub 2024 Sep 7. PMID: 39245434; PMCID: PMC11570342.
13.Christen T, De Mutsert R, Smit RAj, et al. The association between leptin and subclinical cardiovascular disease explained by body fat: Observational and Mendelian randomization analyses. Nutrition Metabolism and Cardiovascular Diseases. 2023;33(5):1077-1086. doi:10.1016/j.numecd.2023.02.013
14.Shin MK, Kim LJ, Davaanyam D, Amorim MR, Lee SM, Tang WY, Polotsky VY. Leptin receptor downregulation in the carotid body treats obesity-induced hypertension. J Neurophysiol. 2025 Mar 1;133(3):892-903. doi: 10.1152/jn.00133.2024. Epub 2025 Feb 4. PMID: 39903168; PMCID: PMC12186234.