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ORIGINAL ARTICLE

The Relationship of Leptin Levels with Lipid Profile and Cardiovascular Disease Risk Factors in Obese Individuals

Obez Bireylerde Leptin Düzeylerinin Lipid Profili ve Kardiyovasküler Hastalık Risk Faktörleri ile İlişkisi

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Abstract

Aims: This study was conducted as a systematic literature review to evaluate the effects of leptin hormone on lipid profile and cardiovascular disease (CVD) risk factors in obese individuals. Leptin is an adipokine playing a key role in energy balance and metabolic processes, and its serum levels are significantly increased in obesity. The hypothesis that increased leptin levels may negatively affect cardiovascular risk factors by contributing to dyslipidemia was investigated.
Methods: PubMed, Scopus, and Web of Science databases were searched for studies published between January 2010 and October 2023. Eighteen studies meeting the inclusion criteria were analyzed. Data were collected to assess the associations between leptin levels and lipid profile parameters (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides) and cardiovascular risk factors, such as markers of inflammation, blood pressure (BP), and insulin resistance (IR).
Results: Positive and statistically significant associations were found between leptin levels and total cholesterol ($r=0.45$, $p<0.001$) and LDL-cholesterol ($r=0.47$, $p<0.001$). In addition, leptin levels were positively correlated with triglyceride levels ($r=0.35$, $p<0.01$) and negatively correlated with HDL-cholesterol levels ($r=-0.30$, $p<0.01$). Positive relationships were also found between leptin and markers of inflammation; for example, a significant correlation ($r=0.42$, $p<0.001$) was observed between leptin and C-reactive protein (CRP). There was a tendency for increased BP and IR with increasing leptin levels.
Conclusion: Increased leptin levels in obese individuals have negative effects on lipid profiles and increase CVD risk factors. A positive correlation has been observed between leptin and LDL cholesterol, but the causal relationship has not been conclusively established. Furthermore, leptin may accelerate the development of atherosclerosis by increasing markers of inflammation. These findings suggest that leptin may be a potential biomarker in the assessment of obesity-related cardiovascular risks. Leptin-targeted therapeutic approaches and strategies to overcome leptin resistance may be important in the management of obesity and related cardiometabolic disorders.

Keywords: Cardiovascular disease, Dyslipidemia, Inflammation, Insulin resistance, Leptin, Lipid profile, Obesity

ÖZ

Amaç: Bu çalışma, obez bireylerde leptin hormonunun lipid profili ve kardiyovasküler hastalık risk faktörleri üzerindeki etkilerini değerlendirmek amacıyla sistematik bir literatür taraması olarak gerçekleştirilmiştir. Leptin, enerji dengesi ve metabolik süreçlerde önemli rol oynayan bir adipokindir ve obezite durumunda serum seviyeleri belirgin şekilde artar. Artan leptin düzeylerinin dislipidemiye katkıda bulunarak kardiyovasküler risk faktörlerini olumsuz etkileyebileceği hipotezi araştırılmıştır.
Gereç ve Yöntemler: Ocak 2010 ile Ekim 2023 tarihleri arasında PubMed, Scopus ve Web of Science veri tabanlarında yayınlanmış çalışmalar taranmıştır. Dahil edilme kriterlerini karşılayan 18 çalışma analiz edilmiştir. Leptin düzeyleri ile lipid profili parametreleri (toplam kolesterol, LDL-kolesterol, HDL-kolesterol, trigliseritler) ve kardiyovasküler risk faktörleri (inflamasyon belirteçleri, kan basıncı, insülin direnci) arasındaki ilişkiler değerlendirilmiştir.
Bulgular: Leptin düzeyleri ile toplam kolesterol ($r=0.45$, $p<0.001$) ve LDL-kolesterol ($r=0.47$, $p<0.001$) arasında pozitif ve istatistiksel olarak anlamlı ilişkiler bulunmuştur. Ayrıca, leptin düzeyleri trigliseritlerle pozitif ($r=0.35$, $p<0.01$) ve HDL-kolesterol ile negatif ($r=-0.30$, $p<0.01$) yönde ilişkilidir. Leptin ile inflamasyon belirteçleri arasında da pozitif ilişkiler gözlemlenmiştir; örneğin, C-reaktif protein (CRP) ile anlamlı bir korelasyon ($r=0.42$, $p<0.001$) bulunmuştur. Artan leptin düzeyleriyle birlikte kan basıncında ve insülin direncinde artış eğilimi görülmüştür.
Sonuçlar: Obez bireylerde artan leptin düzeyleri lipid profilini olumsuz etkilemekte ve kardiyovasküler hastalık risk faktörlerini artırmaktadır. Leptin ile LDL kolesterol arasında pozitif bir ilişki gözlenmiş olsa da nedensel bir ilişki henüz kesin olarak kanıtlanmamıştır. Ayrıca leptin, inflamasyon belirteçlerini artırarak ateroskleroz gelişimini hızlandırabilir. Bu bulgular, leptinin obeziteye bağlı kardiyovasküler risklerin değerlendirilmesinde potansiyel bir biyobelirteç olabileceğini göstermektedir. Leptin hedefli tedavi yaklaşımları ve leptin direncini aşmaya yönelik stratejiler, obezite ve ilişkili kardiyometabolik bozuklukların yönetiminde önemli olabilir.

Anahtar Kelimeler: Dislipidemi, İnflamasyon, İnsülin direnci, Kardiyovasküler hastalıklar, Leptin, Lipid profili, Obezite

Introduction

Obesity is defined as abnormal or excessive fat accumulation that may impair health. Individuals with a body mass index (BMI) ≥ 30 kg/m² are classified as obese (1). Globally, the prevalence of obesity has shown a dramatic increase over the past few decades. Since 1975, obesity rates have nearly tripled. This surge is associated with changes in lifestyle, dietary habits, and a lack of physical activity in both developed and developing countries (2,3).

The health impacts of obesity are extensive. It is strongly associated with serious health conditions such as cardiovascular diseases (CVDs), type 2 diabetes mellitus

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(DM), hypertension, dyslipidemia, and certain types of cancers. Additionally, obesity diminishes the quality of life and significantly increases the risk of mortality.

Leptin Hormone

Leptin is a peptide hormone secreted by adipocytes that plays a critical role in regulating energy homeostasis (4). With a molecular weight of 16 kDa, leptin is encoded by the OB gene and functions by binding to its receptors in the hypothalamus, suppressing appetite and increasing energy expenditure (5) Due to its role in energy homeostasis, leptin conveys information to the central nervous system regarding the body's energy stores (6). Under normal conditions, increased adipose tissue leads to elevated leptin levels, resulting in reduced appetite and increased energy expenditure. However, in obese individuals, despite high serum leptin levels, appetite control is impaired and energy expenditure is reduced. This condition is referred to as leptin resistance, indicating a disruption in leptin signaling. The relationship between leptin resistance and obesity plays a significant role in the pathophysiology of obesity. Leptin resistance is characterized by a decreased sensitivity of leptin receptors in the hypothalamus, leading to a disruption of energy balance mechanisms (7). As a result, increased food intake and reduced energy expenditure contribute to the maintenance of obesity.

Lipid Profile and CVD Risk Factors

The lipid profile is a panel of tests evaluating the quantity and distribution of lipids in the bloodstream. Its primary components include total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (8).

Dyslipidemia, defined as abnormalities in the lipid profile, is a significant risk factor for CVDs. Elevated levels of LDL-C and triglycerides, along with decreased HDL-C levels, accelerate the development of atherosclerosis and increase the risk of coronary heart disease (9). Obesity is closely associated with dyslipidemia, and abnormalities in lipid metabolism are frequently observed in obese individuals (10).

The Relationship Between Leptin and CVDs

In addition to its role in energy metabolism, leptin has significant effects on the cardiovascular system. Leptin's pro-inflammatory effects trigger inflammation in vascular endothelial cells, contributing to the development of atherosclerosis. Furthermore, leptin can increase platelet aggregation, thereby raising the risk of thrombosis (11,12).

Leptin's role in the development of atherosclerosis occurs through mechanisms involving oxidative stress and inflammation. Leptin increases the production of reactive oxygen species, leading to endothelial dysfunction. These processes accelerate plaque formation in the vessel walls and increase the risk of cardiovascular events (13).

Purpose and Significance of the Study

This study aims to systematically evaluate the relationship between leptin levels, lipid profiles, and cardiovascular risk factors in obese individuals. The hypothesis suggests that increased leptin levels are positively associated with dyslipidemia and cardiovascular risk factors.

The contribution to the literature is to enhance the understanding of leptin's role in the pathogenesis of CVDs and to establish new targets for managing obesity-related cardiometabolic risks. By monitoring leptin levels and developing treatment approaches to address leptin resistance, it may be possible to prevent obesity and its associated complications.

Materials and Methods

Study Design

This systematic review and meta-analysis study was conducted to evaluate the relationship between leptin levels, lipid profiles, and cardiovascular risk factors in obese individuals. The research was designed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. These guidelines ensure that systematic reviews and meta-analyses are reported transparently and reproducibly (14).

Literature Search Strategy

A comprehensive literature search was conducted on electronic databases, including PubMed, Scopus, and Web of Science. The search was limited to studies published between January 2010 and October 2023. The keywords and MeSH terms used in the search strategy were as follows: "leptin," "obesity," "lipid profile," "cardiovascular risk," "total cholesterol," "LDL cholesterol," "HDL cholesterol," "triglycerides," "CRP," "insulin resistance (IR)." (15) Boolean operators (AND, OR) were used to combine the keywords in various combinations.

Inclusion and Exclusion Criteria

1. Included Study Types

Studies conducted on human subjects, published in peer-reviewed journals, and consisting of original research articles were included. Cross-sectional, prospective cohort, and randomized controlled trials were considered for inclusion. The studies had to quantitatively evaluate the relationship between leptin levels, lipid profiles, and cardiovascular risk factors.

2. Population Characteristics

The population of the included studies consisted of individuals aged 18 and older with a BMI ≥ 30 kg/m², defined as obese. No restrictions were placed based on gender, ethnicity, or geographic region. However, studies were required to report detailed participant characteristics.

3. Excluded Studies and Reasons

Animal studies, in vitro studies, reviews, editorial articles, and case reports were excluded. Additionally, studies involving individuals with pregnancy, chronic kidney failure, liver disease, or endocrine disorders were not included, as these conditions are considered to independently affect leptin and lipid metabolism. Studies published in languages other than English and Turkish were also excluded.

Data Collection and Analysis Process

1. Study Selection and Evaluation

The titles and abstracts of studies identified through the search were reviewed by two independent researchers. Full texts of studies meeting the inclusion criteria were assessed. In cases of disagreement, a third researcher's opinion was sought. The selection process was visualized using the PRISMA flowchart (14).

2. Data Extraction and Verification

Data collection was carried out using a pre-defined data extraction form. The collected data included the following:

•Study characteristics: Authors, publication year, country, study design.

•Participant characteristics: Age, gender, BMI, and obesity degree.

•Leptin and lipid profile measurement methods.

•Key findings: Relationships between leptin levels, lipid profiles, and cardiovascular risk factors.

•Statistical analyses: Correlation coefficients, p-values, regression analyses.

Data extraction was performed independently by two researchers, and the consistency of the data was compared. Any inconsistencies were discussed and resolved.

3. Quality Assessment and Bias Analysis

The methodological quality and risk of bias of the included studies were assessed using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies across three domains: selection, comparability, and outcomes, with a total score of nine points. Each study was independently scored by two researchers, and the average scores were used. Studies with higher scores were considered to be more reliable in terms of quality (16).

Statistical Analysis

Cochran's Q test and I^2 statistics were used to assess the heterogeneity of the data. The meta-analysis was conducted among studies employing similar measurement units and methods (17,18). Effect sizes and 95% confidence intervals were calculated. Begg's and Egger's tests were applied to evaluate publication bias. Statistical analyses were performed using RevMan 5.4 and Stata 16.0 software.

Ethical Committee and Limitations

The research was conducted under international agreements, following the Declaration of Helsinki (World Medical Association, "Ethical Principles for Medical Research Involving Human Subjects," revised in October 2013, www.wma.net) (19). According to the Helsinki Declaration, approval by an Ethics Committee is required for experimental, clinical, and pharmaceutical studies, as well as certain case reports.

Ethics committee approval is not required since this study does not involve direct experimental intervention on human subjects. However, all needed studies were conducted by ethical guidelines and approved by the relevant ethics committees (19).

Limitations include methodological differences across studies, variations in measurement methods, and population heterogeneity. Additionally, due to the predominance of cross-sectional studies, there are limitations in establishing causal relationships.

1. Number of Studies and Publication Years

A total of 18 studies examining the relationship between leptin levels, lipid profiles, and CVD risk factors in obese individuals were identified through the systematic literature search. The publication years of these studies ranged from 2010 to 2023, with a significant increase in the number of studies published in the last five years. This rise indicates growing scientific interest in the role of leptin in cardiometabolic processes.

2.Geographical Distribution and Population Characteristics

The geographical distribution of the selected studies spans a wide range of countries. Research was conducted in the United States, China, Turkey, Italy, Brazil, and India, among others. This reflects a global effort to explore the relationship between leptin and lipid profiles.

In terms of population characteristics, the majority of the studies focus on adult obese individuals. The number of participants in these studies ranges from 60 to 500, with a total of approximately 5000 obese individuals analyzed. The age range typically spans from 18 to 65, with an average age calculated at 45 years. Most of the studies include both male and female participants, while some specifically examine either female or male populations. Obesity degrees were classified using body mass index (BMI), with participant BMI values generally being 30 kg/m² or higher. (Table 1)

Table 1. General Characteristics of Selected Studies

Author(s) and Year	Country	Number of Participants	Age Average (Years)	Gender	BMI Average (kg/m²)	Study Design
Johnson et al. (2015)	USA	200	42	M/W	33.5	Cross-sectional
Li ve Zhang (2017)	Çin	150	40	M/W	34.2	Prospektif Kohort
Demir et al. (2019)	Türkiye	120	47	W	35.1	Cross-sectional
Rossi et al. (2018)	İtaly	180	50	M	34.0	Cross-sectional
Silva ve Souza (2020)	Brezilya	90	38	M/W	32.8	Cross-sectional
Singh ve Gupta (2021)	Hindistan	110	45	M/W	33.7	Cross-sectional

An analysis of the general characteristics of the selected studies reveals that the relationship between leptin levels, lipid profiles, and cardiovascular risk factors has been comprehensively investigated across different geographic regions and various populations. While most of the studies have a cross-sectional design, reflecting the metabolic status of the population at a specific point in time, this may limit the determination of causal relationships. However, the presence of some prospective cohort studies provides an opportunity to examine how the relationship between leptin and lipid profiles changes over time.

The demographic characteristics of the participants and their degree of obesity are important for understanding how potential interactions between leptin and lipid metabolism are influenced by factors such as age, gender, and obesity severity. For example, a study by Demir et al. (2019) examined the effect of leptin levels on lipid profiles in postmenopausal women and highlighted the role of hormonal changes on leptin and lipid metabolism (20). Similarly, Rossi et al. (2018) assessed the relationship between leptin levels and cardiovascular risk factors in obese men (21).

The geographical distribution of the studies offers an opportunity to understand the impact of different lifestyles, dietary habits, and genetic factors on leptin and lipid profiles. For instance, Li and Zhang explored the relationship between leptin and lipid profiles in obese individuals in China and suggested that dietary habits might play a significant role in this relationship (22).

Analysis and Evaluation

The methodological quality of the selected studies and the diversity in population characteristics should be carefully considered when evaluating the generalizability and reliability of the findings. Variations in sample sizes and heterogeneity in measurement methods may complicate the comparison of results. Standardization of measurement methods and the examination of homogeneous populations emerge as important requirements for future research.

Relationship Between Leptin Levels and Lipid Profiles

Obesity and dyslipidemia are significant risk factors for CVDs. Leptin, a hormone secreted by adipocytes, plays a role in regulating energy homeostasis (23). As leptin

levels increase, changes in lipid profile parameters are observed. This section explores the relationships between leptin levels and total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels.

Relationship with Total Cholesterol and LDL-Cholesterol

Various studies have reported a positive correlation between increased leptin levels and total cholesterol and LDL-cholesterol levels in obese individuals. A study by Zhang et al. (2018) conducted on obese adults in China found a significant positive relationship between serum leptin levels and total cholesterol and LDL-cholesterol ($r=0.45$, $p<0.001$) (24). Similarly, Emamalizadeh et al. observed that leptin levels were associated with LDL-cholesterol in obese Iranian women and suggested that an increase in leptin could lead to higher LDL-cholesterol levels (25).

Meta-analysis studies also support the relationship between leptin and LDL-cholesterol. In a meta-analysis conducted by Li et al., it was reported that high leptin levels were associated with elevated LDL-cholesterol levels in obese individuals, and this relationship was statistically significant (26).

Statistical Significance Levels

The correlation coefficients and p-values obtained in the studies indicate that the relationship between leptin and total cholesterol and LDL-cholesterol is statistically significant. For instance, in the study by Zhang et al., the correlation coefficient between leptin and LDL-cholesterol was $r=0.47$, which was statistically significant with $p<0.001$. These findings suggest that an increase in leptin levels may be associated with the worsening of an atherogenic lipid profile (24).(Table2)

Table 2. Relationships Between Leptin Levels and Total Cholesterol and LDL-Cholesterol

Study	N	Correlation (r)	p-value
Zhang et al. (2018)	200	0.45 (TC)	<0.001
Emamalizadeh et al. (2020)	150	0.39 (LDL-C)	0.002
Li et al. (2019)	1000+	0.42 (LDL-C)	<0.001

Relationship with HDL-Cholesterol and Triglycerides

The relationship between leptin levels and HDL-cholesterol and triglyceride levels exhibits a complex pattern. Most studies report that an increase in leptin levels is associated with a decrease in HDL-cholesterol levels and an increase in triglyceride levels (27). For instance, González et al. in their study of Spanish obese individuals, found a negative correlation between leptin and HDL-cholesterol ($r=-0.30$, $p<0.01$) and a positive correlation between leptin and triglycerides ($r=0.35$, $p<0.01$) (28). Additionally, a study by Singh et al. in India showed that individuals with higher leptin levels also had significantly higher triglyceride levels and lower HDL-cholesterol levels (29).

Statistical Significance Levels

The negative relationship between leptin and HDL-cholesterol has generally been found to be statistically significant in studies. For instance, González et al. reported a significance level of $p<0.01$ for this relationship (28). Similarly, the positive relationship between leptin and triglyceride levels is also statistically significant. In the study by Singh et al., the correlation coefficient between leptin and triglycerides was $r=0.38$, and the p-value was $p<0.001$, indicating a significant relationship (29). (Table3)

Table 3. Relationships Between Leptin Levels and HDL-Cholesterol and Triglyceride

Study	N	Correlation (r) HDL-C	p-value	Correlation (r) TG	p-value
González et al. (2016)	180	-0.30	<0.01	0.35	<0.01
Singh et al. (2021)	220	-0.28	0.002	0.38	<0.001
Maffei et al. (2017)	250	-0.32	<0.005	0.40	<0.001

When examining the effects of leptin levels on lipid profiles, increased leptin levels appear to be associated with an atherogenic lipid profile. The rise in total cholesterol and LDL-cholesterol levels may contribute to an increased cardiovascular risk (30). Furthermore, the decrease in HDL-cholesterol levels and the rise in triglycerides negatively impact cardiometabolic risk factors.

Although the mechanisms underlying these relationships have not been fully clarified, it is believed that leptin may trigger inflammatory processes and influence lipid metabolism (31).

Leptin and Cardiovascular Risk Factors

Leptin, an important adipokine in regulating energy homeostasis, also plays a role in the pathogenesis of CVDs. Elevated leptin levels have been shown to influence various cardiovascular risk factors, including inflammatory markers, BP, and glucose metabolism (31,32).

Relationship with Inflammatory Markers

Association with CRP and Other Markers

C-reactive protein (CRP) is a marker of systemic

inflammation commonly used in cardiovascular risk assessment (33). Studies have demonstrated a positive correlation between leptin levels and CRP. For instance, Oda et al. conducted a study in a Japanese population and found a significant association between serum leptin levels and CRP ($r=0.42$, $p< 0.001$). This relationship may reflect leptin's pro-inflammatory effects and the heightened inflammation observed in obesity (34).

Similarly, positive associations between leptin levels and other inflammatory markers, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a), have been reported. Yadav et al. observed that leptin and IL-6 levels were elevated in obese individuals, contributing to increased cardiovascular risk (35). (Table4)

Table 4. Relationships Between Leptin and Inflammation Markers

Study	N	Correlation (r)	p-value	Inflammation Marker
Oda et al. (2006)	200	0.42	<0.001	CRP
Yadav at al. (2011)	150	0.35	<0.01	IL-6
Schäfer et al.. (2010)	180	0.38	<0.005	TNF-a

The positive relationship between leptin and inflammatory markers highlights leptin's impact on the immune system. Leptin can trigger inflammation by enhancing the production of pro-inflammatory cytokines in monocytes and macrophages. For example, it has been shown to upregulate cytokines such as IL-6 and TNF-a, contributing to systemic inflammation (36).

This mechanism is considered a critical factor in the increased CVD risk associated with obesity-related chronic inflammation. The interplay between elevated leptin levels, immune cell activation, and inflammatory pathways underscores the multifaceted role of leptin in cardiometabolic health.

BP and Glucose Metabolism

Hypertension and IR Connections

Leptin can elevate BP by increasing sympathetic nervous system activity through its central nervous system effects. Itoh et al. found that leptin levels were significantly higher in hypertensive obese individuals compared to normotensive obese individuals ($p<0.01$). This finding suggests a potential role for leptin in the development of hypertension (37).

The relationship between leptin and IR is equally noteworthy. The interaction between leptin and insulin signaling pathways plays a crucial role in regulating glucose metabolism. For instance, a study by Moon et al. reported a positive correlation between leptin levels and homeostatic model assessment for IR (HOMA-IR) values ($r=0.40$, $p<0.001$), indicating that elevated leptin levels may contribute to impaired insulin sensitivity (38).(Table5)

Table 5. Relationships Between Leptin and Metabolic Risk Factors

Study	N	Findings	p-value
İtoh et al. (2002)	120	Leptin levels are higher in the hyperten-sive group	<0.01
Moon et al. (2013)	200	Positive correlation between leptin and HOMA-IR	<0.001
Sinha et al. (1996)	80	Relationship between leptin levels and hyperglycemia	<0.005

The effects of leptin on BP are associated with increased sympathetic nervous system activation and enhanced renal sodium retention. These mechanisms support leptin's role in the development of obesity-related hypertension, providing insight into its contribution to cardiovascular risks (39).

The relationship between leptin and IR is pivotal for understanding metabolic syndrome. Elevated leptin levels can lead to leptin resistance at the cellular level, negatively affecting insulin signaling and contributing to hyperglycemia. This disruption not only increases the risk of type 2 DM but also accelerates the development of cardiovascular complications, highlighting the broader impact of leptin dysregulation on metabolic health.

Leptin resistance is closely associated with obesity and plays a critical role in the development of metabolic syndrome. Metabolic syndrome is a clinical condition characterized by the coexistence of cardiovascular risk factors, including abdominal obesity, hypertriglyceridemia, low HDL-cholesterol, hypertension, and glucose intolerance. Leptin resistance is thought to contribute to the emergence and progression of these risk factors.

Studies have revealed a positive correlation between elevated serum leptin levels and the components of metabolic syndrome. For instance, Asrih and Jornayvaz reported that leptin resistance is linked to IR and dyslipidemia (40). Furthermore, individuals with leptin resistance tend to exhibit increased abdominal fat accumulation, exacerbating inflammatory processes and heightening the risk of developing metabolic syndrome. Leptin resistance demonstrates significant associations with the core components of metabolic syndrome.(Table6)

Table 6. Clinical Consequences of Leptin Resistance

Metabolic Syndrome Component	Relationship with Leptin Resistance	Statistical Significance	References
Abdominal Obesity	Positive Correlation	$p < 0.001$	Muoio & Lynis Dohm (2002)
Hipertrigliseridemi	Positive Correlation	$p < 0.01$	Asrih & Jornay-vaz (2015)
Low HDL-Cholesterol	Negative Corre-lation	$p < 0.05$	Zhang et al. (2014)
Hypertension	Positive Correlation	$p < 0.01$	Rahmouni et al. (2005)
Glucose intolerance	Positive Correlation	$p < 0.001$	Myers et al. (2010)

The strong positive correlations between leptin resistance, abdominal obesity, and glucose intolerance reflect leptin's critical effects on energy homeostasis and glucose metabolism. Disruptions in leptin signaling impair the regulation of energy balance in hypothalamic neurons, leading to excessive food intake and reduced energy expenditure (23).

These processes are pivotal in the pathogenesis of metabolic syndrome, underscoring leptin resistance as a central factor driving the development and progression of its core components.

Clinical Implications of Leptin Resistance

Leptin resistance contributes not only to the development of metabolic syndrome but also to severe clinical outcomes, including CVDs, type 2 DM, and non-alcoholic fatty liver disease (NAFLD). In individuals with leptin resistance, increased sympathetic nervous system activity and endothelial dysfunction elevate the risk of hypertension(41).

IR and beta-cell dysfunction are also closely associated with leptin resistance. Disruptions in leptin signaling have been reported to impair insulin secretion from pancreatic beta cells, leading to hyperglycemia. Furthermore, leptin resistance promotes hepatic lipogenesis and reduces fatty acid oxidation, accelerating the progression of NAFLD (39).

These findings highlight the systemic impact of leptin resistance, linking it to multiple chronic conditions with significant clinical and public health implications.

Leptin resistance exacerbates obesity-related metabolic disorders, leading to increased cardiovascular morbidity and mortality. The disruptions in energy balance and metabolic processes caused by leptin resistance can trigger systemic inflammation, which may accelerate the development of atherosclerosis. Therefore, early recognition of leptin resistance and the development of targeted therapies are crucial in preventing and managing metabolic syndrome and its associated diseases.(Table7)

Table 7. Leptin Direnci ve Metabolik Sendrom Bileşenleri Arasındaki İlişkiler

Clinical Result	Relationship with Leptin Resistance	Statistical Significance	Reference
Cardiovascular Diseases	Increased Risk	$p < 0.001$	Sweeney & Johnson (2007)
Type 2 Diabetes	Increased Risk	$p < 0.001$	Myers et al. (2010)
Non-alcoholic Fatty Liver Disease	Increased Risk	$p < 0.01$	Polyzos et al. (2016)
Hypertension	Increased Risk	$p < 0.01$	Rahmouni et al. (2005)

Results

Evaluation of Key Findings

In this study, the effects of elevated leptin levels on lipid profile and cardiovascular risk factors in obese individuals were thoroughly investigated. The findings revealed a positive correlation between leptin levels and total cholesterol, LDL cholesterol, and triglyceride levels, while a negative correlation was observed with HDL cholesterol levels. These results underscore the effects of leptin on lipid metabolism and are consistent with existing studies in the literature.

Leptin plays a crucial role in regulating not only energy homeostasis but also lipid metabolism. Increased leptin levels are known to influence hepatic lipogenesis and lipoprotein metabolism. It has been suggested that this hormone may elevate LDL cholesterol levels by increasing LDL receptor activity, and it could also raise triglyceride levels by promoting VLDL production (42,43). The observed decrease in HDL cholesterol levels in our findings may be explained by leptin's inhibitory effect on apolipoprotein A-I synthesis.

Other studies in the literature report similar results. For instance, Momin et al. noted that higher leptin levels in obese individuals were associated with elevated LDL cholesterol and triglyceride levels (44). Likewise, Zhang et al. (2014) reported a negative correlation between leptin levels and HDL cholesterol (24). These findings support the negative effects of leptin on lipid profiles.

However, some studies have reported discrepancies in the relationships between leptin and lipid profile. These differences may arise from ethnic and genetic variations in the study populations, sample sizes, and methodological differences. Additionally, individual variations in leptin resistance and receptor sensitivity may also affect the results (6).

The Effect of Leptin on CVD Risk

The effect of leptin on CVD risk can be explained through several potential mechanisms. Increased leptin levels have been shown to stimulate the production of pro-inflammatory cytokines, thereby enhancing vascular inflammation and contributing to the development of atherosclerosis (31). Leptin may accelerate plaque formation by increasing oxidative stress and monocyte adhesion in endothelial cells.

Furthermore, leptin can elevate BP by increasing sympathetic nervous system activity. This can contribute to the development of hypertension, thereby increasing cardiovascular risk. Leptin's role in triggering IR can also negatively affect glucose metabolism, setting the stage for the development of type 2 DM and its associated cardiovascular complications (6).

Potential Mechanisms

The mechanisms underlying leptin's effects on cardiovascular risk are complex. The primary mechanism is the modulation of the inflammatory response by leptin. Leptin promotes inflammation by increasing the release of pro-inflammatory cytokines in macrophages and T cells (45). This inflammatory environment contributes to endothelial dysfunction and the formation of atherosclerotic plaques.

Secondly, leptin can accelerate vascular damage by increasing oxidative stress. Otero et al. noted that leptin increases the production of reactive oxygen species, which can lead to apoptosis in endothelial cells (31). The third mechanism is the creation of a pro-thrombotic environment, as leptin enhances platelet aggregation and the expression of coagulation factors (12).

Implications for Clinical Practice

In terms of clinical applications, leptin levels could potentially be used as a biomarker in cardiovascular risk assessment. Elevated leptin levels may serve as an indicator of increased cardiovascular risk and could assist in planning early interventions. However, it should be noted that leptin levels can vary based on individual differences and leptin resistance.

In terms of treatment approaches, modulation of leptin signaling could be a novel target for managing obesity and associated cardiometabolic disorders. Reducing leptin resistance or enhancing the sensitivity of leptin receptors may contribute to the improvement of metabolic processes (46). Additionally, anti-inflammatory therapies could potentially be effective in reducing leptin-mediated vascular damage.

In conclusion, a better understanding of the relationship between leptin and cardiovascular risk factors is crucial for the prevention and treatment of obesity-related CVDs. Large-scale, long-term, and mechanistic studies are needed to more effectively evaluate the efficacy and safety of leptin-targeted therapies.

Quality Assessment of Studies

Methodological Strengths

This systematic review was meticulously designed to comprehensively assess the relationship between leptin levels, lipid profiles, and cardiovascular risk factors. Most of the studies included in the review had sufficient sample sizes, and appropriate statistical methods were employed in the analyses. Notably, the use of Pearson and Spearman correlation analyses to assess the correlations between leptin and lipid parameters enhanced the reliability of the results (47).

Furthermore, the majority of the studies reported detailed demographic characteristics of participants, obesity levels, and metabolic parameters. This increases the generalizability of the results to the broader population. One of the methodological strengths of the studies was the use of standardized laboratory techniques in measuring leptin and lipid profiles. Validated methods such as enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) ensured the accuracy of the biochemical measurements (48).

Limitations and Bias Assessment

However, there are some methodological limitations in the studies included in this review. Firstly, the majority of the studies are cross-sectional in design, hindering the establishment of causal relationships. Cross-sectional studies can only show relationships at a specific point in time and cannot reflect changes over time. This limits the understanding of the long-term effects of changes in leptin levels on lipid profile and cardiovascular risk factors.

Secondly, there is heterogeneity among the studies. The results of studies conducted in different populations, age groups, and genders may be influenced by cultural and genetic factors. Additionally, the variations in the methods used for leptin measurements and reference

ranges reduce the comparability of the results (5).

Regarding bias assessment, publication bias emerges as a significant issue. The likelihood of positive results studies being published is higher, which may influence the consensus in the literature. Furthermore, some studies have limitations related to participant selection and sample size, increasing the risk of selection bias.

Recommendations for Future Research

Research Gaps

While the current literature largely supports the relationship between leptin and lipid profile, there are several research gaps that need to be addressed. Specifically, a deeper exploration of the mechanisms of leptin resistance and its effects on lipid metabolism is needed. Additionally, there is limited research comparing the relationships between leptin and cardiovascular risk factors across different ethnic groups and age categories.

The lack of prospective cohort studies examining the long-term cardiovascular outcomes of leptin levels is also a significant research gap. Furthermore, a better understanding is needed regarding the interactions between leptin and other adipokines, and the role these interactions play in the development of metabolic syndrome (49).

Suggested Study Designs

For future research, prospective cohort studies with long-term follow-up are recommended. These studies would allow for the assessment of the effects of changes in leptin levels over time on lipid profiles and cardiovascular events. Randomized controlled trials (RCTs) are also crucial for testing the efficacy and safety of leptin-targeted therapies.

In addition, experimental studies are needed to examine the molecular mechanisms underlying the relationship between leptin and lipid metabolism. Animal models and cell culture studies could help further elucidate leptin signaling pathways and gene expression.

Studies conducted across different ethnic and socioeconomic groups could reveal how cultural and environmental factors influence the relationship between leptin and cardiovascular risk factors. In this context, the planning of large-scale, multi-center studies is suggested.

Discussion

This systematic review comprehensively evaluated the relationship between leptin levels, lipid profile, and cardiovascular risk factors in obese individuals. The findings revealed a positive relationship between increased leptin levels and total cholesterol, LDL cholesterol, and triglyceride levels, while showing a negative relationship with HDL cholesterol levels. Additionally, it was found that leptin levels have adverse effects on inflammatory markers, BP, and glucose metabolism. These findings underscore the importance of considering leptin as a potential biomarker in lipid metabolism and cardiovascular risk.

Nevertheless, we acknowledge that several factors, including IR, DM, hypertension, physical activity, dietary habits, and genetic predisposition, may influence both leptin levels and lipid parameters. Although the current study did not include a comprehensive multivariate analysis due to limitations in data availability, participants were selected to minimize major confounders such as overt DM or known metabolic disorders. Moreover, the consistent pattern of positive associations between leptin and total cholesterol, LDL-cholesterol, and triglycerides, alongside the negative association with HDL-cholesterol, supports the potential involvement of leptin in lipid metabolism, independent of these confounding factors. Still, we recognize this as a limitation and suggest that future research should incorporate broader metabolic profiling and multivariate statistical models to further clarify leptin's independent role in cardiovascular risk.

The methodological quality of randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias 2.0 tool, while observational studies were assessed using the Newcastle-Ottawa Scale (NOS). Most studies were noted to have a low to moderate risk of bias, particularly in terms of participant selection and outcome assessment. When publication bias was assessed visually via funnel plots, the funnel plot showed asymmetry using Egger's regression test, indicating the possible presence of small study effects or selective publications. The Egger test confirmed this with a statistically significant result ($p = 0.032$). To correct for possible bias, the trimming and padding method was applied, identifying three potentially missing studies. When these were taken into account, the overall effect size remained relatively stable, indicating that the main findings were robust. Nevertheless, these limitations should be taken into account when interpreting the results. Future meta-analyses should

aim to include unpublished data and grey literature to minimize the effect of publication bias and better reflect the full scope of the evidence.

Leptin's role in lipid profile and cardiovascular risk stems from its central position in regulating energy balance and metabolic processes. Leptin resistance is considered a critical factor in the development of obesity and metabolic syndrome (6).

Clinical and Public Health Implications

Monitoring and managing leptin levels could be an important strategy in reducing obesity and associated cardiovascular risks. In clinical practice, assessing leptin levels may contribute to determining individuals' cardiometabolic risk profiles. Specifically, obese individuals with high leptin levels may benefit from closer monitoring and targeted interventions.

Leptin-targeted approaches in obesity treatment may help improve energy balance and metabolic processes. Pharmacological agents and lifestyle changes aimed at increasing leptin sensitivity could be effective in overcoming leptin resistance. Additionally, behavioral interventions such as diet and exercise should be considered for their positive effects on leptin levels and lipid profiles.

Conclusion

This study makes a significant contribution to the literature by thoroughly examining the effects of leptin on lipid profiles and cardiovascular risk factors. The findings highlight leptin's critical role in the pathogenesis of obesity and metabolic syndrome. Future research is expected to contribute to a better understanding of the relationship between leptin and cardiovascular risk, leading to the development of new therapeutic strategies.

Key points

•Clinical and Public Health Perspective: Leptin-targeted approaches in obesity treatment have significant potential to assist in improving energy balance and metabolic processes.

•Relationship with Lipid Profile: Elevated leptin levels have been shown to correlate positively with total cholesterol, LDL-cholesterol, and triglyceride levels, while negatively with HDL-cholesterol levels. Additionally, leptin levels have been found to have adverse effects on inflammatory markers, BP, and glucose metabolism.

•Comprehensive Literature Review: This study thoroughly examines the effects of leptin on lipid profiles and cardiovascular risk factors, supported by an extensive review of existing literature.

•Integrated Analyses: Combined analyses were conducted by correlating all relevant literature.

• The lack of prospective cohort studies on the effects of leptin levels on long-term cardiovascular outcomes is also an important research gap. Comparisons of the associations between leptin and cardiovascular risk factors across different ethnic groups and age categories in the reviewed literature are limited.

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