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Molecular Insights into Adipokines in Metabolic Syndrome: Implications for Novel Therapeutic Strategies

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ABSTRACT

Background: Adipokines are bio-active peptides released by adipose tissue which control glucose and lipid metabolism, play important roles in pathophysiology of metabolic syndrome (MetS). The main objective of this systematic review was to collect molecular evidence of adipokine dysregulation in MetS and fully evaluate its clinical, genetic, and epigenetic implications. **Methodology:** Articles published since January 2014 to January 2026 were searched from different databases like PubMed, Scopus, Web of Science, and Google Scholar, by following PRISMA 2020 guidelines. Inclusion criteria were adults, MetS, and quantitative data on adipokines and their association with clinical or genetic variables. The quality was measured using the Newcastle-Ottawa Scale, ROBINS-I tool, and GRADE frameworks. **Results:** 12 out of 85 records met the inclusion criteria. MetS populations were always associated with an increase in pro-inflammatory adipokines (leptin, resistin, chemerin, visfatin) and a decrease in adiponectin, which are strictly linked to insulin resistance and inflammation. The severity of MetS was more strongly associated with visceral adipose tissue expression as compared to circulating levels alone. Adiponectin and leptin genetic variations (e.g., ADIPOQ, 73 CpG) and epigenetic changes (211 CpGs) controlled the expression of adipokines. The quality was quite average, with observational designs making it hard to make causal inferences. **Conclusion:** The dysregulation of adipokines is the core of MetS pathophysiology with tissue-specific expression and epigenetic regulation being the factors involved in metabolic dysfunction. Long-term, multi-omics longitudinal studies are necessary in the future to confirm therapeutic targets and allow individual interventions.

Keywords: Metabolic Syndrome, Adipokines, Leptin, Adiponectin, Insulin Resistance, Polymorphism

Introduction

Metabolic syndrome (MetS) refers to a group of interrelated cardiometabolic conditions such as central obesity, insulin resistance, and hypertension, which combined to contribute risk of type 2 diabetes mellitus and cardiovascular disease [1]. Beyond energy storage, adipose tissue is an active endocrine gland which produces bioactive peptides called adipokines regulating glucose and lipid metabolism, appetite, and inflammatory reactions [2]. Various adipokines, including leptin, adiponectin, resistin, and chemerin, have been identified to contribute to pathophysiology of MetS [3,4].

There is new evidence to show that insulin resistance, systemic inflammation and visceral adiposity are linked to altered circulating and tissue-specific adipokine profiles [5]. These molecular signatures give an idea about mechanisms that drive the progression of MetS and might be used as biomarkers [6,7]. The expression of adipokines in visceral adipose tissue gives supplementary data to the levels of adipokines in circulation as to the metabolic risk. Moreover, the adipokines mediate adipose tissue and distal organ crosstalk, whereas genetic polymorphisms and epigenetic changes regulate adipokine expression, linking metabolic dysregulation to the environment [8,9]. There are still major gaps in research despite increasing evidence. There are limited studies that combine clinical, molecular and epigenetic data concurrently and in many cases, generalizability is restricted due to methodological heterogeneity [10].

It is necessary to clarify the differential roles of visceral and subcutaneous adipose tissue in the circulation of adipokines profiles [11,12]. Also, even though the epigenetic mechanisms that govern individual adipokines have been discovered, their contribution to the overall adipokine imbalance in adult MetS groups is not well-studied. It is necessary to address these gaps to determine credible biomarkers [13].

The main purpose of this systematic review was to synthesize existing molecular data on the dysregulation of adipokines in metabolic syndrome (MetS) and thoroughly assess its clinical, genetic, and epigenetic consequences. This specifically addressed the connections among circulating and tissue-specific adipokines, metabolic and inflammatory consequences, modulatory impacts of genetic and epigenetic variables. The review also evaluated the quality of the methodology and possible biases of the study included to examine the reliability of the evidence. The results can be used in the identification of biomarkers, uncovering possible therapeutic targets and aid personalized interventions towards MetS.

Methodology

The systematic review was based on the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 as shown in Figure 1 to ensure strict methodology and transparency [14].

Inclusion and Exclusion Criteria: Eligibility criteria were an adult population (18 years and older) with metabolic syndrome, quantitative measures of circulating or tissue specific adipokines (leptin, adiponectin, resistin, chemerin, visfatin or PAI-1) and a correlation with clinical, genetic or epigenetic variables. Animal research, in vitro research, case reports, conference abstracts, reviews, and non-English articles were not included.

Data Sources and Search String used: Articles published from January 2014 to January 2026 were searched in PubMed, Scopus, and Google scholar. The search strategy was a combination of MeSH and keywords "Metabolic Syndrome" OR "Insulin Resistance" AND "Adipokines" OR "Leptin" OR "Adiponectin" OR "Resistin" AND "Genetic Polymorphism" OR "Epigenetics" OR "DNA Methylation". There were Boolean operators and database-specific filters.

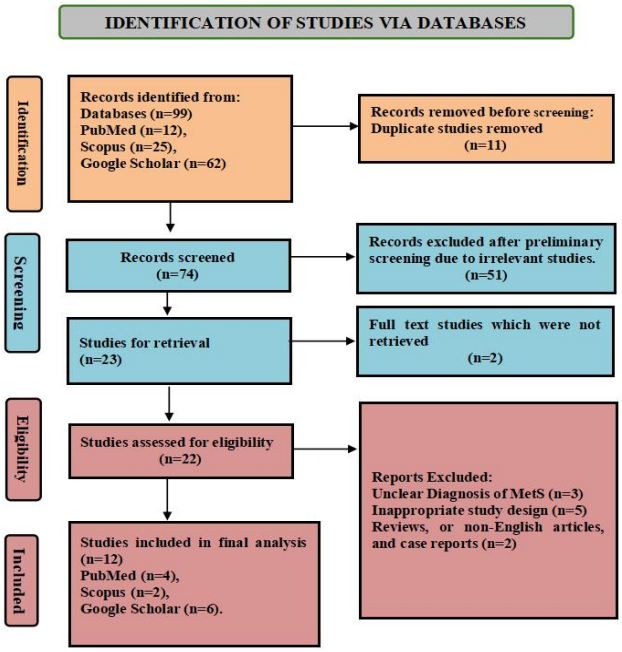

Figure 1: PRISMA Flow Diagram for Systematic Study Selection. The flowchart was prepared according to the PRISMA guidelines 2020, describing identification, screening, eligibility, and final selection in the systematic review.

Study Selection and Data Extraction: Title/abstract screening and full-text eligibility assessment were performed by two independent reviewers. Any disagreement was solved with the help of a third reviewer in consensus. Data extraction was performed by two independent reviewers. Standardized form was employed to extract: author/year, study design, sample size, characteristics of the participants, what adipokines were measured, source of tissue (circulating/adipose), genetic/epigenetic, and key findings.

Primary Outcome and Quality Assessment: The main findings were correlations between adipokine maladjustment and metabolic/ inflammatory variables. Secondary outcomes were the genetic and epigenetic modulatory effects. Two independent reviewers have identified the risk of bias by using study-specific instruments, such as Cochrane RoB2 tool, Newcastle-Ottawa Scale (NOS), and Joanna Briggs Institute (JBI) checklist. Design-specific tools were used to determine risk of bias. The Cochrane RoB 2 tool was used to assess randomized trials, Newcastle Ottawa Scale (NOS) was used to assess case-control and cohort studies, and Joanna Briggs Institute (JBI) checklist was used to assess cross-sectional ones. Findings are reported individually in each section based on assessment tool to maintain methodological validity.

Results

85 research articles were initially identified among the database searches. 11 duplicates were then eliminated resulting in a total of 74 records. Screening of title, and abstract eliminated 23 studies, and 51 articles were retrieved. Out of these 13 was not retrievable, and 38 full-text articles were assessed as eligible. Additional articles (26) were filtered out based on lack of clear diagnosis of metabolic syndrome (n=10), poor study design (n=5), and irrelevant studies (n=11). Finally, this systematic review included twelve studies that met the inclusion criteria**.** A summary of the 12 studies included on adipokine dysregulation in metabolic syndrome is presented in Table 1. The table shows study design, country, population characteristics, sample size, diagnostic criteria, adipokines explored and key molecular findings. Research has been carried out in various countries and on four continents with the different designs such as randomized controlled trials, prospective cohorts, case-control studies, tissue-specific analyses, and an epigenome-wide meta-analysis. The table allows comparing the patterns of adipokine consistent dysregulation high leptin, resistin, chemerin, visfatin and low adiponectin and absorbing the new evidence on tissue-specific expression, genetic polymorphisms, and epigenetic changes, and therapeutic treatments.

Table 1: Characteristics of Included Studies

Author, Year (Contry)	Study Design	Population / Model	Sample Size	MetS Criteria Used	Adipokine (s) Investigated	Main Molecular Findings
Chu et al., 2012[15]	Cross-sectional study	Overweight and obese adults with varying MetS	N = 92 adults (59 men, 33 women)	NCEP- ATP III criteria	Chemerin, Adiponectin	↑ Chemerin and ↓ Adiponectin with insulin resistance, dyslipidemia and increased MetS

South Korea		traits vs those without				prevalence, suggesting a mutual regulation of pro-inflammatory and protective adipokines.
Chedraui et al., 2014 [16] Ecuador	Comparative clinical study	Postmenopausal women with vs without MetS	N = 100 (57 with MetS, 43 without MetS)	AHA criteria	Leptin, Resistin, Adiponectin, Visfatin, Adipsin	Evidence of adipokine imbalance in MetS (↑ leptin, resistin, visfatin, adipsin; ↓ adiponectin) linked to insulin resistance, which validates its involvement in the pathophysiology of MetS.
Panahi et al., 2016[17] Iran	Controlled trial	Patients with metabolic syndrome	N = 117 enrolled (59 curcumin, 58 placebo)	NCEP-ATP III criteria	Adiponectin, Leptin, Leptin/Adiponectin ratio	Demonstrated that adipokines modulation enhances metabolic parameters, which provides adipokines as therapeutic targets in MetS.
Barliana MI, et al. 2019 [18] Indonesia	Case-control study	Adult males >18y with vs without central obesity; SNP rs2241766 in APM1 gene	N- 107 subjects (54 with central obesity and 53 controls)	Central obesity; formal MetS criteria not applied	Adiponectin	The central obesity and changes in HDL were associated with ADIPOQ polymorphism, showing genetic regulation of adipokine-associated MetS risk.
Frühbeck G et al.2019[19] Spain	Cross-sectional clinical	Adult humans varied by MetS (lean, obese, with type 2 diabetes, with metabolic syndrome)	N = 292 adults (135 males, 157 females)	Clinician-diagnosed MetS	Adiponectin, Leptin, Adiponectin/ Leptin ratio	↓ Adiponectin ↑ Leptin in MetS; ratio of Adpn /Lep is low, reflecting dysfunction of adipose tissue, chronic inflammation, and insulin resistance; ratio is better than either adipokine as molecular biomarker.
Ouerghi et al. 2020 [20] Tunisia	Cross-sectional clinical	Young males with vs without MetS	N = 38 (11 MetS, 27 patients without MetS)	NCEP-ATP III	Chemerin, Visfatin	Verified dysregulation of inflammatory adipokines in relation to cardiometabolic risk in MetS.
Sigit et al. 2021 [21] Indonesia and Netherlands	Cross-sectional observational study	Adults from population-based cohorts (NEO study)	N = 8,063 total (1,461 Indonesian,6, 602 Dutch)	MetS diagnosed according to standard criteria	Leptin, Adiponectin	Evidence of ethnic variation in the leptin-adiponectin relations with MetS, indicating population-specific control.
Khademi et al. 2022 [22] Iran	Case-control study	Patients with MetS stratified by vitamin D status (insufficient vs sufficient)	N = 195 total (65 MetS patients with vitamin D insufficiency; 130 MetS patients with vitamin D sufficiency)	MetS diagnosed according to standard criteria	Leptin, Adiponectin, Visfatin, Resistin; Adiponectin/ Leptin ratio	Vitamin D deficiency worsened adipokine imbalance and inflammatory conditions in MetS.
Singh et al., 2024[23] India	Cross-sectional study	Adults with metabolic syndrome vs healthy controls from Western Uttar Pradesh population	N= 264, 164 MetS (88 males and 76 females) and 100 controls (54 males and 46 females)	IDF criteria for metabolic syndrome screening	Adiponectin, PAI-1	Reduction in adiponectin and PAI-1 increase were associated with vascular risk in MetS.
Cheng et al., 2025 [24] China	Prospective cohort study	Community-based adults (longitudinal data from the Cardiovascular-Kidney-Metabolic syndrome study)	6,199 individuals (mean age at baseline: 61.9 years; 57.25% female)	CKM syndrome stages (based on the new AHA definition of Cardiovascular-Kidney-Metabolic syndrome)	Adiponectin	An increase in adiponectin levels indicated a protective metabolic effect by predicting slow activities in CKM progression.
Lara-Guzmán et al., 2025 [25]	Cross-sectional observational study	Individuals with abdominal obesity cardiometabolical	N = 116 (LH: 29, LA:29, OH: 29,	Abdominal obesity + cardiometabolic status	Chemerin, Leptin, Adiponectin,	Adipokine imbalance distinguished between metabolically unhealthy and healthy obese phenotypes.

Colombia		ly normal vs abnormal	OA:29			
Sinke et al., 2026 [26] Netherlands, Germany, UK	Meta-analysis (EWAS)	Adults from five European population-based cohorts	N = 2,791 for adiponectin analysis; N = 3,661 for leptin analysis	Metabolic syndrome risk factors (accessed via association with MetS-related traits)	Adiponectin, Leptin	Identified DNA methylation of ADIPOQ and SREBF1 that control adipokines in metabolic disease.

MetS = Metabolic Syndrome, NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III, AHA = American Heart Association, IDF = International Diabetes Federation, CKM = Cardiovascular-Kidney-Metabolic, NEO Study = Netherlands Epidemiology of Obesity Study, SNP = Single Nucleotide Polymorphism, APM1 / ADIPOQ = Adiponectin Gene, HDL = High-Density Lipoprotein, PAI-1 = Plasminogen Activator Inhibitor-1, EWAS = Epigenome-Wide Association Study, DNA = Deoxyribonucleic Acid, RNA = Ribonucleic Acid

A total of 12 observational studies examining adipokine dysregulation in metabolic syndrome were included; they included cross-sectional studies, case-control studies, prospective cohorts, randomized controlled trials, and an epigenome-wide meta-analysis. In general, there were consistent trends in increased levels of pro-inflammatory adipokines (leptin, resistin, chemerin, visfatin), and decreased adiponectin in MetS groups, which were strongly correlated with insulin resistance, systemic inflammation, and visceral adiposity. Adipokine expression by visceral adipose tissue showed better correlations with MetS severity than circulating concentrations alone, whereas genetic polymorphisms and patterns of DNA methylation of major loci (ADIPOQ, SREBF1) were found to mediate adipokine profiles. Curcumin supplementation as a therapeutic intervention with sufficient levels of vitamin D demonstrated potentiality in correcting adipokine dysregulation.

Design-specific instruments the Cochrane RoB2 tool used to evaluate the risk of bias in RCT, the Newcastle-Ottawa Scale to address cohort and case-control studies, and the JBI checklist to address cross-sectional studies) were used to assess risk of bias of the included studies. Table 2 sums up this evaluation of the single randomized controlled trial as decided by Cochrane RoB2, the Newcastle-Ottawa Scale score of the cohort study and the case-control study and the assessment of the risk of bias in the cross-sectional studies based on the JBI checklist. Overall, it summarizes the results, and demonstrated that overall quality is considered moderate. As anticipated, the use of observational designs is associated with the limitations to causal inference.

Table 2: Risk of Bias Assessment Using Various Tools

Risk of Bias Assessment Using Cochrane RoB2 (Randomized Controlled Trials)						
Study	**Randomization**	**Deviations from Intended Intervention**	**Missing Data**	**Outcome Measurement**	**Selective Reporting**	**Overall Risk**
Panahi et al., 2016[17]	Low	Low	Low	Low	Low	Low
Risk of Bias Assessment Using Newcastle–Ottawa Scale (NOS) (For case controls & cohorts)						
Study	**Selection (0–4)**	**Comparability (0–2)**	**Outcome/ Exposure (0–3)**	**Total Score (0–9)**	**Quality**	
Barliana MI, et al. 2019 [18]	3	1	2	6	Moderate	
Khademi et al., 2022 [22]	4	2	2	8	High	
Cheng et al., 2025[24]	4	2	3	9	High	
Risk of Bias Assessment Using JBI Checklist (Cross-Sectional Studies)						
Study	**Inclusion Criteria**	**Measurement Validity**	**Confounding Addressed**	**Statistical Analysis**	**Overall Risk**	
Chu et al., 2012[15]	Yes	Yes	Partially	Appropriate	Moderate	
Chedraui et al., 2014 [16]	Yes	Yes	Partially	Appropriate	Moderate	
Querghi et al., 2020 [20]	Yes	Yes	Partially	Appropriate	Moderate	
Sigit et al., 2021 [21]	Yes	Yes	Yes	Appropriate	Low	
Frühbeck G et al.2019 [19]	Yes	Yes	Partially	Appropriate	Moderate	
Singh et al., 2024[23]	Yes	Yes	Partially	Appropriate	Moderate	
Lara-Guzmán et al., 2025 [25]	Partially	Yes	Limited	Appropriate	Moderate–High	
Sinke et al., 2026 [26]	Yes	Yes	Yes	Appropriate	Low	

Discussion

This systematic review combines the molecular evidence of twelve studies that examined adipokine dysregulation in metabolic syndrome and identified similar patterns of pro-inflammatory adipokine upregulation and adiponectin down-regulation in different populations. These results indicate that patients with MetS show high levels of leptin, resistin, chemerin, and visfatin in circulation and low concentrations of adiponectin and that it is strongly related to insulin resistance and systemic inflammation [27,28]. Such data are consistent with the mechanistic data summarized by Molecules, according to which adipokines are characterized as the primary link between inflammation of adipose tissue and the impairment of insulin signaling and cardiometabolic risk [29,30]. Likewise, the evidence of Nutr Metab Cardiovasc Dis confirms the relationship between leptin resistance and hypoadiponectinemia and MetS components in all ethnic groups [31].

Notably, tissue-specific levels proved that visceral adipose expression of adipokines is better related to MetS severity than when it is circulated alone, which supports the idea that visceral adiposity is metabolically more harmful than subcutaneous fat [32]. The current observation corresponds to secretion specifics of depots in International Journal of Molecular Sciences [33], in which the visceral adipose tissue had a more pro-inflammatory adipokine signature. Moreover, interventional results that indicate that the leptin/ adiponectin ratio improves without changes in adipokines with inadequate vitamin D status when supplemented with curcumin and becomes normalized indicate that adipokine imbalance can be altered, which can be used to support its therapeutic importance [34,35].

In addition to the circulating changes, this review brings out the increased role of genetic and epigenetic control of adipokines in MetS. The phenotypes of central obesity and the phenotype of HDL changes were associated with polymorphisms in the ADIPOQ (APM1) locus, which confirms the previously reported haplotype phenotypes in Scientific Reports [36]. More convincingly, meta-analysis of epigenome-wide analysis of CpG sites that affect the adiponectin and leptin concentrations pointed to ADIPOQ and SREBF1 as the possible causative agents. These results are in agreement with the mechanistic observations made in Frontiers in Cell and Developmental Biology which focus on DNA methylation as a control over adipogenesis and adipokine transcription in metabolic disease [37]. The overlap of clinical phenotypes, tissue-specific expression and epigenetic modulation adds to the biological feasibility of adipokines not being biomarkers only but active agents in the MetS development [38]. Interestingly, there is prospective cohort evidence showing that increased levels of adiponectin are predictors of slowed cardiovascular-, kidney-, and metabolism-based (CKM) syndrome progression, which argues further in favor of a protective and even causal role [39,40]. Altogether, the considered studies are combined to provide molecular, clinical, and population-wide information, which supports the notion of adipokines as mechanistic bridges between adipose malfunction and systemic metabolism disruptions.

The large methodological heterogeneity of diagnostic criteria, adipokine assays and covariate adjustments limits the quantitative synthesis of this review and the lack of randomized trials limits the causal inference to the effect of the findings. Furthermore, English-language restriction and possible residual confounding although validated risk-of-bias instruments (NOS, RoB2, ROBINS-I, JBI) were used could have brought about selection and reporting bias. The studies included for this study were predominantly cross-sectional, which restricted the ability to interpret the dynamics of adipokines in terms of time and causation. This reduced statistical power, reproducibility, and generalizability further due to the use of small sample sizes, single measurements over time, incomplete adjustment of confounders, methodological variability, and ethnic heterogeneity.Further studies should focus on large-scale longitudinal and multi-omics in order to define causal relationships between adipokines and metabolic syndrome, as well as standardize diagnostic and assay technologies. Strong interventional studies and more sophisticated causal strategies, such as single-cell profiling and Mendelian randomization, are required to prove the causative or the causal effect of adipokines on metabolic dysfunction.

Conclusion

The systematic review demonstrates the adipokine dysregulation as a key characteristic of metabolic syndrome (MetS) with greater pro-inflammatory adipokines and lower adiponectin levels, which have a strong positive correlation with insulin resistance and cardiometabolic risks. Greater associations were found between visceral adipose tissue expression and disease severity, and genetic polymorphics and DNA methylation (e.g., ADIPOQ, SREBF1) also control adipokines profiles. Although there is heterogeneity in methods, there is empirical evidence that adipokines have become a mechanistic driver, biomarker, and possible therapeutic target in MetS.

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