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Biochemical Characterization of Novel Adipokines and Their Physiological Role in Insulin Sensitivity: A Systematic Review

Abida Jaffar[1*], Maher Sohail Yaseen[2], Romana Mehwish[3], Aina Khurshid[4], Amna Riaz[5] and Hera Farooq[5]

[1]Department of Biochemistry, Nishtar Medical University, Multan, Pakistan
[2]Department of Physiology, Dera Ghazi Khan Medical College, Dera Ghazi Khan, Pakistan
[3]Department of Physiology, Bakhtawar Amin Medical and Dental College, Multan, Pakistan
[4]Department of Biochemistry, Multan Medical and Dental College, Multan, Pakistan
[5]Department of Physiology, Multan Medical and Dental College, Multan, Pakistan

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***Corresponding Author:**
Abida Jaffar
Department of Biochemistry, Nishtar Medical University, Multan, Pakistan
dr.abidajaffar@gmail.com

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ABSTRACT

Novel adipokines have garnered attention for their roles in glucose regulation and the early development of metabolic imbalance. Several of these molecules influence insulin signalling, inflammation, and adipose tissue function, but their behavior across different clinical settings remains incompletely understood. **Objectives:** To synthesize recent human evidence on novel adipokines and insulin sensitivity, evaluate the consistency of their associations across various populations, and assess their potential relevance as early metabolic biomarkers. **Methods:** A systematic search was conducted across PubMed, Scopus, and Google Scholar for human studies published between 2019 and 2024. Original English-language studies measuring at least one novel adipokine alongside an insulin-related marker were included. Data were organized into structured tables and synthesised narratively. Risk of bias was assessed using the Joanna Briggs Institute (JBI) criteria for observational studies. **Results:** Eighteen studies met the inclusion criteria. Omentin-1 showed the most consistent inverse association with insulin resistance and was reduced in obesity, metabolic syndrome, PCOS, and NAFLD. Chemerin demonstrated a reproducible positive association with insulin-resistant states and higher inflammatory burden. Nesfatin-1 showed variable behaviour across disease stages and populations. Visfatin, Vaspin, DLK1, and Galanin displayed emerging but less consistent associations. Adiposity, inflammation, and residual confounding influenced the strength and direction of reported relationships. **Conclusions:** Several novel adipokines may act as early markers of metabolic stress and altered insulin action. Omentin-1 appears protective, whereas Chemerin aligns with insulin resistance across multiple populations. Other adipokines show context-dependent responses. Clinical application remains limited by heterogeneity in study design, population characteristics, and laboratory methods.

INTRODUCTION

Insulin resistance has become one of the most common metabolic concerns worldwide, affecting both adults and younger populations [1]. Over the past decade, researchers have shifted attention from traditional metabolic markers toward newer biological signals originating in adipose tissue. These signals, known as adipokines, include a growing group of recently identified molecules such as Omentin-1, Nesfatin-1, Chemerin, Vaspin, Visfatin, DLK1, and Galanin. Each of these molecules appears to interact with energy balance, inflammation, and glucose handling in different ways [2, 3]. Because adipose tissue is now recognised as an active endocrine organ, understanding how these adipokines behave may offer new insights into early metabolic dysfunction. Some adipokines seem to support healthy insulin signalling, while others worsen inflammation or impair glucose uptake [4, 5]. However,

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findings across human studies are not uniform, with reported effects varying according to population characteristics, disease stage, adiposity, and laboratory methodology. Recent studies have explored these molecules in adolescents with PCOS, adults with metabolic syndrome, pregnant women with GDM, and individuals with obesity or type 2 diabetes [6, 7].

Although this expanding literature suggests a meaningful link between adipokines and insulin sensitivity, results remain fragmented and sometimes contradictory across populations. As a result, it remains unclear which adipokines demonstrate the most reliable associations with early insulin resistance. A structured synthesis of contemporary human evidence is therefore needed to clarify consistent patterns, identify adipokines with stronger translational potential, and highlight sources of heterogeneity that limit interpretation. The purpose of this review is to gather and interpret recent human studies on novel adipokines and insulin sensitivity, highlight consistent trends across populations, and identify gaps where evidence remains uncertain. This review aimed to provide a clearer framework for understanding the potential metabolic relevance of emerging adipokines and their future role in research and clinical risk stratification.

METHODS

This systematic review was conducted to synthesize recent human evidence on the relationship between novel adipokines and insulin sensitivity. The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigour. Given the heterogeneity of study designs, populations, and laboratory methods, a structured narrative synthesis approach was adopted rather than quantitative pooling. The methodological steps of literature identification, screening, eligibility assessment, and final inclusion followed the PRISMA 2020 framework. A PRISMA flow diagram was constructed to summarize the study selection process, including records identified, duplicates removed, exclusions at each stage, and the final number of studies included in the qualitative synthesis. A comprehensive literature search was performed across PubMed, Scopus, and Google Scholar to identify relevant studies published between January 2019 and December 2024. The time restriction was applied to capture contemporary evidence focusing on recently characterised adipokines and modern assay techniques. The search strategy used a broad combination of keywords and Medical Subject Headings (MeSH), including "novel adipokines," "omentin-1," "nesfatin-1," "chemerin," "visfatin," "vaspin," "DLK1," "galanin," combined with "insulin sensitivity," "insulin resistance," "HOMA-IR," "fasting insulin," "glucose tolerance," and "metabolic markers." Reference lists of all included studies were manually screened to minimise the risk of missing relevant articles, in line with PRISMA recommendations. Eligibility criteria were defined a priori according to the review objectives. Only original human studies published in English were included. Eligible studies were required to measure at least one novel adipokine in blood samples and report at least one insulin-related or metabolic outcome, such as HOMA-IR, fasting insulin, fasting glucose, β-cell indices, glucose tolerance, or metabolic syndrome components. Animal studies, reviews, meta-analyses, case reports, and studies lacking insulin-related outcomes were excluded to maintain consistency and comparability of evidence. After removal of duplicate records, titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. Study selection was performed using predefined inclusion and exclusion criteria in accordance with PRISMA 2020 guidance. Reasons for exclusion at the full-text stage were documented and are summarised in the PRISMA flow diagram. Data from each eligible study were extracted into structured tables. Extracted variables included author, year, country, study design, sample size, population characteristics (e.g., PCOS, GDM, obesity, T2DM), adipokines measured, insulin-sensitivity or metabolic outcomes, and key findings. Studies were descriptively grouped by population type to allow contextual interpretation of adipokine insulin sensitivity relationships across different metabolic states. Given the inclusion of diverse populations (PCOS, GDM, obesity, T2DM, metabolic syndrome, and pediatric cohorts), results were synthesised within population-specific contexts rather than pooled across groups. This strategy reduced clinical heterogeneity and allowed interpretation of adipokine behaviour within comparable metabolic settings. Because included studies employed different commercial assays and laboratory platforms for adipokine measurement, direct comparison of absolute concentration values was not attempted. Instead, emphasis was placed on the direction and consistency of associations between adipokines and insulin-related outcomes. This approach aligns with PRISMA guidance for narrative synthesis when methodological heterogeneity precludes meta-analysis. Information on adjustment for major confounders such as BMI, age, sex, and comorbidities was extracted for each study. Studies that reported statistical adjustment for these variables were considered methodologically stronger, while those with limited adjustment were noted accordingly. Residual confounding was acknowledged as an inherent limitation of observational research. Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools,

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selected because they are specifically designed for heterogeneous observational study designs, including cross-sectional, case-control, and cohort studies. Each study was evaluated across domains of sample selection, exposure measurement, outcome assessment, and handling of confounders, in line with PRISMA 2020 recommendations for methodological appraisal. Due to clinical and methodological heterogeneity, meta-analysis was not performed. Findings were synthesised narratively and presented in structured tables, integrating epidemiological patterns with biochemical and mechanistic evidence. This study summarizes the identification, screening, eligibility assessment, and final inclusion of studies for the systematic review. A total of 412 records were identified across databases, and 18 studies met the final inclusion criteria for the qualitative synthesis (Figure 1).

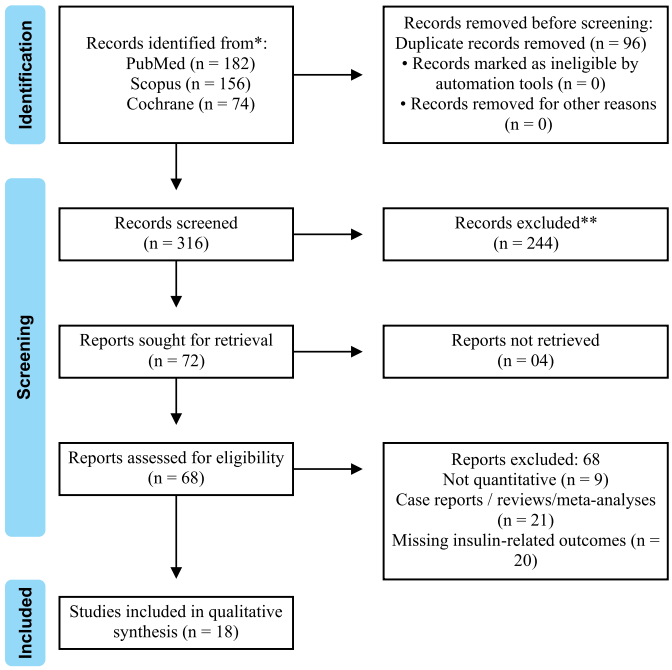

Figure 1: Study Selection Process

RESULTS

The relationship between novel adipokines and insulin sensitivity has been evaluated in 18 human studies conducted across diverse populations and metabolic conditions. These studies cover a broad range of clinical contexts, including obesity, polycystic ovary syndrome, gestational diabetes mellitus, type 2 diabetes mellitus, metabolic syndrome, and pediatric populations, facilitating comparative evaluation of adipokine–insulin sensitivity relationships across diverse demographic groups. Omentin-1 and Nesfatin-1 were most frequently evaluated, followed by Chemerin and Visfatin, primarily in relation to HOMA-IR and fasting insulin indices. Across these heterogeneous populations, Omentin-1 showed the most consistent inverse association with insulin resistance, while Chemerin demonstrated the most reproducible positive association with insulin-resistant states, indicating stronger reliability across human studies. A consistent pattern was observed whereby lower levels of Omentin-1 or Nesfatin-1, and higher levels of Chemerin or Visfatin, clustered with obesity, prediabetes, diabetes, and related insulin-resistant conditions. In contrast, Nesfatin-1 and Visfatin showed greater variability across disease states, suggesting population- and stage-dependent effects (Table 1).

Table 1: Characteristics of Human Studies (2019–2024) Evaluating Novel Adipokines in Relation to Insulin Sensitivity or Metabolic Status

Sr. No.	References	Country	Study Design	Population/Setting	Adipokine (S)	Insulin-Sensitivity / Metabolic Outcomes	Very Brief Key Finding
1	[8]	Mexico	Cross-sectional	Term newborns of obese vs normal-weight mothers	Omentin-1 (cord blood)	Cord HOMA-IR, insulin, glucose indices	Cord Omentin-1 levels are inversely related to maternal obesity and neonatal insulin resistance markers
2	[9]	Turkey	Case-control	Adolescent girls with PCOS vs controls	Omentin-1	HOMA-IR, fasting insulin	Omentin-1 is significantly lower in PCOS, associated with insulin resistance
3	[10]	Saudi Arabia	Case-control	Adults with metabolic syndrome, T2DM, and controls	Nesfatin-1, Galanin	HOMA-IR, lipids, glucose	Nesfatin-1 is associated with adiposity and metabolic syndrome
4	[11]	Iran	Cross-sectional	Healthy, obese, and T2DM adults	Nesfatin-1	BMI, glucose	Nesfatin-1 varied with weight status and diabetes
5	[12]	Egypt	Case-control	Newly diagnosed T2DM, prediabetes, and controls	Nesfatin-1	Fasting glucose	Nesfatin-1 is lower in prediabetes and T2DM, suggesting early dysglycaemia
6	[13]	Germany	Longitudinal intervention	Children with obesity	Omentin-1	HOMA-IR, insulin	Omentin-1 increased with weight loss and improved insulin sensitivity
7	[14]	Egypt	Case-control	Females with PCOS vs controls	Chemerin	HOMA-IR, BMI	Chemerin positively correlated with insulin resistance

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8	[15]	Turkey	Prospective case–control	Women with PCOS	Nesfatin-1, DLK1	IR indices	Both adipokines lower and linked with metabolic risk
9	[16]	Turkey	Prospective case–control	Pregnant women with GDM	Nesfatin-1, DLK1	Glucose tolerance	Altered adipokines associated with gestational insulin resistance
10	[17]	China	Case–control	T2DM with/without cognitive dysfunction	Nesfatin-1	IR indices	Higher Nesfatin-1 in advanced metabolic-neurological disease
11	[18]	Turkey	Cross-sectional	Obese adolescents with NAFLD	Omentin-1	HOMA-IR, HbA1c	Lower Omentin-1 associated with hepatic insulin resistance
12	[19]	Poland	Cross-sectional	Chronic liver disease / COVID-19	Chemerin, Omentin, Vaspin	HOMA-IR	Associations with insulin resistance were context-dependent
13	[20]	China	Cross-sectional	Adults with metabolic syndrome	Omentin-1	IR surrogates	Lower Omentin-1 independently predicted metabolic syndrome
14	[21]	Egypt	Case–control	Prediabetes, T2DM, controls	Nesfatin-1	HOMA-IR	Nesfatin-1 predicted dysglycaemia and insulin resistance
15	[22]	China	Cross-sectional	Normal glucose vs prediabetes vs T2DM	Nesfatin-1	β-cell indices	Nesfatin-1 is associated with β-cell function
16	[23]	China	Case–control (genetic)	Pregnant women with GDM	Chemerin	HOMA-IR	Higher Chemerin linked to gestational insulin resistance
17	[24]	Poland	Cross-sectional	Central obesity	Omentin-1	Glucose tolerance	Omentin-1 is associated with obesity-related insulin impairment
18	[25]	Pakistan	Case–control (genetic)	Obesity-related metabolic syndrome	Visfatin (SNPs)	Glucose, lipids	Visfatin polymorphisms linked with insulin-resistant phenotype

The biochemical characteristics and proposed physiological roles of key novel adipokines implicated in insulin sensitivity are summarised across experimental and clinical studies. Omentin-1 and Vaspin are predominantly described as insulin-sensitising adipokines, acting through enhancement of insulin signalling pathways, reduction of low-grade inflammation, and improvement of endothelial function. These biochemical properties support the consistent inverse associations observed for Omentin-1 across multiple populations in Table 1. Chemerin, by contrast, is characterised as a pro-inflammatory adipokine that promotes adipocyte dysfunction and impaired glucose uptake. This mechanistic profile aligns with the consistent positive association between Chemerin and insulin resistance reported across PCOS, GDM, and obesity-related studies. Nesfatin-1, DLK1, and Galanin demonstrate more complex biological roles involving appetite regulation, adipogenesis, β-cell function, and neuroendocrine signalling, which may explain their less consistent associations across studies (Table 2).

Table 2: Biochemical Profile of Novel Adipokines Implicated in Insulin Sensitivity

Sr. No.	Adipokine	Main Source/Tissue Distribution	Key Biochemical/Molecular Features	Proposed Mechanisms Related to Insulin Sensitivity	Overall Effect on Insulin Sensitivity (Human Data)
1	Omentin-1	Highly expressed in visceral adipose tissue, especially stromal vascular cells; also, in endothelium and intestine	34-kDa secreted glycoprotein; enhances insulin-stimulated glucose uptake in adipocytes; linked to anti-inflammatory signalling	Activates Akt/AMPK pathways, promotes GLUT4 translocation, improves endothelial function, and reduces low-grade inflammation, which together favour better insulin signalling	Generally, insulin-sensitising; lower levels are seen in obesity, metabolic syndrome, PCOS, and NAFLD, and are associated with higher HOMA-IR
2	Nesfatin-1	Hypothalamus, pancreatic β-cells, adipose tissue, gastrointestinal tract	An 82-amino-acid peptide derived from nucleobindin-2, involved in appetite control, glucose homeostasis, and stress response	Modulates insulin secretion from β-cells, affects peripheral glucose uptake, and interacts with autonomic and inflammatory pathways; circulating levels shift across obesity, prediabetes, and T2DM	Data are mixed but overall suggest a role in glucose regulation; altered levels observed in obesity, prediabetes, T2DM, and PCOS, often tracking insulin resistance and dyslipidaemia
3	Chemerin	White adipose tissue, liver, skin; also expressed in immune cells	Secreted as prochemerin and activated by proteolytic cleavage; binds CMKLR1, GPR1, and CCRL2 receptors; has chemoattractant and adipokine actions	Influences adipogenesis, adipocyte glucose uptake, and inflammatory cell recruitment; higher levels promote chronic low-grade inflammation and may blunt insulin signalling in adipose and liver tissue	Predominantly insulin-resistance promoting; concentrations rise in obesity, metabolic syndrome, PCOS and GDM and correlate positively with HOMA-IR and adverse metabolic traits

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4	Vaspin	Primarily visceral adipose tissue; also, liver and skeletal muscle	Serine protease inhibitor (serpin A12); thought to counteract proteases that impair insulin signalling	May protect insulin receptor signalling by inhibiting proteases such as kallikrein 7; experimental data suggest improved glucose tolerance and reduced inflammation	Human studies are limited; available data suggest a compensatory, insulin-sensitising role with higher levels in early obesity and insulin resistance
5	Visfatin / NAMPT	Visceral adipose tissue, liver, skeletal muscle, and immune cells	Enzyme in nicotinamide adenine dinucleotide (NAD^+) biosynthesis; also acts as a cytokine-like adipokine	Alters β-cell function, NAD^+-dependent metabolic pathways, and inflammatory signalling; may modulate insulin secretion and peripheral insulin sensitivity	Findings are inconsistent: some studies link higher visfatin to improved β-cell function, others show association with obesity, metabolic syndrome, and insulin resistance
6	DLK1 (Pref-1)	Preadipocytes, mesenchymal stem cells, fetal tissues; low in mature adipocytes	Transmembrane/soluble protein from the EGF-like family; inhibits adipocyte differentiation	By blocking adipogenesis, influences fat mass distribution and adipokine secretion profile; altered levels may affect whole-body insulin sensitivity via changes in adipose tissue quality	Limited human data; in PCOS and GDM, altered DLK1 levels are associated with adverse metabolic risk markers, suggesting a potential link to insulin resistance
7	Galanin	Widely expressed neuropeptide; also present in pancreatic islets and gastrointestinal tract	29–30 amino acid peptide acting via GalR1–3 receptors; involved in appetite regulation, autonomic tone, and glucose homeostasis	Modulates insulin secretion and hepatic glucose production; interacts with sympathetic activity and other neuropeptides that influence insulin sensitivity	Human evidence is still emerging; altered galanin levels in metabolic syndrome point towards a role in obesity-related insulin resistance, but directionality remains unclear

The mechanistic links between novel adipokines and insulin sensitivity are supported by evidence outlining key cellular and molecular pathways involved in metabolic regulation. Omentin-1 and Vaspin primarily enhance insulin sensitivity through activation of PI3K/Akt and AMPK pathways, improved glucose transport, and attenuation of inflammatory signalling. Chemerin exerts opposing effects by activating MAPK and NF-κB pathways, contributing to chronic inflammation and adipose and hepatic insulin resistance. These contrasting mechanisms provide biological plausibility for the stronger and more consistent associations observed for Omentin-1 and Chemerin in the clinical studies summarised in Table 1. Visfatin, Nesfatin-1, DLK1, and Galanin influence insulin sensitivity through more indirect or context-dependent mechanisms, which may account for the heterogeneity reported across populations and disease stages (Table 3).

Table 3: Proposed Mechanisms Through Which Novel Adipokines Influence Insulin Sensitivity (Summary of Human-Relevant Evidence)

Sr. No.	Adipokine	Key Cellular/Molecular Pathways	Mechanism Affecting Insulin Sensitivity	Direction Of Effect (Based on Human Studies)
1	Omentin-1	PI3K/Akt pathway activation; AMPK stimulation; suppression of TNF-α and IL-6	Enhances insulin-stimulated glucose uptake; improves endothelial nitric oxide activity; reduces inflammatory signalling that interferes with insulin receptor responses	Improves insulin sensitivity; low levels linked with higher HOMA-IR and metabolic syndrome
2	Nesfatin-1	Modulates β-cell Ca^{2+} signalling; interacts with autonomic pathways; regulates stress-related peptides; influences GLUT4 activity	Affects insulin secretion, appetite, and peripheral glucose uptake; may modify energy homeostasis and oxidative stress	Mixed effect; altered levels seen in obesity, prediabetes, T2DM, and PCOS; often tracks with insulin resistance
3	Chemerin	CMKLR1 receptor activation; MAPK and NF-κB pathways; modulation of adipogenesis	Increased chemerin enhances inflammatory signalling, adipocyte dysfunction, and impaired glucose transport; it contributes to hepatic and adipose insulin resistance	Promotes insulin resistance; high levels correlate with high HOMA-IR, PCOS, GDM, metabolic syndrome
4	Vaspin	Serpin inhibition of proteases (e.g., kallikrein 7) improves insulin receptor signalling; reduces ER stress	Protects insulin receptor substrates from degradation; attenuates inflammation; enhances glucose tolerance under metabolic stress	Compensatory insulin-sensitising effect; often elevated in early obesity/IR as a protective response
5	Visfatin (NAMPT)	NAD^+ biosynthesis pathway; SIRT1 activation; inflammatory cytokine modulation	Influences β-cell survival, insulin secretion, and NAD^+-dependent metabolic reactions; may affect hepatic glucose output and adipocyte inflammation	Inconsistent evidence; linked to both improved β-cell function and higher metabolic-risk phenotypes
6	DLK1 (Pref-1)	Inhibition of adipocyte differentiation; Notch/EGF-like signalling pathways	Alters adipogenesis and adipocyte number; indirectly affects whole-body insulin sensitivity by modifying adipose tissue quality	Possible insulin-resistance link; altered levels in PCOS and GDM associate with adverse metabolic markers

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7	Galanin	GalR1–3 receptor signalling; modulation of autonomic output; effects on hepatic glucose production	Regulates insulin and glucagon secretion; influences sympathetic drive and hepatic glucose metabolism	Emerging evidence; patterns suggest involvement in obesity-related insulin resistance, but the direction is not fully established

The methodological quality of the included studies was evaluated using the Joanna Briggs Institute risk-of-bias criteria. Most studies demonstrated low risk of bias in exposure and outcome measurement, reflecting the use of validated biochemical assays for adipokine and metabolic marker assessment. The main methodological limitation across studies was incomplete adjustment for confounding factors such as BMI, age, sex, and comorbidities, which may partly explain variability in adipokine insulin sensitivity relationships across populations. Studies that addressed major confounders were generally rated as low risk, while those with limited adjustment were classified as moderate risk. This finding supports cautious interpretation of results, particularly for adipokines showing inconsistent associations across heterogeneous study designs (Table 4).

Table 4: Risk of Bias Assessment of Included Studies (Using JBI Criteria)

Sr. No.	References	Study Design	Sample Selection	Measurement of Exposure (Adipokine)	Measurement of Outcome (Insulin Sensitivity / Metabolic Markers)	Confounding Factors Addressed	Overall Risk of Bias
1	[8]	Cross-sectional	Low	Low	Low	Moderate	Low
2	[9]	Case-control	Low	Low	Low	Moderate	Low
3	[10]	Case-control	Low	Low	Low	Moderate	Low
4	[11]	Cross-sectional	Moderate	Low	Low	High	Moderate
5	[12]	Case-control	Low	Low	Low	Moderate	Low
6	[13]	Longitudinal intervention	Low	Low	Low	Moderate	Low
7	[14]	Case-control	Low	Low	Low	Moderate	Low
8	[15]	Prospective case-control	Low	Low	Low	Moderate	Low
9	[16]	Prospective case-control	Low	Low	Low	Moderate	Low
10	[17]	Case-control	Moderate	Low	Low	High	Moderate
11	[18]	Cross-sectional	Low	Low	Low	Moderate	Low
12	[19]	Cross-sectional	Low	Moderate	Moderate	High	Moderate
13	[20]	Cross-sectional	Low	Low	Low	Moderate	Low
14	[21]	Case-control	Low	Low	Low	Moderate	Low
15	[22]	Cross-sectional	Low	Low	Low	Moderate	Low
16	[23]	Case-control	Low	Low	Low	Moderate	Low
17	[24]	Cross-sectional	Low	Low	Low	Moderate	Low
18	[25]	Case-control	Low	Low	Low	Moderate	Moderate

DISCUSSION

This review of recent human studies highlights that several novel adipokines appear to be closely linked with insulin sensitivity and metabolic health across a wide range of populations. Importantly, these associations were examined across heterogeneous clinical settings, including obesity, PCOS, GDM, T2DM, metabolic syndrome, and pediatric cohorts, allowing assessment of both consistency and variability in adipokine behaviour. The evidence gathered in Table 1 shows that lower circulating levels of Omentin-1 are repeatedly observed in settings of obesity, metabolic syndrome, central adiposity, and impaired glucose tolerance. For example, in a longitudinal intervention study of children with obesity, Omentin-1 increased significantly after weight loss and was inversely correlated with HOMA-IR ($r = -0.33$) both cross-sectionally and over time [13]. This pattern supports an insulin-sensitising role of Omentin-1 in visceral fat depots, consistent with the biochemical profile described in Table 2, where Omentin-1 is shown to activate Akt/AMPK pathways and promote GLUT4-mediated glucose uptake. The relative consistency of this inverse association across populations suggests that Omentin-1 may represent one of the more reliable adipokine indicators of early insulin resistance in human studies. In contrast, adipokines such as Chemerin emerged as markers of insulin resistance in multiple studies. In the cross-sectional study by Zhao *et al.* Chemerin levels correlated positively with insulin resistance measures and adiposity in a large adult cohort [26]. Similar findings were reported in other human studies, including those by Al-Mansoori *et al.* and Roy *et al.* [27, 28]. This aligns with the mechanistic summary in current review, where Chemerin is proposed to activate NF-κB and MAPK pathways, promoting adipocyte dysfunction and chronic low-grade inflammation. Across PCOS, GDM, and obesity-related cohorts, the direction of association for Chemerin (higher levels with greater insulin resistance) remained largely consistent, reinforcing its role as a deleterious adipokine in metabolic dysregulation. The findings on

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Nesfatin-1 were less straightforward. This review found that Nesfatin-1 levels are altered across metabolic states such as prediabetes, T2DM, and PCOS, but sometimes in opposite directions. For example, one Egyptian study reported lower Nesfatin-1 levels in newly diagnosed T2DM and prediabetes compared with controls, which may reflect early down-regulation during initial stages of glucose intolerance. In contrast, a Chinese study reported higher Nesfatin-1 levels in T2DM patients with cognitive impairment, suggesting complex regulation in more advanced or comorbid disease states. This heterogeneity indicates that Nesfatin-1 may function as a context-dependent adipokine, showing compensatory behaviour in some settings and pathological associations in others. In accordance with these observations, other studies have also described variable Nesfatin-1 responses across obesity and insulin-resistant states, indicating that its behaviour may shift with disease severity, inflammatory burden, and metabolic stage [29, 30]. Importantly, this review emphasises that adipokine–insulin sensitivity relationships are rarely independent of adiposity, inflammation, and other metabolic modifiers. Many included studies adjusted for BMI or waist circumference; however, fewer accounted for lifestyle factors, visceral fat distribution, or inflammatory markers in detail. For instance, although the Omentin-1 intervention study adjusted for weight loss, residual confounding by changes in adipose tissue quality could not be fully excluded. This limitation underscores the difficulty of disentangling direct adipokine effects from the broader metabolic milieu in observational human studies. Similar concerns have been raised by other researchers, who note that adipokine signalling often overlaps with inflammatory load and fat distribution, complicating causal interpretation [31, 32]. From a clinical perspective, these findings carry potentially meaningful implications. Adipokines such as Omentin-1 and Chemerin show sufficient consistency to be considered candidates for early metabolic risk stratification, particularly in populations at risk of insulin resistance. However, before translation into clinical biomarkers, several barriers remain. These include heterogeneity in study populations, lack of standardised assay platforms, and inconsistent adjustment for confounders.

As highlighted in this review, variability in assay methods and reporting units limits cross-study comparability and precludes the definition of universal diagnostic thresholds. Other clinical reports have similarly cautioned that adipokine-based markers require careful validation before routine clinical use [33-35]. The strengths of this review include its focus on recent human evidence (2019–2024), exclusion of animal and non-English studies, and integration of biochemical, mechanistic, and epidemiological findings. Future research should prioritise longitudinal designs, standardised laboratory assays, and rigorous control of confounding factors to clarify causal relationships and biomarker potential. Ultimately, novel adipokines hold promise as tools for understanding and potentially intervening in early metabolic dysfunction, but their clinical application requires further validation.

CONCLUSIONS

This review synthesises contemporary human evidence demonstrating that novel adipokines are meaningfully associated with insulin sensitivity and metabolic health. Among the adipokines reviewed, Omentin-1 and Chemerin showed the most consistent and reproducible associations with insulin resistance across heterogeneous populations, whereas Nesfatin-1 displayed a more variable, context-dependent pattern. While the mechanistic pathways outlined in results provide biologically plausible explanations for these relationships, translation into clinical practice remains premature.

Authors' Contribution

Conceptualization: AJ, AR
Methodology: AJ, RM, AK, AR, HF
Formal analysis: AJ
Writing and drafting: AJ, MSY, AR, HF
Review and editing: AJ, AR, RM, AK, HF, MSY

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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