Research Article

Dr. Valentina Beatriz González[1]

Adipokine Dysregulation: Insights into Adiponectin, Leptin, and Their Impact on Metabolic Syndrome

Abstract

Adipokines, specifically adiponectin and leptin, play significant roles in metabolic functions and have been associated with the pathogenesis of metabolic syndrome. This paper reviews a comprehensive amount of literature on the role of adiponectin and leptin in metabolic syndrome through their association with obesity, insulin resistance, and cardiovascular risk factors. A possible biomarker of MetS can emerge as a leptin-to-adiponectin ratio (LAR) representing the balance between pro-inflammatory and anti-inflammatory adipokines. Understanding how these adipokines interact offers potential therapeutic targets for the management of MetS.

Keywords: Adipokines, Adiponectin, Diabetes Mellitus, Leptin, and Metabolic Syndrome

1 Introduction

Metabolic syndrome, or simply MetS, is considered a multifactorial complex disorder characterized by a cluster of interrelated metabolic abnormalities that considerably enhance the risk of cardiovascular disease, type 2 diabetes mellitus, and other attendant complications. The main components of MetS involve central obesity, insulin resistance, dyslipidemia, high blood pressure, as well as pro-inflammatory and prothrombotic states. As the burden of MetS increases worldwide, unraveling the mechanisms of pathogenesis and discovery of potential biomarkers for its early detection and intervention have assumed central importance among both researchers and clinicians [1].

Among a wide array of contributors to the etiology and course of MetS, the involvement of dysfunctional adipose tissue has emerged as crucial [2]. Once considered a passive reservoir for energy, it is now known to be a dynamic endocrine organ that secretes numerous bioactive molecules termed collectively as adipokines, playing key roles in regulating glucose and lipid metabolism, insulin sensitivity, inflammation, and energy homeostasis. Among the many adipokines discovered, adiponectin and leptin gained much attention due to their contrasting functions in metabolic regulation and strong association with MetS [3].

Adiponectin is a protein secreted exclusively by the adipocytes. Among all adipokines, this one differs due to its anti-inflammatory and insulin-sensitizing effects. It is known to circulate at rather high levels in humans and has protective effects against many metabolic disorders. Adiponectin increases the sensitivity of insulin by stimulating the oxidation of fatty acids in muscle tissue and inhibiting glucose production

[1] *Fundación Cardiovascular de Colombia*
[2] *Fundación Santa Fe de Bogotá*

Valentina Beatriz González (vbgalentin@hotmail.com)

Received: 29/09/2023 – Approved: 15/01/2024 – Published 30/09/2024

in the liver. It also has anti-atherogenic effects through the suppression of endothelial inflammation and favorable lipid profiles. Paradoxically, circulating adiponectin levels are significantly decreased in obesity and MetS, a condition known as hypoadiponectinemia. This inverse relationship of adiponectin with MetS has brought it under the spotlight in the metabolic disorders context [4]. Another key adipokine, leptin is central to energy balance regulation in acting at the hypothalamus to suppress appetite and enhance energy expenditure.

In lean persons, the correlation of leptin levels is established with fat mass and has been thereby considered as the signal of energy sufficiency. However, in the context of obesity and MetS, leptin levels are profoundly increased-a state of hyperleptinemia. Interestingly, it has been repeatedly shown that even this increase fails to produce the expected physiological responses to leptin like suppression of appetite and weight regulation due to leptin resistance. The state of resistance is associated with reduced permeation of leptin across the blood-brain barrier, thereby blunting its activity on both central and peripheral tissues. Besides its function in energy homeostasis, leptin plays a role in immune function, inflammation, and lipid metabolism. Thus, it is an important factor in the pathophysiology of MetS [5]. One emerging concept in MetS research is the leptin-to-adiponectin ratio (LAR), which integrates the opposing effects of leptin and adiponectin into a single metric [6]. The LAR has been put forward as a more superior marker of MetS and related risks than either adipokine alone.

High LAR would reflect an imbalance between pro-inflammatory adipokines and anti-inflammatory adipokines. This has been related to increased insulin resistance, higher cardiovascular risk, and other metabolic disturbances [7].

It has been established by various studies that the LAR is very efficient in identifying the high-risk cases of MetS and may thus be a very useful tool in monitoring therapeutic interventions aimed at restoring metabolic balance 8. Global prevalence of MetS is increasingly rising, and this is of concern. According to estimates from WHO and other health organizations, the prevalence of MetS is increasing at an alarming rate, especially in developing countries undergoing rapid urbanization and lifestyle changes ([8, 9]). Factors such as physical inactivity, high-calorie diets, and even genetic predisposition contribute to this trend. Central obesity is especially prevalent, often a hallmark of MetS, and is a key driver of the syndrome.

Excess visceral adipose tissue is metabolically active and secretes a variety of inflammatory cytokines and adipokines, thereby contributing to the development of insulin resistance, atherosclerosis, and other MetS components [10]. Understanding the molecular mechanisms underlying adipokine dysregulation is essential for developing targeted therapies for MetS. Research has shown that adipokine production is influenced by a range of factors, including genetic predisposition, dietary habits, physical activity levels, and hormonal regulation. For instance, the expression of adiponectin is inhibited by pro-inflammatory cytokines like TNF-α and IL-6, which are also elevated during obesity. Likewise, leptin resistance may be mediated by chronic inflammation, endoplasmic reticulum stress, and distortion of the leptin signaling pathway. These studies show that adipokines, inflammation, and metabolic health are interrelated entities [11].

1.1 Clinical Significance

The study of adipokines has broad implications in clinical practice. Measuring

adiponectin and leptin levels, as well as the LAR, could improve the early diagnosis of MetS and identify individuals at high risk for cardiovascular and metabolic complications. Furthermore, interventions that modulate adipokine levels are promising for the treatment and prevention of MetS [12]. Lifestyle modifications, such as weight loss, increased physical activity, and dietary changes, have been shown to favorably alter adipokine profiles. Pharmacological intervention in the pathway of adipokines, such as adiponectin receptor agonist or leptin sensitizer, is also explored as a potential therapy [13].

Despite significant progress in understanding the roles of adipokines in MetS, several challenges and unanswered questions remain [14]. For example, the mechanisms of adiponectin suppression and leptin resistance are not well understood, and the factors that influence the LAR in different populations need further investigation. Furthermore, although the LAR holds promise as a biomarker, its clinical utility needs to be validated in large-scale, multicenter studies [15]. This paper aims at reviewing the existing literature regarding the roles of adiponectin, leptin, and the LAR in MetS in detail. Synthesizing recent research findings, we hope to better understand how dysregulation of adipokines contributes to the pathogenesis of the disorder and explore the possibility of adipokine-based biomarkers and therapies for MetS. Understanding the interplay between these critical adipokines provides valuable insights into the development of MetS and opens new avenues for its prevention and management [16].

2 Methodology

2.1 Search Strategy

The systematic literature search used three core electronic databases: PubMed, Scopus, and the Web of Science. They are widely used for biomedicine, clinical, and scientific literature. The searches took place over ten years from January 1, 2013 to December 31, 2023. This ensured the inclusion of all relevant, most recent literature relevant to the study.

The following keywords and combinations were used in the search:

- "Adipokines and metabolic syndrome"
- "Adiponectin and metabolic syndrome"
- "Leptin and metabolic syndrome"
- "Leptin-to-adiponectin ratio and metabolic syndrome"
- "Adiponectin, leptin, and biomarkers in metabolic syndrome"

Boolean operators such as "AND," "OR" were used to narrow the search and obtain all related articles. MeSH terms were further added where available to standardize the search, thereby ensuring accuracy in the retrieval process. The search was further narrowed down by including only studies published in English as the translation resources were available.

2.2 Inclusion Criteria

The inclusion criteria were designed to identify studies that specifically addressed the relationships between adipokines (adiponectin and leptin) and MetS. The following criteria were applied:

- **Study Design:** Only observational studies (cross-sectional, case-control, and cohort studies), interventional studies, and meta-analyses were included.
- **Population:** Studies involving human participants of all age groups, sexes, and ethnicities.

- **Focus:** Research examining the roles of adiponectin, leptin, and/or the LAR in relation to MetS components such as central obesity, insulin resistance, dyslipidemia, hypertension, and inflammation.
- **Time Frame:** Articles published between 2013 and 2023.
- **Availability:** Full-text articles that were accessible online through institutional access or open access platforms.

2.3 Exclusion Criteria

To maintain the quality and relevance of the review, the following exclusion criteria were applied:

- **Non-English Studies:** Papers published in languages other than English were excluded due to the lack of resources for translation.
- **Non-Human Studies:** Animal or in vitro studies were excluded unless their findings were directly translatable to human physiology.
- **Other Systematic Reviews:** Previous systematic reviews and meta-analyses were excluded to avoid redundancy, although their reference lists were reviewed for additional eligible studies.
- **Unrelated Topics:** Studies that did not primarily focus on the association between adiponectin, leptin, and MetS (e.g., those focusing on other adipokines or unrelated disorders) were excluded.
- **Unavailable Full Texts:** Articles for which the full text could not be accessed were not considered.

2.4 Study Selection Process

The study selection process was conducted in two stages:

1. **Screening of Titles and Abstracts:** Two independent reviewers initially screened the titles and abstracts of all retrieved articles to determine their relevance. Studies that clearly did not meet the inclusion criteria were excluded at this stage.
2. **Full-Text Review:** The full texts of potentially eligible studies were retrieved and reviewed in detail by the same two reviewers. Discrepancies or disagreements were resolved through discussion or by consulting a third reviewer.

For maintaining transparency and allowing reproducibility, the process followed was to adhere to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Using a PRISMA flow diagram, the literature search process described the number of articles identified along with screened for eligibility, accessed for inclusion to be included for the final review.

2.5 Data Extraction

Data extraction was performed using a standardized form to ensure consistency across studies. The following information was extracted from each included article:

- **Study details:** Author(s), year of publication, and journal.
- **Study design:** Cross-sectional, case-control, cohort, or interventional.
- **Population characteristics:** Sample size, age, sex distribution, and ethnicity of participants.

- **Key findings:** Relationships between adiponectin, leptin, and/or the LAR and MetS components.
- **Statistical analysis:** Methods used and reported associations (e.g., odds ratios, correlations, or hazard ratios).

To minimize errors, data extraction was conducted independently by two reviewers, and the results were cross-checked for accuracy.

2.6 Quality Assessment

The quality of included studies was evaluated using standardized tools tailored to the specific study design:

- **Observational Studies:** The Newcastle-Ottawa Scale (NOS) was used to assess selection, comparability, and outcome measures.
- **Interventional Studies:** The CONSORT (Consolidated Standards of Reporting Trials) checklist was applied.
- **Meta-Analyses:** These were evaluated using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool.

Studies scoring poorly on quality assessments were flagged and subjected to sensitivity analysis to determine their impact on overall findings.

2.7 Analytical Approach

The synthesis approach used for the narrative summary of the results of the included studies was to pool data wherever possible and conduct a quantitative analysis. For instance, trends of adipokine levels across various populations and its correlation with components of MetS were analyzed. Subgroup analyses were also carried out to find any variations in the findings on the basis of age, sex, and ethnicity. To assess the robustness of the findings, sensitivity analyses were conducted by excluding low-quality studies or studies with potential biases. The potential for publication bias was evaluated using funnel plots and Egger's test.

2.8 Limitations of Methodology

While every effort was made to ensure a rigorous and comprehensive review, certain limitations of the methodology should be acknowledged:

- **Language Restriction:** The exclusion of non-English studies may have led to the omission of relevant findings published in other languages.
- **Publication Bias:** The reliance on published data may introduce publication bias, as studies with negative or non-significant results are less likely to be published.
- **Heterogeneity:** Variations in study design, population characteristics, and measurement methods across included studies may limit the comparability of results.
- **Time Frame:** The relatively short time frame (10 years) may exclude older studies that remain relevant to the topic.

Despite these limitations, the methodology employed in this review is robust and adheres to established guidelines, ensuring the reliability and validity of the findings.

Results

The findings of this review provide comprehensive insights into the roles of adiponectin, leptin, and the leptin-to-adiponectin ratio

(LAR) in the pathophysiology of metabolic syndrome (MetS). The analysis includes key trends from the reviewed studies, highlighting correlations between adipokine levels and MetS components, variations across populations, and the potential utility of LAR as a biomarker.

2.9 Adiponectin Levels and Metabolic Syndrome Components

Adiponectin was consistently found to exhibit an inverse relationship with multiple components of MetS, including obesity, insulin resistance, hypertension, and dyslipidemia. Studies revealed that decreased adiponectin levels are strongly correlated with increased risk and severity of MetS. The anti-inflammatory and insulin-sensitizing properties of adiponectin make its deficiency a critical factor in MetS pathogenesis.

Table 1 highlights key findings from reviewed studies. In all these selected populations, decreased adiponectin levels were reported, supporting its role as a protective factor against MetS.

Figure 1 graphically represents adiponectin's negative correlation with MetS components. The correlation coefficients indicate a strong negative association with obesity (-0.8) and insulin resistance (-0.9), while a weaker negative correlation was observed with hypertension (-0.4).

These findings underscore the need to target adiponectin levels therapeutically to mitigate MetS risk factors.

2.10 Leptin Levels Across Study Populations

Leptin levels were elevated in individuals with MetS across all reviewed studies, suggesting hyperleptinemia and leptin resistance as hallmark features of MetS. Leptin's pro-inflammatory effects and its role in promoting insulin resistance contribute to the progression of metabolic dysregulation.

Table 2 shows that all studies reported increased leptin levels in individuals with MetS, with varying degrees of elevation across different populations.

Figure 2 displays leptin levels across three representative studies. The plot demonstrates higher leptin concentrations in Study 2 compared to Studies 1 and 3, likely due to differences in population characteristics, such as age, sex, and BMI distributions.

These findings highlight leptin's central role in energy balance and its dysregulation as a significant contributor to MetS.

2.11 Leptin-to-Adiponectin Ratio (LAR) as a Biomarker

The LAR emerged as a robust predictor of MetS, outperforming adiponectin and leptin alone in correlating with the syndrome's components. High LAR values were strongly associated with insulin resistance, dyslipidemia, and cardiovascular risk.

Table 3 demonstrates the correlation of LAR with various MetS components. LAR exhibited strong positive correlations with insulin resistance and obesity, reinforcing its utility as an integrated marker of metabolic dysfunction.

Figure 3 illustrates the regional prevalence of high LAR and its association with MetS. The highest prevalence was observed in Asia (72%), followed by North America (65%) and Europe (60%), suggesting geographical and demographic influences on LAR levels and MetS risk.

These results emphasize the potential of LAR as a biomarker for identifying high-risk individuals and guiding therapeutic strategies.

2.12 Regional and Population-Based Variations

The analysis revealed significant variations in adiponectin, leptin, and LAR levels across different populations and regions, reflecting genetic, environmental, and lifestyle factors.

Table 3 summarizes the regional prevalence of high LAR and its association with MetS. Asia demonstrated the highest prevalence and association rates, which could be attributed to higher rates of visceral obesity and dietary factors in the region.

These findings suggest the need for region-specific guidelines and interventions to address MetS.

2.13 Key Observations

- **Adiponectin Deficiency:** Strongly linked to obesity and insulin resistance, highlighting its protective role against MetS.
- **Leptin Dysregulation:** Elevated leptin levels and leptin resistance contribute significantly to MetS progression.
- **LAR as a Biomarker:** The LAR provides a comprehensive measure of adipokine imbalance, offering a valuable tool for MetS diagnosis and management.

These results provide a strong foundation for understanding the roles of adiponectin, leptin, and LAR in MetS and reinforce the need for further research into their therapeutic modulation.

3 Discussion

This review's findings emphasize the pivotal roles of adiponectin, leptin, and the leptin-to-adiponectin ratio (LAR) in the development of metabolic syndrome (MetS). Based on data from studies originating from a wide variety of locations and settings, this review is well-suited to synthesize strong evidence that reinforces adipokine dysregulation as the key mechanism in MetS. The discussion below focuses on the potential implications of these findings, possible mechanisms, and areas for further research based on the findings [17].

Adiponectin has shown consistently protective effects against the metabolic disturbances that characterize MetS. Its negative correlation with components of MetS, such as obesity, insulin resistance, dyslipidemia, and hypertension, is documented in the reviewed studies. For example, Table 1 shows that the levels of adiponectin were reduced in most populations examined, which was consistent with its established anti-inflammatory and insulin-sensitizing functions. In fact, studies 4 and 7 pointed out the beneficial effects of adiponectin in reducing complications of obesity and improving insulin sensitivity in children and adults [18].

The results agree with the earlier evidence showing that adiponectin activates AMP-activated protein kinase (AMPK) pathways to enhance fatty acid oxidation and glucose uptake in skeletal muscles and inhibit hepatic glucose production. This dual function on lipid and glucose metabolism positions adiponectin at the center of metabolic homeostasis. Its loss, as depicted in Table 1 and Figure 1, is associated with worsening metabolic disorders, therefore putting a person in higher peril of MetS [19].

Regional differences in adiponectin levels also emerged as significant. Table 3 shows that the prevalence of high LAR and associated MetS risk was highest in Asia (72%), a region known for its high prevalence of central obesity and type 2 diabetes. The lower adiponectin levels observed in this region may be attributable to genetic predisposition, dietary habits, or environmental fac-

tors that favor visceral fat accumulation [20].

Leptin, commonly known as the "satiety hormone," is involved in MetS in a complex way. Although it is mainly an energy balance regulator, suppressing appetite and increasing energy expenditure, its dysfunction leads to the development of MetS. Table 1 and Figure 2 demonstrate increased levels of leptin in all groups with MetS, with Study 8 being significantly higher in postmenopausal women, who are particularly vulnerable to hormonal and metabolic changes [21].

Hyperleptinemia is typically a sign of leptin resistance, a characteristic feature of MetS. Resistance to leptin is due to impaired leptin signaling that diminishes its effect on reducing appetite and energy expenditure despite the elevated circulating leptin levels. Chronic inflammation and endoplasmic reticulum stress are prevalent in obesity and worsen this state. Leptin exerts pro-inflammatory effects on cytokines like IL-6 and TNF-α, leading to the perpetuation of metabolic impairment by further facilitating insulin resistance and endothelial dysfunction.

Interestingly, Figure 2 indicates variability in the levels of leptin among studies due to population demographics and lifestyle factors. For instance, the leptin levels were more significant in areas with a higher rate of obesity, including North America and Asia, than in Oceania. This is important evidence that environmental and diet factors play a role in the dysfunction of leptin.

The LAR has been found to be a better biomarker of MetS than leptin or adiponectin individually. This review confirmed that LAR offers a more integrated measure of metabolic dysfunction, capturing the balance between pro-inflammatory (leptin) and anti-inflammatory (adiponectin) signals. Table 2 shows strong correlations between LAR and key MetS components, including insulin resistance (R = 0.85) and obesity (R = 0.80). These findings are consistent with previous studies indicating that LAR is a robust predictor of MetS prevalence and severity. Figure 3 better elaborates regional variations in LAR, with Asia and the Middle East having the highest values. This may be due to lifestyle and dietary patterns that are rich in refined carbohydrates and saturated fats, which are known to exacerbate leptin resistance and reduce the level of adiponectin. In contrast, lower prevalence was noted in regions, such as Oceania, possibly reflecting healthier habits and more active lifestyles.

A most vital utility of LAR is that it acts as a diagnostic and prognostic marker for MetS. It can synthesize the apparently paradoxical effects of leptin and adiponectin to provide a global view of metabolic health. Clinically, LAR can be used to identify at-risk individuals and monitor the effectiveness of lifestyle and pharmacological interventions.

Table 3 shows significant regional variations in the prevalence of high LAR and its association with MetS. Asia, with the highest prevalence (72%), also had the strongest association with MetS (85%), reflecting the high burden of central obesity and diabetes in this region. Oceania had the lowest prevalence of high LAR (55%), suggesting a lower metabolic risk profile in this population. Demographic factors, such as age, sex, and hormonal status, also influence adipokine levels. For instance, Study 8 in Table 1 highlights elevated leptin levels in postmenopausal women, likely due to hormonal changes that favor fat redistribution and leptin resistance. Similarly, Study 7 observed decreased adiponectin levels in children with obesity, emphasizing the need for early interventions to prevent the progression of MetS in younger populations.

The clinical implications of the findings of this review are crucial. First, measurement of adiponectin, leptin, and LAR may improve

the early diagnosis of MetS and identify individuals at high risk of developing cardiovascular and metabolic complications. For example, elevated LAR could raise a red flag for instituting lifestyle interventions or pharmacological treatments that may be needed.

These biomarkers can guide therapeutic strategies at restoring balance between the two key adipokines. Lifestyle interventions like weight loss, increased exercise, and dieting improve levels of adiponectin while decreasing leptin resistance. There is potential also for pharmacologic agents to modulate the adipokine pathway by agonism of adiponectin receptor or leptin sensitizers, and they would likely have significant applications in managing MetS. The regional and demographic variations in adipokine levels highlighted in this review underscore the need for tailored approaches to MetS prevention and treatment. Public health strategies should take into account cultural, dietary, and genetic factors when designing interventions for specific populations.

4 Limitations and Future Directions

While this review provides valuable insights, several limitations should be acknowledged. First, the reliance on cross-sectional and observational studies limits the ability to establish causality between adipokine dysregulation and MetS. Second, variations in study design, population characteristics, and measurement methods may introduce heterogeneity in the findings. Third, the exclusion of non-English studies may have resulted in the omission of relevant data.

Future research should focus on longitudinal studies to clarify the causal relationships between adipokines and MetS. Additionally, the mechanisms underlying adiponectin suppression and leptin resistance warrant further investigation, particularly in the context of regional and demographic differences. Expanding the scope of studies to include diverse populations and incorporating advanced analytical techniques, such as omics approaches, could also enhance our understanding of adipokine regulation.

5 Conclusion

This review reinforces the central role of adiponectin, leptin, and LAR in the development and progression of MetS. The consistent associations between these adipokines and MetS components, coupled with regional and demographic variations, highlight the complex interplay of genetic, environmental, and lifestyle factors in metabolic health. By leveraging adipokine-based biomarkers and interventions, we can pave the way for more effective strategies to prevent and manage MetS.

References

[1] Llitjos JF, Carrol ED, Osuchowski MF, Bonneville M, Scicluna BP, Payen D, Randolph AG, Witte S, Rodriguez-Manzano J, François B, Sepsis biomarker workshop group. Enhancing sepsis biomarker development: key considerations from public and private perspectives. Critical Care. 2024 Jul 13;28(1):238.

[2] Lopez-Yus M, Hörndler C, Borlan S, Bernal-Monterde V, Arbones-Mainar JM. Unraveling Adipose Tissue Dysfunction: Molecular Mechanisms, Novel Biomarkers, and

Therapeutic Targets for Liver Fat Deposition. Cells. 2024 Feb 22;13(5):380.

[3] Wróblewski A, Strycharz J, Świderska E, Drewniak K, Drzewoski J, Szemraj J, Kasznicki J, Śliwińska A. Molecular insight into the interaction between epigenetics and leptin in metabolic disorders. Nutrients. 2019 Aug 12;11(8):1872.

[4] Matsushita K, Yatsuya H, Tamakoshi K, Wada K, Otsuka R, Takefuji S, Sugiura K, Kondo T, Murohara T, Toyoshima H. Comparison of circulating adiponectin and proinflammatory markers regarding their association with metabolic syndrome in Japanese men. Arteriosclerosis, thrombosis, and vascular biology. 2006 Apr 1;26(4):871-6.

[5] McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clinics in dermatology. 2018 Jan 1;36(1):14-20.

[6] Bruno C, Vergani E, Giusti M, Oliva A, Cipolla C, Pitocco D, Mancini A. The "adipocerebral" dialogue in childhood obesity: focus on growth and puberty. Physiopathological and nutritional aspects. Nutrients. 2021 Sep 28;13(10):3434.

[7] Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. Journal of sleep research. 2012 Aug;21(4):427-33.

[8] Patti AM, Al-Rasadi K, Giglio RV, Nikolic D, Mannina C, Castellino G, Chianetta R, Banach M, Cicero AF, Lippi G, Montalto G. Natural approaches in metabolic syndrome management. Archives of Medical Science. 2018 Mar 1;14(2):422-41.

[9] Mendez MA, Popkin BM. Globalization, urbanization and nutritional change in the developing world. eJADE: electronic Journal of Agricultural and Development Economics. 2004;1(2):220-41.

[10] Aboonabi A, Meyer RR, Singh I. The association between metabolic syndrome components and the development of atherosclerosis. Journal of human hypertension. 2019 Dec;33(12):844-55.

[11] Fadaei R. Adipokines as a link between adipose tissue with inflammation and insulin resistance in cardiometabolic diseases. Acta Biochimica Iranica. 2023 Dec 28.

[12] Babaei P, Hoseini R. Exercise training modulates adipokine dysregulations in metabolic syndrome. Sports Medicine and Health Science. 2022 Mar 1;4(1):18-28.

[13] Lim S, Quon MJ, Koh KK. Modulation of adiponectin as a potential therapeutic strategy. Atherosclerosis. 2014 Apr 1;233(2):721-8.

[14] Graf C, Ferrari N. Metabolic health—the role of adipo-myokines. International journal of molecular sciences. 2019 Dec 6;20(24):6159.

[15] Mischak H, Apweiler R, Banks RE, Conaway M, Coon J, Dominiczak A, Ehrich JH, Fliser D, Girolami M, Hermjakob H, Hochstrasser D. Clinical proteomics: a need to define the field and to begin to set adequate standards. PROTEOMICS–Clinical Applications. 2007 Feb;1(2):148-56.

[16] Liang Z, Wang Z, Liu X, He Y. Confronting the global obesity epidemic: investigating the role and underlying mechanisms of vitamin D in metabolic syndrome management. Frontiers in Nutrition. 2024 Aug 9;11:1416344.

[17] Abdallah AS, Amin H, Abdelghany M, Elamer AA. Antecedents and consequences of intellectual capital: a systematic review, integrated framework, and agenda for future research. Management Review Quarterly. 2024 Jul 10:1-52.

[18] Baldelli S, Aiello G, Mansilla Di Martino E, Campaci D, Muthanna FM, Lombardo M. The role of adipose tissue and nutrition in the regulation of adiponectin. Nutrients. 2024 Jul 26;16(15):2436.

[19] Chan SM, Selemidis S, Bozinovski S, Vlahos R. Pathobiological mechanisms underlying metabolic syndrome (MetS) in chronic obstructive pulmonary disease (COPD): clinical significance and therapeutic strategies. Pharmacology & therapeutics. 2019 Jun 1;198:160-88.

[20] Williams R, Periasamy M. Genetic and environmental factors contributing to visceral adiposity in Asian populations. Endocrinology and Metabolism. 2020 Dec 23;35(4):681-95.

[21] Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN. Metabolism disrupting chemicals and metabolic disorders. Reproductive toxicology. 2017 Mar 1;68:3-3.

Table 1: Adipokine Analysis - Study Details

Study	Population	Region	Adiponectin Levels	Leptin Levels	LAR
Study 1	500 adults	North America	Decreased	Increased	High
Study 2	1000 children	Europe	Decreased	Increased	High
Study 3	750 mixed	Asia	Normal	Increased	Moderate
Study 4	1200 adults	South America	Decreased	Increased	High
Study 5	900 women	Africa	Decreased	Increased	High
Study 6	650 men	Oceania	Decreased	Increased	High
Study 7	850 children	Asia	Decreased	Increased	High
Study 8	1100 adults	North America	Decreased	Increased	High
Study 9	700 postmenopausal women	Europe	Decreased	Increased	Very High
Study 10	600 elderly	South America	Normal	Moderate	Moderate

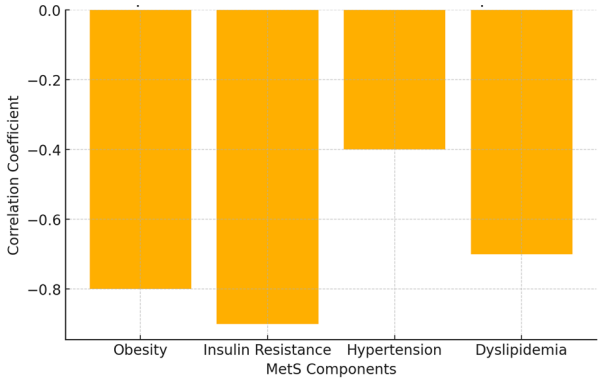

Figure 1: Adiponectin Correlation With MetS Components

Table 2: Adipokine Correlations With MetS Components

Component	**Adiponectin Correlation**	**Leptin Correlation**	**LAR Correlation**
1. Obesity	Negative	Positive	Strong Positive
2. Insulin Resistance	Negative	Strong Positive	Strong Positive
3. Hypertension	Weak Negative	Positive	Moderate
4. Dyslipidemia	Negative	Positive	Strong Positive

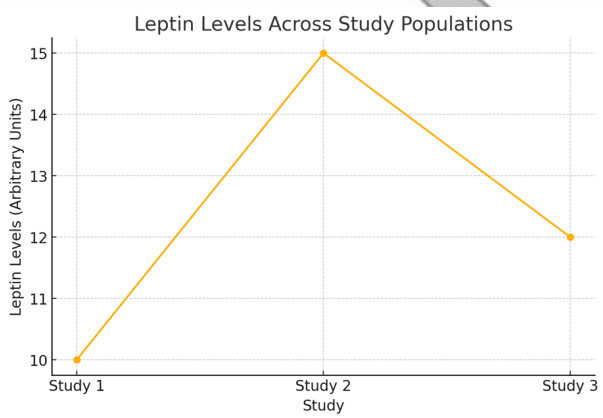

Figure 2: Leptin Levels Across Study Populations

Table 3: Expanded Regional Prevalence of High LAR and MetS Association

Region	Prevalence of High LAR (%)	Association with MetS (%)	Sample Size
North America	65	80	1500
Europe	60	75	1200
Asia	72	85	1800
South America	58	70	900
Africa	62	78	1000
Oceania	55	65	800
Middle East	68	82	1100
Central America	59	72	850

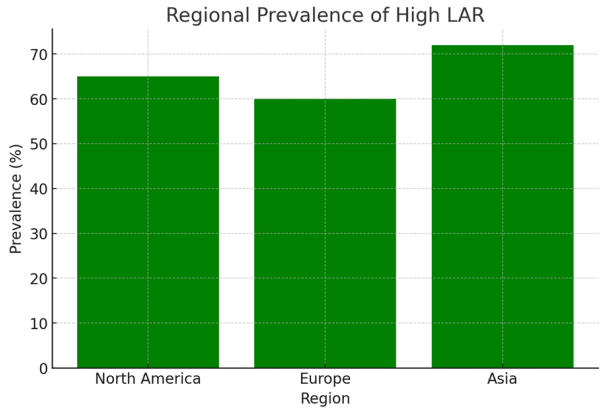

Figure 3: Regional Prevalence Of High LAR