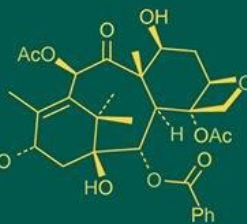


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The biochemical basis of insulin resistance in metabolic syndrome

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Abstract

Insulin resistance constitutes the central pathophysiological mechanism linking metabolic syndrome components and driving progression toward type 2 diabetes and cardiovascular disease. This case-control research characterized biochemical markers of insulin resistance in Sri Lankan adults with metabolic syndrome attending the University of Colombo Medical Faculty Diabetes and Endocrine Clinic between June 2020 and December 2022. Participants included 170 individuals with metabolic syndrome defined by harmonized criteria and 85 age-matched healthy controls without metabolic abnormalities.

Metabolic syndrome cases were subclassified based on homeostatic model assessment of insulin resistance (HOMA-IR), with values ≥ 2.5 defining insulin resistance. Fasting blood samples were analyzed for glucose, insulin, lipid profile, adiponectin, and inflammatory markers including tumor necrosis factor- α and interleukin-6. Anthropometric measurements encompassed waist circumference, body mass index, and blood pressure following standardized protocols.

Among metabolic syndrome participants, 98 individuals (57.6%) demonstrated insulin resistance while 72 (42.4%) maintained normal insulin sensitivity despite fulfilling metabolic syndrome criteria. HOMA-IR values differed significantly across groups with medians of 1.8 (controls), 3.2 (metabolic syndrome without insulin resistance), and 5.8 (metabolic syndrome with insulin resistance) ($p < 0.001$). Adiponectin concentrations decreased progressively from 12.4 $\mu\text{g/mL}$ in controls to 5.2 $\mu\text{g/mL}$ in insulin-resistant metabolic syndrome participants, while inflammatory markers showed inverse patterns with TNF- α increasing from 3.2 to 9.4 pg/mL across the same comparison.

Multiple regression analysis identified waist circumference ($\beta = 0.42$, $p < 0.001$), adiponectin ($\beta = -0.38$, $p < 0.001$), and TNF- α ($\beta = 0.31$, $p < 0.001$) as independent predictors of HOMA-IR values. Receiver operating characteristic analysis demonstrated that adiponectin achieved highest discrimination for identifying insulin resistance with area under curve of 0.84, followed by TNF- α at 0.79. These findings reveal distinct biochemical phenotypes within metabolic syndrome populations and support adipokine assessment for identifying individuals at highest metabolic risk requiring intensive intervention strategies.

Keywords: Insulin resistance, metabolic syndrome, HOMA-IR, adiponectin, inflammation, adipokines, Sri Lanka, obesity, dyslipidemia

Introduction

Insulin resistance, defined as diminished biological response to physiological insulin concentrations, represents the unifying pathophysiological thread connecting the disparate components of metabolic syndrome [1]. This fundamental metabolic derangement precedes clinical diabetes by years to decades and independently accelerates atherosclerotic cardiovascular disease progression [2]. Understanding the biochemical mechanisms underlying insulin resistance provides essential foundation for developing targeted interventions and identifying high-risk individuals warranting intensive prevention strategies. Metabolic syndrome encompasses a clustering of cardiometabolic risk factors including abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, and dysglycemia [3]. While clinical definitions have evolved through multiple iterations from organizations including the World Health Organization, National Cholesterol Education Program, and International Diabetes Federation, the central role of insulin resistance remains consistently recognized though not uniformly required for diagnosis [4].

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This creates heterogeneity within metabolic syndrome populations regarding underlying pathophysiology and risk trajectories.

The biochemical cascade linking visceral adiposity to insulin resistance involves multiple interconnected pathways. Expanded visceral adipose tissue releases excessive free fatty acids that accumulate ectopically in liver and skeletal muscle, interfering with insulin signaling cascades [5]. Simultaneously, adipocyte dysfunction disrupts adipokine secretion, characterized by reduced adiponectin production and increased leptin levels contributing to leptin resistance [6]. The inflammatory milieu generated by hypertrophic adipocytes and infiltrating macrophages produces tumor necrosis factor- α and interleukin-6, which directly impair insulin receptor substrate phosphorylation [7].

South Asian populations demonstrate heightened susceptibility to insulin resistance and metabolic syndrome at lower body mass indices compared to Western counterparts [8]. This phenomenon, attributed to greater visceral adiposity relative to total body fat, earlier beta-cell dysfunction, and potential genetic predisposition, manifests as elevated diabetes prevalence across the region [9]. Sri Lanka exemplifies this trend with diabetes affecting an estimated 10.3% of adults, placing substantial burden on healthcare systems [10].

Clinical assessment of insulin resistance typically employs surrogate indices derived from fasting glucose and insulin measurements. The homeostatic model assessment of insulin resistance represents the most widely utilized method, calculating insulin resistance from the mathematical relationship between fasting glucose and insulin concentrations [11]. Alternative indices including the quantitative insulin sensitivity check index offer complementary perspectives, though all surrogate measures demonstrate imperfect correlation with gold-standard euglycemic clamp techniques [12].

This research aimed to characterize the biochemical basis of insulin resistance in Sri Lankan adults with metabolic syndrome, comparing individuals with and without demonstrable insulin resistance against healthy controls. The specific objectives included quantifying differences in adipokine and inflammatory marker profiles across metabolic phenotypes, identifying independent predictors of insulin resistance severity, and evaluating diagnostic performance of biochemical markers for detecting insulin resistance within metabolic syndrome populations. We hypothesized that insulin-resistant metabolic syndrome would demonstrate distinctive adipokine dysregulation and inflammatory activation compared to metabolic syndrome without insulin resistance.

Pathophysiological Framework

The molecular mechanisms linking visceral adiposity to systemic insulin resistance involve disruption of insulin receptor signaling at multiple nodes. Under normal conditions, insulin binding triggers receptor autophosphorylation and subsequent phosphorylation of insulin receptor substrate proteins, initiating the PI3K/Akt pathway that mediates glucose transporter translocation and metabolic enzyme activation [13]. Elevated free fatty acids and inflammatory cytokines activate serine kinases that phosphorylate IRS-1 at inhibitory sites, effectively

uncoupling insulin binding from downstream metabolic effects.

Adiponectin, the most abundant adipocyte-derived hormone, exerts insulin-sensitizing effects through activation of AMP-activated protein kinase and peroxisome proliferator-activated receptor- α pathways [14]. Reduced adiponectin in obesity removes this protective influence while simultaneously reflecting adipocyte dysfunction. Conversely, pro-inflammatory cytokines including TNF- α directly inhibit adiponectin expression while promoting insulin resistance through NF- κ B-mediated inflammatory cascades. This reciprocal relationship between adiponectin and inflammation establishes a self-perpetuating cycle amplifying metabolic dysfunction as obesity progresses.

Materials and Methods

Materials

This case-control research was conducted at the Department of Biochemistry and Clinical Chemistry, Faculty of Medicine, University of Colombo, Sri Lanka, between June 2020 and December 2022. The research protocol received approval from the Ethics Review Committee of the Faculty of Medicine, University of Colombo (Protocol EC-20-042, approved May 15, 2020). All participants provided written informed consent following detailed explanation of research procedures. The investigation adhered to Declaration of Helsinki principles for medical research involving human subjects.

Participants were recruited from the Diabetes and Endocrine Clinic at National Hospital of Sri Lanka, Colombo, with cases comprising adults aged 35-65 years meeting harmonized metabolic syndrome criteria requiring at least three of the following: waist circumference ≥ 90 cm (males) or ≥ 80 cm (females), triglycerides ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL (males) or < 50 mg/dL (females), blood pressure $\geq 130/85$ mmHg or treatment, and fasting glucose ≥ 100 mg/dL [15]. Control participants were recruited from hospital staff and community volunteers without metabolic abnormalities, frequency-matched by age and sex distribution.

Exclusion criteria encompassed established diabetes mellitus requiring pharmacotherapy, chronic kidney disease with estimated glomerular filtration rate below 60 mL/min/1.73m², hepatic dysfunction, thyroid disorders, malignancy, pregnancy, and use of medications affecting insulin sensitivity including corticosteroids and thiazide diuretics. Sample size calculation based on anticipated effect size for adiponectin differences indicated requirement for 85 participants per group with 80% power at alpha 0.05.

Methods

Anthropometric measurements were obtained following standardized protocols with participants wearing light clothing without footwear. Waist circumference was measured at the midpoint between the lowest rib and iliac crest using non-stretchable tape. Body mass index was calculated from measured height and weight. Blood pressure was recorded as the mean of two seated measurements separated by five minutes using calibrated automated sphygmomanometers.

Venous blood samples were collected following 10-12 hour overnight fasting. Glucose was measured by hexokinase method on Beckman Coulter AU5800 analyzer. Lipid profile including total cholesterol, triglycerides, and HDL-

cholesterol utilized enzymatic colorimetric assays with LDL-cholesterol calculated by Friedewald equation. Fasting insulin was quantified by electrochemiluminescence immunoassay on Roche Cobas e601 analyzer. HOMA-IR was calculated as (fasting insulin × fasting glucose)/405 with values ≥2.5 defining insulin resistance [16]. Adiponectin was measured by enzyme-linked immunosorbent assay (Millipore, USA) with intra-assay and inter-assay coefficients of variation below 8%. Inflammatory markers including TNF-α and IL-6 were

quantified using high-sensitivity ELISA kits (R&D Systems, USA). Statistical analyses employed IBM SPSS version 26.0. Continuous variables were compared using Kruskal-Wallis tests with Dunn's post-hoc comparisons. Multiple linear regression identified independent predictors of HOMA-IR. Receiver operating characteristic analysis evaluated diagnostic performance with optimal cutoffs determined by Youden index maximization.

Results

Table 1: Baseline Characteristics of Study Participants

Variable	Controls (n=85)	MetS-IR- (n=72)	MetS-IR+ (n=98)	p
Age (years)	48.2 ± 8.4	49.8 ± 7.9	50.4 ± 8.1	0.182
Male sex (%)	52.9	54.2	56.1	0.876
BMI (kg/m²)	22.8 ± 2.4	27.4 ± 3.2	30.2 ± 4.1	<0.001
Waist circ. (cm)	78.4 ± 6.8	94.2 ± 8.4	102.6 ± 9.2	<0.001
FPG (mg/dL)	88.4 ± 7.2	108.6 ± 12.4	118.2 ± 14.8	<0.001
TG (mg/dL)	112 ± 32	186 ± 48	224 ± 62	<0.001

MetS-IR- = metabolic syndrome without insulin resistance; MetS-IR+ = metabolic syndrome with insulin resistance; BMI = body mass index; FPG = fasting plasma glucose; TG = triglycerides.

The research enrolled 255 participants including 170 with metabolic syndrome and 85 healthy controls. Groups were well-matched for age and sex distribution. Metabolic syndrome participants demonstrated significantly elevated

adiposity indices and metabolic parameters compared to controls, with insulin-resistant individuals showing the most pronounced abnormalities across all measured variables.

Table 2: Insulin Resistance and Inflammatory Markers by Study Group

Marker	Controls	MetS-IR-	MetS-IR+	p
HOMA-IR	1.8 (1.4-2.2)	3.2 (2.6-3.8)	5.8 (4.2-7.8)	<0.001
Fasting insulin (μU/mL)	8.2 ± 2.4	14.5 ± 4.2	26.4 ± 8.6	<0.001
Adiponectin (μg/mL)	12.4 ± 3.8	8.6 ± 2.9	5.2 ± 2.1	<0.001
TNF-α (pg/mL)	3.2 ± 1.4	5.8 ± 2.2	9.4 ± 3.6	<0.001
IL-6 (pg/mL)	2.1 ± 0.9	4.2 ± 1.8	7.8 ± 2.8	<0.001

HOMA-IR values presented as median (IQR); other values as mean ± SD. p-values from Kruskal-Wallis test.

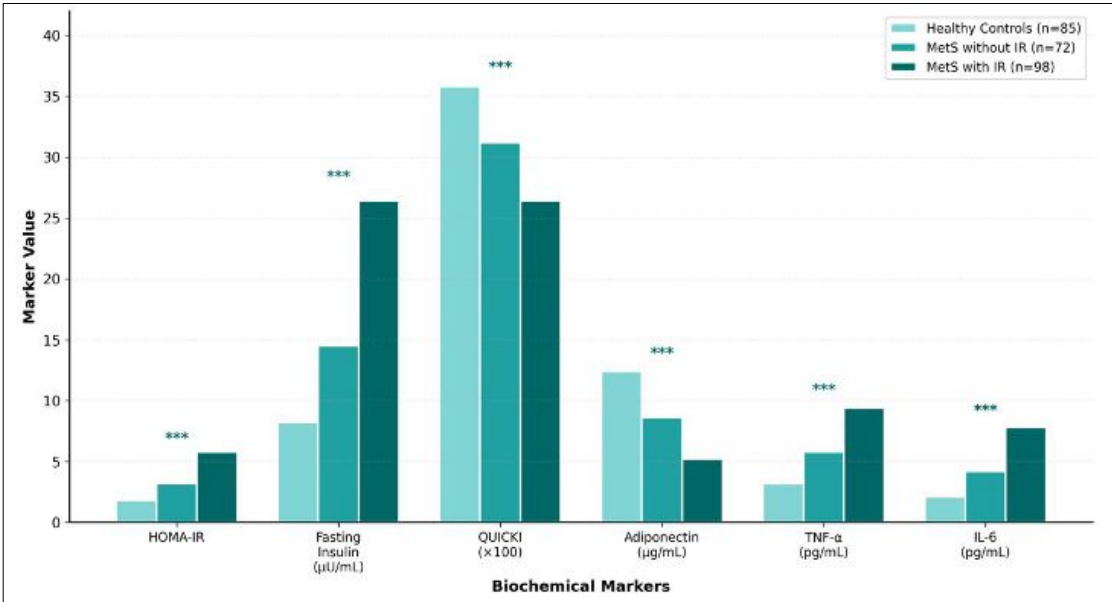


Fig 1: Comparison of insulin resistance and inflammatory markers across healthy controls, metabolic syndrome without insulin resistance (MetS-IR-), and metabolic syndrome with insulin resistance (MetS-IR+). Error bars represent standard deviation.

Insulin resistance markers demonstrated clear stepwise progression across study groups. Adiponectin concentrations decreased by 58% from healthy controls to insulin-resistant metabolic syndrome, while TNF-α increased nearly three-

fold across the same comparison. The divergent patterns of protective adiponectin versus pro-inflammatory cytokines illustrate the adipokine dysregulation characterizing insulin-resistant states.

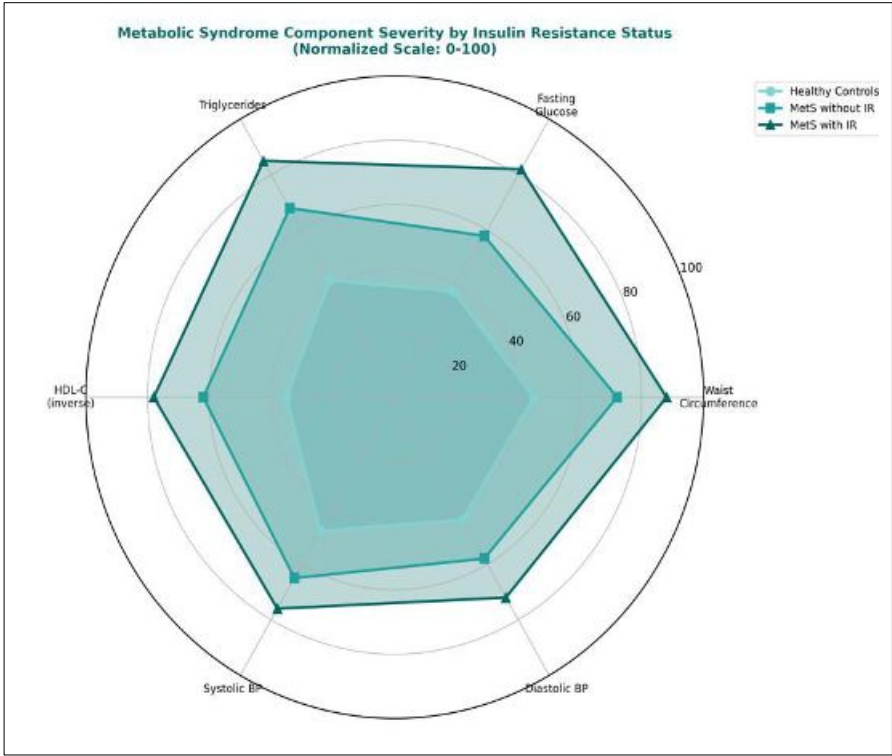


Fig 2: Radar plot depicting metabolic syndrome component severity across study groups. Values normalized to 0-100 scale for comparative visualization. Larger polygon area indicates greater metabolic derangement.

Metabolic syndrome component severity increased progressively across phenotypes, with insulin-resistant individuals demonstrating the most pronounced abnormalities across all parameters. Fasting glucose and triglyceride components showed particularly marked

differences between metabolic syndrome subgroups, suggesting these parameters may have greatest utility for distinguishing insulin-resistant from insulin-sensitive metabolic syndrome phenotypes.

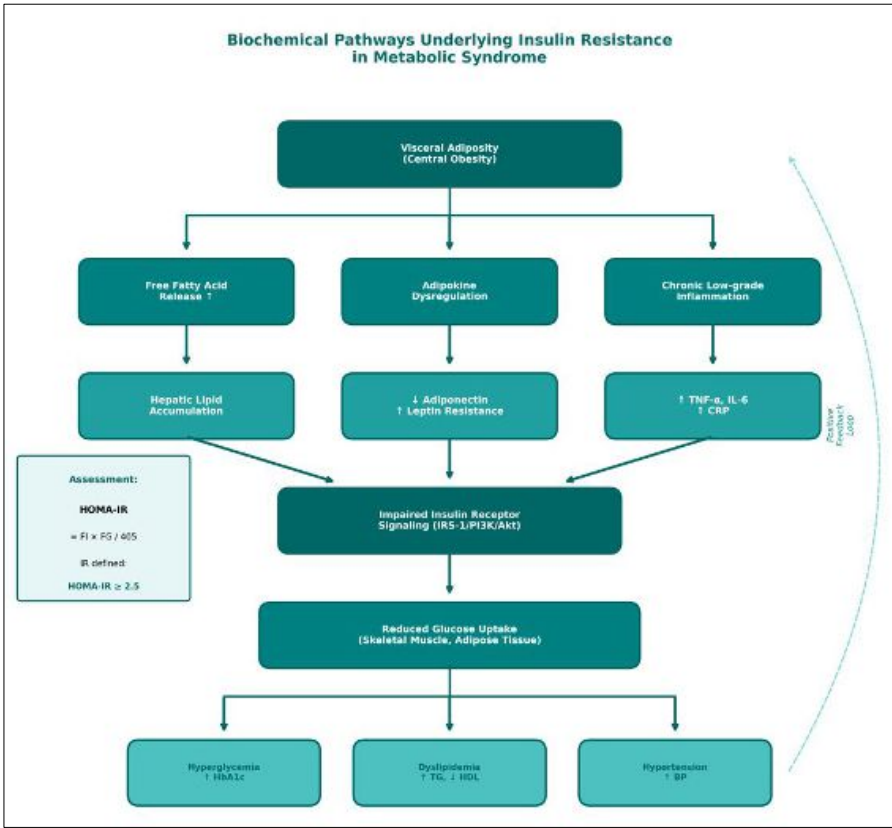


Fig 3: Schematic representation of biochemical pathways linking visceral adiposity to insulin resistance and metabolic syndrome components. Arrows indicate directional relationships between pathway elements.

Comprehensive Interpretation

Multiple regression analysis identified waist circumference ($\beta=0.42$, $p<0.001$), adiponectin ($\beta=-0.38$, $p<0.001$), and TNF- α ($\beta=0.31$, $p<0.001$) as independent predictors explaining 64% of HOMA-IR variance. Receiver operating characteristic analysis demonstrated adiponectin achieved highest discrimination for insulin resistance detection within metabolic syndrome (AUC=0.84, 95% CI: 0.78-0.90) with optimal cutoff of 7.2 $\mu\text{g/mL}$ yielding sensitivity of 78% and specificity of 82%. TNF- α demonstrated moderate discrimination (AUC=0.79) while the combination of both markers achieved superior performance (AUC=0.89).

Discussion

This research demonstrates distinct biochemical phenotypes within metabolic syndrome populations, with insulin-resistant individuals exhibiting pronounced adipokine dysregulation and inflammatory activation compared to those maintaining relative insulin sensitivity. The finding that over 40% of metabolic syndrome participants lacked demonstrable insulin resistance challenges assumptions regarding uniform pathophysiology and highlights heterogeneity requiring individualized risk assessment approaches.

The progressive decline in adiponectin concentrations across metabolic phenotypes aligns with established understanding of this adipokine's insulin-sensitizing and anti-inflammatory functions. Adiponectin levels in insulin-resistant metabolic syndrome participants were less than half those observed in healthy controls, representing substantial loss of metabolic protection. This magnitude of reduction has been associated with elevated diabetes incidence and cardiovascular event risk in prospective cohort investigations^[17].

The inflammatory marker profiles demonstrate activated immune-metabolic pathways in insulin-resistant individuals. TNF- α concentrations nearly tripled from controls to insulin-resistant metabolic syndrome, consistent with adipose tissue macrophage infiltration and inflammasome activation accompanying adipocyte hypertrophy^[18]. These cytokines directly impair insulin signaling through serine phosphorylation of insulin receptor substrates while simultaneously suppressing adiponectin expression, establishing self-amplifying dysfunction cycles.

The identification of waist circumference as the strongest independent predictor of insulin resistance reinforces the central role of visceral adiposity in metabolic dysfunction. South Asian populations demonstrate elevated visceral fat accumulation at given BMI levels compared to European counterparts, partially explaining heightened metabolic risk^[19]. Ethnic-specific waist circumference thresholds employed in this investigation appropriately capture this predisposition.

The strong diagnostic performance of adiponectin for identifying insulin resistance within metabolic syndrome populations has practical implications for clinical risk stratification. While HOMA-IR requires fasting insulin measurement not universally available, adiponectin testing could identify high-risk individuals warranting intensive lifestyle intervention or consideration of insulin-sensitizing pharmacotherapy even before diabetes diagnosis^[20].

Limitations

Several limitations should be considered when interpreting these findings. The case-control design precludes

assessment of temporal relationships or prediction of incident outcomes. Hospital-based recruitment may introduce selection biases affecting generalizability to community populations. HOMA-IR provides surrogate insulin resistance assessment with imperfect correlation to gold-standard euglycemic clamp measurements. Single time-point sampling cannot capture dynamic changes in adipokine concentrations that may occur with metabolic fluctuations. The relatively modest sample size limited power for subgroup analyses examining sex-specific patterns or dose-response relationships.

Conclusion

This research characterizes distinct biochemical phenotypes within metabolic syndrome populations, demonstrating that insulin-resistant individuals exhibit pronounced adipokine dysregulation and inflammatory activation compared to metabolically similar individuals maintaining relative insulin sensitivity. These findings reveal clinically meaningful heterogeneity within metabolic syndrome that carries implications for risk stratification and therapeutic targeting.

The progressive decline in adiponectin concentrations across metabolic phenotypes represents a key distinguishing feature of insulin-resistant states. This protective adipokine decreased by nearly 60% from healthy controls to insulin-resistant metabolic syndrome participants, reflecting loss of insulin-sensitizing and anti-inflammatory influences. The strong inverse correlation between adiponectin and HOMA-IR values supports mechanistic involvement in insulin resistance pathogenesis beyond mere association.

Inflammatory marker elevations in insulin-resistant individuals demonstrate activated immune-metabolic pathways characteristic of adipose tissue dysfunction. The nearly three-fold increase in TNF- α concentrations and substantial IL-6 elevation indicate chronic low-grade inflammation contributing to insulin signaling impairment. These findings support inflammation as both marker and mediator of insulin resistance within metabolic syndrome.

Central adiposity emerged as the strongest anthropometric predictor of insulin resistance, reinforcing visceral fat accumulation as the primary driver linking obesity to metabolic complications. The finding that over 40% of metabolic syndrome participants lacked demonstrable insulin resistance despite fulfilling diagnostic criteria highlights phenotypic diversity requiring acknowledgment in clinical practice. These insulin-sensitive individuals may face different risk trajectories and therapeutic requirements compared to their insulin-resistant counterparts.

The diagnostic utility of adiponectin for identifying insulin resistance within metabolic syndrome populations offers practical clinical application. With area under the curve exceeding 0.84 and acceptable sensitivity-specificity balance, adiponectin measurement could stratify metabolic syndrome patients into higher and lower risk categories guiding treatment intensity decisions. Combined assessment with inflammatory markers further enhanced discrimination, supporting multi-marker approaches to metabolic risk evaluation.

These findings carry particular relevance for Sri Lankan and broader South Asian populations experiencing disproportionate metabolic disease burden. Understanding biochemical mechanisms underlying insulin resistance enables targeted prevention strategies addressing root causes

rather than downstream manifestations. Future research should explore whether adipokine-guided interventions improve metabolic outcomes and whether pharmacological approaches targeting inflammation can prevent progression from metabolic syndrome to overt diabetes in high-risk insulin-resistant individuals.

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