

BIOMARKERS IN OBESITY-RELATED METABOLIC SYNDROME: FROM PATHOPHYSIOLOGY TO CLINICAL APPLICATION

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Abstract

Obesity-related metabolic syndrome (MetS) represents a complex, multifactorial disorder characterized by central obesity, insulin resistance, dyslipidemia, hypertension, and chronic low-grade inflammation. Its rising global prevalence underscores the urgent need for comprehensive understanding and early detection strategies. While traditional clinical and biochemical parameters provide insight into overt metabolic dysfunction, they often fail to capture upstream molecular disturbances.

Recent research has identified a spectrum of novel biomarkers that reflect the pathophysiological mechanisms underlying MetS, including inflammatory mediators (high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor- α , monocyte chemoattractant protein-1, plasminogen activator inhibitor-1), adipokines and hormonal regulators (adiponectin, leptin, resistin, visfatin, ghrelin, glucagon-like peptide-1), oxidative stress and endothelial dysfunction markers (malondialdehyde, 8-isoprostane, oxidized LDL, asymmetric dimethylarginine, paraoxonase-1), thyroid function indicators (TSH, free thyroxine, anti-thyroid peroxidase antibodies), vitamin D, and genetic/epigenetic modulators (microRNAs and DNA methylation patterns).

This review summarizes current evidence on these biomarkers, highlighting their roles in elucidating disease mechanisms, enabling early risk assessment, guiding therapeutic interventions, and supporting precision medicine approaches. Future research directions are proposed to standardize assays, validate findings across diverse populations, and develop integrated multi-marker panels to optimize the management of obesity-related MetS.

keywords: obesity, metabolic syndrome, adipokines, inflammation, insulin resistance

Introduction

Obesity is a multifactorial chronic disease and a major driver of metabolic syndrome (MetS), which significantly contributes to global morbidity and mortality through its close association with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), and certain malignancies [1].

The worldwide prevalence of obesity has tripled over the past four decades, and current estimates suggest that more than one-fourth of the adult population meets the diagnostic criteria for MetS. This escalating trend underscores the urgent need for a deeper understanding of the molecular mechanisms linking excessive adiposity to metabolic and cardiovascular complications. Visceral adipose tissue, once considered a passive fat-storage depot, is now recognized as a highly active endocrine and paracrine organ. It secretes a wide spectrum of bioactive molecules, including adipokines, cytokines, chemokines, and hormones, which play essential roles in regulating energy balance, glucose and lipid metabolism, appetite control, and vascular homeostasis. Under physiological conditions, these mediators maintain metabolic equilibrium [2, 3].

However, in obesity, the excessive expansion of adipose tissue, particularly the visceral compartment, leads to adipocyte hypertrophy, hypoxia, macrophage infiltration, and dysregulated secretion of inflammatory and metabolic factors. This state of chronic, low-grade inflammation, termed metaflammation, represents a key pathogenic link between obesity, insulin resistance, and endothelial dysfunction [4].

The interplay between adipose tissue inflammation and systemic metabolic alterations creates a vicious cycle that contributes to insulin resistance, oxidative stress, lipotoxicity, and atherogenesis. Pro-

inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) stimulate hepatic production of high-sensitivity C-reactive protein (hs-CRP), while dysregulated adipokines such as leptin, adiponectin, resistin, and visfatin modulate glucose uptake and lipid oxidation [5].

Simultaneously, hormonal pathways involving ghrelin, glucagon-like peptide-1 (GLP-1), and thyroid hormones further influence appetite regulation, thermogenesis, and energy expenditure. Together, these alterations form the biochemical and molecular substrate of MetS. Despite extensive research, traditional clinical and biochemical parameters, including waist circumference, fasting plasma glucose, triglycerides, HDL cholesterol, and blood pressure, provide only a limited snapshot of this complex metabolic landscape. These parameters capture downstream manifestations of metabolic dysfunction rather than the upstream molecular disturbances that precede overt disease [6].

As a result, early identification of individuals at risk for MetS or its complications remains challenging. Recent advances in molecular biology and clinical biochemistry have led to the identification of a range of novel biomarkers that more accurately reflect the underlying pathophysiological processes. These include inflammatory mediators (hs-CRP, IL-6, TNF- α), metabolic and hormonal regulators (ghrelin, visfatin, GLP-1, resistin), thyroid function indicators (TSH, free thyroxine FT4), and anti-thyroid peroxidase antibodies (anti-TPO), and vitamin D as a metabolic modulator [7, 8, 9].

Collectively, these biomarkers provide insight into the continuum from subclinical metabolic dysregulation to manifest disease and have potential utility for early detection, prognosis, and therapeutic monitoring. Future research directions are proposed to standardize assays, validate findings across diverse populations, and develop integrated multi-marker panels to optimize the management of obesity-related MetS. Therefore, elucidating the clinical relevance and interconnections of these emerging biomarkers represents a major step toward precision medicine in obesity-related metabolic syndrome. Their integration into diagnostic and prognostic algorithms could enhance risk stratification, enable individualized interventions, and ultimately improve patient outcomes.

This review summarizes current evidence on these biomarkers, highlighting their roles in elucidating disease mechanisms, enabling early risk assessment, guiding therapeutic interventions, and supporting precision medicine approaches.

Pathophysiological Background

The metabolic derangements underlying metabolic syndrome (MetS) arise from a complex interplay between adipose tissue dysfunction, insulin resistance, and systemic inflammation. Central to this process is the expansion and remodeling of adipose tissue in response to chronic energy surplus. As adipocytes enlarge (hypertrophy) and proliferate (hyperplasia), their capacity for lipid storage becomes dysregulated, leading to increased lipolysis and the release of excess free fatty acids (FFAs) into the circulation. These FFAs accumulate ectopically in the liver, skeletal muscle, and pancreas, triggering lipotoxicity, mitochondrial overload, and insulin signaling impairment [10, 11].

The dysfunctional adipose tissue microenvironment is characterized by hypoxia, oxidative stress, and immune cell infiltration, particularly of macrophages and T lymphocytes. Activated macrophages within adipose tissue shift from an anti-inflammatory (M2) to a pro-inflammatory (M1) phenotype, releasing cytokines such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). These mediators amplify local and systemic inflammation, further impairing insulin receptor signaling via serine phosphorylation of insulin receptor substrate-1 (IRS-1) and downregulation of glucose transporter type 4 (GLUT4). The resulting insulin resistance disrupts glucose uptake and enhances hepatic gluconeogenesis, perpetuating hyperglycemia and hyperinsulinemia [12, 13].

At the same time, oxidative stress plays a pivotal role in the pathogenesis of MetS. Mitochondrial dysfunction in obese states enhances the production of reactive oxygen species (ROS), leading to lipid peroxidation, protein oxidation, and endothelial damage. Oxidative stress also stimulates nuclear factor kappa B (NF- κ B) and c-Jun N-terminal kinase (JNK) pathways, further promoting inflammatory cytokine production and apoptotic signaling [14].

The adipokine profile is markedly altered in obesity: adiponectin, a protective adipokine with anti-inflammatory and insulin-sensitizing effects, is suppressed, while leptin, resistin, and visfatin are elevated, contributing to metabolic imbalance. Excess leptin induces central leptin resistance, undermining appetite control and energy expenditure, while resistin links adipose inflammation to systemic insulin resistance. In parallel, the dysregulation of gut-derived hormones such as ghrelin and glucagon-like peptide-1 (GLP-1) affects appetite regulation, satiety signaling, and glucose homeostasis. The convergence of these metabolic and inflammatory insults extends to the vascular endothelium, where insulin resistance and oxidative stress reduce nitric oxide (NO) bioavailability, impair vasodilation, and promote endothelial dysfunction, a hallmark of cardiovascular risk in MetS [15].

Viewed integratively, these interrelated mechanisms of lipotoxicity, metaflammation, oxidative stress, and hormonal imbalance create a biochemical milieu conducive to the development of diabetes, atherosclerosis, and other metabolic complications. Understanding these molecular pathways has enabled the identification of novel circulating biomarkers that reflect specific aspects of adipose dysfunction, inflammation, oxidative injury, and endocrine dysregulation. Their characterization offers new avenues for early metabolic risk assessment, patient stratification, and targeted therapeutic intervention in obesity-related metabolic syndrome.

Novel Biomarkers in Obesity-Related Metabolic Syndrome

Inflammatory Biomarkers

Chronic low-grade inflammation, often termed metaflammation, is a defining feature of metabolic syndrome (MetS) and represents a key link between obesity, insulin resistance, and cardiovascular complications. Adipose tissue in obese individuals functions as an immunoreactive organ, producing pro-inflammatory cytokines and acute-phase reactants that exert systemic effects. Several circulating inflammatory biomarkers have emerged as clinically relevant indicators of metabolic dysfunction and cardiometabolic risk [16].

High-sensitivity C-reactive protein (hs-CRP)

Synthesized in the liver under stimulation by interleukin-6 (IL-6) and other cytokines, hs-CRP is a robust and sensitive marker of systemic inflammation. Elevated hs-CRP levels are consistently associated with central obesity, insulin resistance, and atherosclerotic risk. Numerous studies have demonstrated that hs-CRP concentrations correlate positively with waist circumference, fasting insulin, and triglycerides, and inversely with HDL cholesterol and adiponectin levels. Importantly, weight reduction achieved through dietary modification, physical activity, or bariatric surgery leads to a significant decline in hs-CRP, underscoring its value as a dynamic marker of inflammation and therapeutic response. From a clinical perspective, hs-CRP levels above 3 mg/L indicate high cardiovascular risk, while levels below 1 mg/L are considered protective. Despite its nonspecificity, hs-CRP remains one of the most practical inflammatory biomarkers in assessing overall metabolic and vascular inflammation in obese individuals [17].

Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine secreted by adipocytes, macrophages, and skeletal muscle. In obesity, its chronic elevation perpetuates hepatic CRP production and interferes with insulin receptor signaling, contributing to insulin resistance. IL-6 also stimulates hepatic glucose output and lipolysis, promoting dyslipidemia and hepatic steatosis.

Circulating IL-6 concentrations correlate with visceral adiposity and metabolic severity, and decrease following weight loss or anti-inflammatory interventions. Interestingly, acute exercise transiently increases IL-6 in a beneficial, anti-inflammatory context, suggesting context-dependent dual roles of this cytokine in metabolic regulation [18].

Tumor necrosis factor-alpha (TNF- α)

TNF- α , produced primarily by adipose tissue macrophages, represents one of the earliest identified mediators linking obesity and insulin resistance. It disrupts insulin signaling through serine phosphorylation of insulin receptor substrate-1 (IRS-1), reducing glucose uptake in peripheral tissues.

Moreover, TNF- α enhances lipolysis, increases free fatty acid flux, and stimulates endothelial adhesion molecule expression, thus promoting vascular inflammation and atherogenesis. Elevated TNF- α levels in obesity typically decline following significant weight reduction, insulin sensitizer therapy (e.g., metformin, thiazolidinediones), or bariatric surgery, positioning it as both a pathogenic mediator and a potential therapeutic target in MetS [19].

Monocyte chemoattractant protein-1 (MCP-1)

MCP-1 plays a critical role in recruiting monocytes into adipose tissue, driving macrophage accumulation and polarization toward the pro-inflammatory M1 phenotype. This enhances local cytokine release and systemic inflammation, aggravating insulin resistance. Circulating MCP-1 levels correlate with body mass index (BMI), insulin resistance indices, and carotid intima-media thickness, implicating it in the early stages of vascular dysfunction in obese patients [20].

Plasminogen activator inhibitor-1 (PAI-1)

PAI-1 links inflammation, thrombosis, and metabolic dysregulation. Elevated PAI-1 levels in MetS contribute to impaired fibrinolysis and a prothrombotic state, increasing cardiovascular risk. Adipose tissue, particularly visceral fat, serves as a major source of PAI-1, and its levels parallel insulin resistance and hypertriglyceridemia. Reduction in PAI-1 concentrations after weight loss or improved glycemic control further highlights its prognostic value in assessing metabolic and vascular health. Collectively, these inflammatory biomarkers reflect the interconnected nature of immune and metabolic signaling in obesity-related MetS. They not only serve as measurable indicators of disease activity but also represent potential therapeutic targets for anti-inflammatory and insulin-sensitizing interventions [21].

Adipokines and Hormonal Biomarkers

Adipokines, peptide hormones secreted predominantly by adipose tissue, play a pivotal role in linking energy metabolism, inflammation, and insulin sensitivity. Dysregulated adipokine secretion is one of the earliest biochemical disturbances in obesity and underlies the development of insulin resistance and endothelial dysfunction that define metabolic syndrome (MetS). Alongside adipokines, several gut- and pancreas-derived hormones are involved in the metabolic cross-talk between adipose tissue, liver, muscle, and the central nervous system [22].

Adiponectin

Adiponectin is the most abundant adipokine with potent insulin-sensitizing, anti-inflammatory, and anti-atherogenic effects. It enhances fatty acid oxidation and glucose uptake through activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- α (PPAR- α) pathways. Low circulating adiponectin levels are a hallmark of visceral obesity and are inversely associated with insulin resistance, dyslipidemia, and cardiovascular risk. Increasing adiponectin concentration through lifestyle modification or pharmacologic means (e.g., thiazolidinediones) has been associated with improved metabolic profiles [23].

Leptin

Leptin, produced proportionally to adipose mass, regulates appetite and energy expenditure via hypothalamic signaling. In obesity, chronic hyperleptinemia reflects a state of leptin resistance, in which central satiety signaling is blunted despite elevated circulating leptin levels. This phenomenon promotes persistent hyperphagia, weight gain, and sympathetic overactivity, contributing to hypertension and endothelial dysfunction [24].

Resistin

Originally described as an adipocyte-derived factor linking obesity and diabetes, resistin is now recognized as being predominantly secreted by macrophages in humans. It exerts pro-inflammatory actions by upregulating tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), impairing insulin signaling, and promoting vascular smooth muscle proliferation. Elevated resistin levels are associated with increased risk of atherosclerosis, coronary artery disease, and insulin resistance [25].

Visfatin (NAMPT)

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT), functions both as an enzyme in nicotinamide adenine dinucleotide (NAD⁺) biosynthesis and as a pro-inflammatory adipokine. It exhibits insulin-mimetic activity and enhances glucose uptake in adipocytes, but its chronic elevation in obesity and type 2 diabetes mellitus (T2DM) is linked to systemic inflammation and endothelial dysfunction. The dual metabolic and inflammatory roles of visfatin make it a promising, though controversial, biomarker for metabolic stress [26].

Ghrelin

Ghrelin, a peptide hormone secreted mainly by gastric endocrine cells, stimulates appetite and promotes adiposity through hypothalamic neuropeptide Y (NPY) pathways. Paradoxically, circulating ghrelin levels are reduced in obesity, possibly reflecting a compensatory downregulation of hunger signaling. After bariatric surgery, particularly sleeve gastrectomy, ghrelin concentrations decline sharply, which contributes to postoperative appetite suppression and metabolic improvement [27].

Glucagon-like peptide-1 (GLP-1)

GLP-1 is an incretin hormone secreted by intestinal L cells in response to nutrient ingestion. It enhances glucose-dependent insulin secretion, inhibits glucagon release, slows gastric emptying, and promotes satiety. Impaired GLP-1 secretion or action is frequently observed in states of obesity and insulin resistance. Pharmacologic GLP-1 receptor agonists (e.g., liraglutide, semaglutide) have demonstrated profound metabolic and cardiovascular benefits, positioning GLP-1 as both a therapeutic target and a functional biomarker of metabolic health. When considered together, these adipokines and hormonal mediators form an intricate regulatory network that influences energy balance, insulin sensitivity, and vascular function. Measuring their circulating levels may help identify subclinical metabolic dysfunction and stratify cardiometabolic risk beyond traditional criteria [28, 29].

Oxidative Stress and Endothelial Dysfunction Biomarkers

Oxidative stress is a critical mediator in the pathogenesis of metabolic syndrome (MetS), linking adipose tissue dysfunction, insulin resistance, and vascular injury. Excess nutrient flux and mitochondrial overload in obesity lead to the overproduction of reactive oxygen species (ROS), which damage lipids, proteins, and DNA. Persistent oxidative stress contributes to endothelial dysfunction, promotes atherogenesis, and exacerbates metabolic dysregulation [30]. Several circulating biomarkers have emerged as indicators of oxidative damage and endothelial impairment:

Malondialdehyde (MDA) and 8-isoprostane

Both are well-established markers of lipid peroxidation, reflecting oxidative injury to cellular membranes. Elevated levels are correlated with visceral adiposity, insulin resistance, and increased cardiovascular risk in obese individuals [31].

Asymmetric dimethylarginine (ADMA) and nitrotyrosine

These biomarkers indicate endothelial nitric oxide (NO) pathway impairment. ADMA is an endogenous inhibitor of nitric oxide synthase, reducing NO bioavailability, while nitrotyrosine reflects peroxynitrite-mediated protein nitration. Elevated concentrations are linked to endothelial dysfunction, hypertension, and increased atherothrombotic risk in MetS [32].

Oxidized low-density lipoprotein (oxLDL)

OxLDL is both a marker and a mediator of atherosclerosis. It promotes vascular inflammation, foam cell formation, and plaque instability, while its circulating levels mirror systemic oxidative burden and cardiovascular risk in obesity-related MetS [33].

Paraoxonase-1 (PON1)

PON1 is an HDL-associated enzyme with antioxidant properties that protect lipids from oxidative modification. In obesity and insulin-resistant states, PON1 activity is reduced, linking oxidative stress with dyslipidemia and endothelial dysfunction. Restoration of PON1 activity through lifestyle or pharmacological interventions may provide cardiovascular protection. Collectively, these biomarkers

provide insight into the redox and vascular disturbances in obesity and MetS and can serve as early indicators of cardiometabolic risk [34].

Thyroid Function Biomarkers

Thyroid hormones are central regulators of energy homeostasis, basal metabolic rate, and lipid/glucose metabolism. Alterations in thyroid function are common in obesity and can both contribute to and result from metabolic dysregulation. Key biomarkers include:

Thyroid-stimulating hormone (TSH)

Mild elevations in TSH with normal free thyroxine (FT4) levels, known as subclinical hypothyroidism, are frequently observed in obese individuals. This may represent an adaptive response to increased energy demands or adiposity-related endocrine alterations. Weight reduction and improved metabolic health typically normalize TSH levels.

Free thyroxine (FT4)

FT4 levels may vary in relation to energy balance, metabolic rate, and body composition. Altered FT4 can influence basal metabolic rate, lipolysis, and thermogenesis, linking thyroid function directly to metabolic homeostasis [35, 36].

Anti-thyroid peroxidase antibodies (anti-TPO)

Anti-TPO antibodies indicate autoimmune thyroid inflammation and are more prevalent in obese populations. Autoimmune thyroiditis may exacerbate insulin resistance, dyslipidemia, and systemic inflammation, further compounding metabolic derangements. Monitoring anti-TPO can therefore provide insight into thyroid-related contributions to MetS. The integrated assessment of thyroid hormones and autoantibodies, alongside adipokines and inflammatory markers, allows a more comprehensive understanding of endocrine-metabolic interactions in obesity-related MetS and may guide targeted interventions [37].

Vitamin D as a Metabolic Modulator

Vitamin D deficiency is highly prevalent among individuals with obesity, primarily due to sequestration of 25-hydroxyvitamin D (25(OH)D) in adipose tissue and reduced exposure to sunlight. Low serum vitamin D levels have been consistently associated with insulin resistance, dyslipidemia, chronic low-grade inflammation, and increased cardiometabolic risk. Mechanistically, vitamin D exerts anti-inflammatory and insulin-sensitizing effects by modulating cytokine production, enhancing insulin receptor expression, and improving pancreatic β -cell function. Supplementation of vitamin D in deficient individuals has been shown to modestly improve glycemic control, lipid profiles, and inflammatory markers, although the magnitude of benefit may vary depending on baseline metabolic status and dosing strategies. Beyond its role as a nutrient, vitamin D can be considered both a biomarker of metabolic health and a modifiable factor in obesity-related metabolic syndrome (MetS). Its measurement provides insight into endocrine-metabolic interactions and may inform personalized supplementation strategies aimed at mitigating metabolic derangements [38, 39].

Genetic and Epigenetic Biomarkers

Advances in molecular biology have highlighted microRNAs (miRNAs) and epigenetic modifications as early indicators of metabolic dysregulation, offering a molecular fingerprint of obesity-related MetS.

MicroRNAs (miRNAs)

Circulating miRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally and influence multiple metabolic pathways.

miR-122 and miR-34a are closely linked to hepatic steatosis, dyslipidemia, and insulin resistance. Elevated levels reflect liver metabolic stress and may predict progression toward non-alcoholic fatty liver disease (NAFLD) and T2DM.

miR-146a and miR-155 modulate adipose tissue inflammation, influencing macrophage polarization, cytokine production, and systemic insulin sensitivity. Their dysregulation mirrors the inflammatory component of MetS and may serve as therapeutic targets or monitoring tools [40].

Epigenetic Modification

Epigenetic changes, including DNA methylation, histone modifications, and chromatin remodeling, influence the expression of genes regulating lipid and glucose metabolism. For example, methylation of promoters of genes involved in insulin signaling, adipogenesis, and lipid transport can occur in response to environmental exposures, diet, or obesity itself. Such modifications may serve as early predictors of MetS susceptibility, inform risk stratification, and indicate potential responsiveness to lifestyle or pharmacologic interventions. Genetic and epigenetic biomarkers provide a high-resolution molecular perspective of metabolic dysfunction. They offer the potential for precision medicine approaches, enabling individualized risk assessment, early detection of subclinical metabolic derangements, and tailored therapeutic strategies [41].

In Table 1 are summarized the novel biomarkers in obesity-related metabolic syndrome (MetS).

Table 1. Summary of novel biomarkers in obesity-related metabolic syndrome (MetS)

| Biomarker | Primary Source / Origin | Pathophysiological Role | Clinical Significance in Obesity-related MetS |
|--------------------------------|--|---|---|
| Inflammatory biomarkers | | | |
| hs-CRP | Liver (stimulated by IL-6, TNF- α) | Acute-phase reactant; reflects systemic low-grade inflammation and vascular injury. | Correlates with central obesity, insulin resistance, and CVD risk; declines with weight loss or anti-inflammatory therapy |
| IL-6 | Adipocytes, macrophages, skeletal muscle | Promotes hepatic CRP synthesis, impairs insulin signaling, and increases hepatic glucose output | A marker of visceral adiposity and insulin resistance; it decreases after lifestyle or surgical weight reduction |
| TNF- α | Adipose tissue macrophages | Inhibits insulin receptor signaling (IRS-1 phosphorylation), enhances lipolysis, and endothelial activation | Links obesity to insulin resistance and endothelial dysfunction, a therapeutic target for anti-inflammatory interventions |
| MCP-1 | Adipocytes, endothelial cells | Recruits monocytes/macrophages into adipose tissue; amplifies local inflammation | Correlates with BMI, HOMA-IR, and early vascular dysfunction |
| PAI-1 | Visceral adipose tissue, liver | Inhibits fibrinolysis; promotes thrombosis and inflammation | Elevated in MetS; reflects prothrombotic risk and improves with weight loss |

| Biomarker | Primary Source / Origin | Pathophysiological Role | Clinical Significance in Obesity-related MetS |
|--|--|--|--|
| Adipokines and hormonal biomarkers | | | |
| Adiponectin | Adipocytes (mainly subcutaneous) | Activates AMPK and PPAR- α \rightarrow \uparrow fatty-acid oxidation, \uparrow glucose uptake | Low in visceral obesity; inversely related to insulin resistance and CVD risk |
| Leptin | Adipocytes (proportional to fat mass) | Regulates appetite and energy expenditure via hypothalamic signaling | Hyperleptinemia with leptin resistance indicates impaired satiety and sympathetic overactivity |
| Resistin | Macrophages, adipose tissue | Promotes TNF- α and IL-6 release; induces insulin resistance | Associated with atherosclerosis and inflammatory insulin resistance |
| Visfatin (NAMPT) | Visceral adipose tissue, liver | Enzyme in NAD ⁺ biosynthesis; insulin-mimetic and pro-inflammatory actions | Elevated in obesity and T2DM, a marker of metabolic and vascular stress |
| Ghrelin | Gastric endocrine (X/A-like) cells | Stimulates appetite (NPY/AgRP neurons); affects GH release and glucose metabolism | Paradoxically reduced in obesity; a sharp postoperative decline after sleeve gastrectomy contributes to weight loss. |
| GLP-1 | Intestinal L-cells | Incretin: enhances insulin secretion, inhibits glucagon, and delays gastric emptying. | Impaired secretion in obesity; GLP-1R agonists improve glycemia and CVD outcomes |
| Oxidative stress / endothelial dysfunction biomarkers | | | |
| Malondialdehyde (MDA) | Product of lipid peroxidation | Reflects oxidative damage to membranes and lipoproteins | Elevated in obesity and insulin resistance, a marker of systemic oxidative stress |
| 8-isoprostane | Oxidized arachidonic acid (cell membranes) | Stable indicator of lipid peroxidation and oxidative burden | Correlates with visceral fat and CVD risk |
| ADMA | Endogenous metabolite (arginine methylation) | Competitive inhibitor of nitric-oxide synthase \rightarrow \downarrow NO bioavailability | A marker of endothelial dysfunction, hypertension, and atherogenesis |
| Nitrotyrosine | Circulating nitrated proteins | Indicates peroxynitrite-mediated oxidative protein injury | Reflects endothelial oxidative stress and vascular inflammation |

| Biomarker | Primary Source / Origin | Pathophysiological Role | Clinical Significance in Obesity-related MetS |
|---------------------------------------|---|--|--|
| Oxidized LDL (oxLDL) | Modified LDL particles | Promotes foam-cell formation and atherosclerosis | Surrogate of atherogenic oxidative burden elevated in MetS |
| Paraoxonase-1 (PON1) | HDL-associated enzyme (liver-derived) | Antioxidant; hydrolyzes lipid peroxides and protects LDL/HDL | Reduced activity in obesity and insulin resistance; restoration improves vascular protection |
| Thyroid-related biomarkers | | | |
| TSH | Pituitary | Stimulates thyroid hormone production; elevated in subclinical hypothyroidism | Mildly increased in obesity, normalizes with weight loss, and reflects an adaptive metabolic response. |
| FT4 | Thyroid gland | Regulates basal metabolism, thermogenesis, and lipid/carbohydrate turnover | Altered levels influence energy expenditure and fat oxidation |
| Anti-TPO antibodies | Autoimmune lymphocytes | Indicate autoimmune thyroiditis and chronic inflammation | More prevalent in obese individuals; associated with dyslipidemia and insulin resistance |
| Vitamin D | Skin synthesis, diet (stored in adipose tissue) | Modulates cytokine production, enhances insulin sensitivity, and β -cell function. | Deficiency linked to obesity, inflammation, and insulin resistance; supplementation improves metabolic profile |
| Genetic/epigenetic biomarkers | | | |
| miR-122, miR-34a | Liver-derived circulating miRNAs | Regulate lipid metabolism and insulin signaling; elevated in NAFLD | Predict hepatic steatosis and MetS progression |
| miR-146a, miR-155 | Adipose tissue macrophages | Control inflammatory signaling (NF- κ B pathway) and insulin sensitivity | Reflect metaflammation and insulin resistance severity |
| DNA methylation/histone modifications | Various metabolic tissues | Epigenetic silencing or activation of metabolic genes | Early predictor of MetS susceptibility; potential target for personalized interventions |

Clinical Applications of Novel Biomarkers

The integration of novel biomarkers in clinical practice provides a multidimensional approach to the assessment, monitoring, and management of obesity-related metabolic syndrome (MetS). By reflecting distinct pathogenic processes ranging from inflammation and adipokine dysregulation to oxidative stress and endocrine alterations, these biomarkers enable more precise evaluation of metabolic risk than traditional clinical parameters alone.

Early Detection

Combined assessment of inflammatory markers (hs-CRP, IL-6, TNF- α), adipokines (adiponectin, leptin, resistin, visfatin), and hormonal mediators (ghrelin, GLP-1, thyroid hormones, vitamin D) can identify subclinical metabolic dysfunction before overt hyperglycemia, dyslipidemia, or hypertension develops. Early recognition allows timely lifestyle or pharmacologic interventions to prevent progression to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).

Risk Stratification

Inclusion of hs-CRP, adiponectin, oxidized LDL (oxLDL), and PAI-1 in predictive models enhances cardiovascular risk assessment beyond conventional lipid profiles. These biomarkers provide insight into systemic inflammation, endothelial dysfunction, and atherogenic burden, facilitating identification of high-risk individuals who may benefit from intensive monitoring or early therapeutic interventions.

Therapeutic Monitoring

Dynamic changes in biomarkers such as ghrelin, GLP-1, visfatin, leptin, and inflammatory cytokines following lifestyle modification, pharmacotherapy, or bariatric surgery reflect metabolic reprogramming and improved insulin sensitivity. For example, reductions in hs-CRP, IL-6, and TNF- α indicate decreased systemic inflammation, while increased adiponectin and normalized ghrelin levels signal improved adipose tissue function and appetite regulation. Monitoring these changes can guide treatment efficacy and personalized adjustment of interventions.

Precision Medicine

Multi-marker panels, coupled with omics-based profiling (genomics, epigenomics, transcriptomics, metabolomics), offer the potential to tailor interventions according to an individual's molecular signature. Machine learning algorithms integrating biomarker and clinical data may allow predictive modeling for MetS progression, individualized risk assessment, and optimized therapeutic strategies.

Future Perspectives

Despite promising evidence, the translation of novel biomarkers into routine clinical practice remains limited.

Key challenges include:

- Methodological variability and differences in assay standardization complicate inter-study comparisons.
- Lack of universally accepted cut-off values for many novel biomarkers.
- Insufficient longitudinal validation to establish predictive utility across diverse populations and age groups.

Future research priorities should include:

- Large-scale, multi-ethnic cohort studies to validate biomarkers and define reference ranges.
- Integration of biochemical, genetic, and epigenetic markers with clinical variables using machine learning and systems biology approaches.
- Development of multi-marker panels that capture the multifactorial nature of MetS for early detection, personalized therapy, and real-time monitoring of disease progression.

Combining traditional and novel biomarkers offers the potential to shift from reactive to proactive management, enabling the early identification of individuals at risk and the implementation of personalized preventive strategies.

Conclusion

Obesity-related metabolic syndrome is a complex, multifactorial disorder driven by the interplay of inflammation, oxidative stress, adipokine imbalance, hormonal dysregulation, and nutrient-related deficiencies such as vitamin D.

Novel biomarkers reflecting these pathophysiological processes provide critical insights into disease mechanisms, enhance diagnostic precision, and support personalized therapeutic strategies. Their integration into clinical practice holds promise for early detection of metabolic disturbances, improved risk stratification, and monitoring of therapeutic response, laying the groundwork for precision medicine in obesity and MetS management.

Continued research, standardization of assays, and longitudinal validation are essential to fully realize the potential of these biomarkers and translate scientific advances into improved patient outcomes.

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