Research Article ISSN 2641-4333

Neurology - Research & Surgery

Metabolic Syndrome as a Multisystem Network Disorder: Therapeutic Potential of Regenerative Peptide Biology

Mike KS Chan[1,2,3], Krista Casazza[4], Michelle BF Wong[3], Dmytro Klokol[3] and Jonathan RT Lakey[2,4]*

[1]*European Wellness Academy, Klosterstrasse 205ID, 67480, Edenkoben, Germany.*

[2]*European Wellness BioMedical Group, Klosterstrasse 205ID, 67480, Edenkoben, Germany.*

[3]*Lincoln University College, Petaling Jaya, Selangor, Malaysia.*

[4]*University of California Irvine, Department of Surgery and Biomedical Engineering, Irvine CA, USA.*

***Correspondence:**
Jonathan RT Lakey, PhD, MSM, Professor Emeritus, Departments of Surgery and Biomedical Engineering, University of California Irvine, USA, Tel: 714 851 8856.

Received: 15 Dec 2025; **Accepted:** 27 Jan 2026; **Published:** 07 Feb 2026

Citation: Mike KS Chan, Krista Casazza, Michelle BF Wong, et al. Metabolic Syndrome as a Multisystem Network Disorder: Therapeutic Potential of Regenerative Peptide Biology. Neurol Res Surg. 2026; 9(1): 1-6.

ABSTRACT

Metabolic syndrome is increasingly recognized as a systems-level disorder arising from the coordinated breakdown of peptide-governed metabolic networks that regulate mitochondrial bioenergetics, endocrine signaling, inflammatory tone, and inter-organ communication. Beyond the conventional cluster of central adiposity, insulin resistance, dyslipidemia, and hypertension, metabolic syndrome reflects a deeper collapse in the physiological integrity of incretins, adipokines, myokines, hepatokines, mitochondrial-derived peptides (MDPs), and aging-related regulators such as Klotho. Dysregulation of these interconnected peptide systems precipitates mitochondrial dysfunction, adipose inflammatory remodeling, impaired nutrient sensing, endothelial injury, and accelerated metabolic aging. Current therapeutic strategies largely address downstream metabolic abnormalities but do not correct these foundational defects in peptide signaling and mitochondrial resilience.

Keywords

Metabolic syndrome, Peptide signaling networks, Mitochondrial bioenergetics, Incretins and adipokines.

Introduction

Metabolic syndrome has historically been defined by central adiposity, insulin resistance, dyslipidemia, hypertension, and chronic low-grade inflammation. Metabolic syndrome currently affects nearly one-quarter of the global adult population and continues to rise across diverse socioeconomic settings [1]. However, metabolic syndrome has more recently been recognized as a complex, multisystem disorder arising from the coordinated breakdown of endocrine, inflammatory, mitochondrial, and inter-organ peptide communication networks that normally maintain glucose homeostasis, lipid partitioning, vascular function, and energy balance [2]. This shift emerged as contemporary mechanistic research revealed the beyond the clustering of an aggregate of cardiometabolic risk factors, resided a progressive failure of metabolic peptide signaling architecture. Within this architecture regulatory peptides originating from the gut, adipose tissue, pancreas, skeletal muscle, endothelium, and mitochondria lose temporal coordination under conditions of caloric excess, physical inactivity, circadian disruption, and inflammatory stress [2]. Most notably, dysregulation of incretin hormones (GLP-1, GIP), adipokines (adiponectin, leptin, resistin), pancreatic peptides (insulin, amylin, PP), myokines (irisin, myonectin), hepatokines (FGF21), and mitochondrial-derived peptides (MOTS-c, humanin, SHLPs) which mechanistically link nutrient sensing, insulin receptor activity, mitochondrial efficiency, endothelial nitric oxide bioavailability, and immune-metabolic stability [3,4]. Disturbances in one (or more) of these systems shift the metabolic milieu toward oxidative stress, mitochondrial dysfunction, impaired autophagy, ectopic lipid deposition, endoplasmic reticulum (ER) stress, and chronic meta-inflammation, creating self-reinforcing cycles that accelerate cardiometabolic deterioration. Aging-related decline in protective peptides (e.g. Klotho) [5,6], further amplifies oxidative

injury, insulin resistance, and endothelial dysfunction [7].

Given the dynamic peptide-centric disintegration of metabolic regulation, emerging regenerative peptide therapeutics, including mitochondrial-derived peptides (MDPs), Mito Organelles (MOs), Nano Organo-Peptides (NOPs), Klotho fragments, and multi-receptor incretin-based constructs, represent a mechanistically rational next-generation intervention. Rather than targeting downstream manifestations such as hyperglycemia or dyslipidemia, these biologics aim to restore the upstream peptide-governed networks that maintain cellular resilience, mitochondrial integrity, metabolic flexibility, and cross-organ communication [8]. By enhancing mitochondrial bioenergetics, suppressing inflammatory signaling, rebalancing adipokine networks, restoring incretin sensitivity, and reversing peptide-governed aging pathways, peptide therapeutics hold potential to modify the trajectory of metabolic syndrome at a foundational biological level. Collectively, these insights position regenerative peptide therapeutics as a coherent, systems-level strategy capable of addressing the root biological failures driving metabolic syndrome, thereby offering a promising foundation for true disease-modifying interventions. This review aims to integrate current understanding of metabolic syndrome as a disorder of disrupted peptide signaling and inter-organ communication, and to delineate how next-generation peptide therapeutics may be leveraged to reestablish metabolic resilience through targeted modulation of mitochondrial function, inflammatory pathways, and endocrine crosstalk.

The Peptide Network Governing Metabolic Homeostasis

Metabolic homeostasis is regulated by an intricate, multi-organ peptide signaling network linking the gut, pancreas, adipose tissue, liver, skeletal muscle, immune system, and brain, as outlined in the uploaded metabolic syndrome chapter. Enteroendocrine peptides such as GLP-1, GIP, PYY, and pancreatic polypeptide modulate gastric emptying, insulin secretion, satiety signaling, and vagal neurocircuitry [9]. Concurrently, adipokines (e.g., leptin, adiponectin, resistin, visfatin, omentin, chemerin), govern lipid utilization, brown adipose thermogenesis, hepatic glucose production, endothelial tone, and systemic inflammation [10]. Pancreatic peptides (insulin, amylin), myokines (irisin, myonectin), and hepatokines (FGF21) further regulate glucose disposal, fatty acid oxidation, and mitochondrial biogenesis. Disruption of this peptide ecosystem, whether through diminished secretion, receptor desensitization, altered enzymatic degradation, or cytokine-mediated suppression (or other deregulatory pathway) produces hallmark abnormalities of metabolic syndrome including the incretin defect, leptin resistance, hypoadiponectinemia, and inflammatory adipokine shift [11]. This peptide-network deterioration precedes clinical metabolic derangement, suggesting that metabolic syndrome is fundamentally a disorder of dysregulated peptidergic inter-organ communication rather than isolated endocrine failure.

Mitochondrial Dysfunction and Loss of Mitochondrial Peptide Signaling

Mitochondrial dysfunction constitutes a central pathogenic axis of metabolic syndrome, underlying insulin resistance, impaired oxidative phosphorylation, ectopic lipid accumulation, and systemic inflammatory activation [12,13]. Chronic nutrient overload, lipotoxicity, glucotoxicity, and cytokine-mediated oxidative stress disrupt mitochondrial integrity, producing electron transport chain inefficiency, excessive ROS generation, impaired mitophagy, and depletion of mitochondrial antioxidant defenses. Recent evidence has shown that the mitochondrial genome encodes a class of mitochondrial-derived peptides (MDPs), e.g., MOTS-c, humanin, and small humanin-like peptides (SHLPs), that function as regulatory mitokines governing cellular stress adaptation, AMPK activation, insulin sensitivity, and mitochondrial proteostasis [14].

Dysregulation or depletion of these peptides diminishes mitochondrial–nuclear communication, reduces fatty acid oxidation capacity, impairs glucose uptake, and increases vulnerability to apoptosis. Notably, MOTS-c has been shown to translocate to the nucleus during metabolic stress to regulate adaptive gene expression programs, a mechanism that becomes blunted in obesity and metabolic syndrome, further amplifying metabolic inflexibility [15]. As mitochondrial dysfunction propagates across insulin-responsive tissues, particularly skeletal muscle, liver, adipose tissue, and vascular endothelium, these abnormalities drive the global metabolic rigidity and oxidative burden that characterize the syndrome. The resulting decline in cellular energy sensing creates an environment where metabolic signals are both excessive and ineffective, reinforcing the cycle of insulin resistance, inflammatory activation, and lipid dysregulation.

Adipose Tissue Remodeling and the Shift Toward Meta-Inflammation

Adipose tissue undergoes profound structural and functional remodeling in metabolic syndrome. This remodeling transforms adipose from a metabolically flexible endocrine organ to a site of immune activation, hypoxia, and secretory dysfunction [16]. Hypertrophic, fibrotic adipose depots, as a consequence of caloric imbalance or other deregulatory mechanism induces a shift from hyperplasia, characterized by adipocyte proliferation, to pathological hypertrophy, which reduces vascular density, increases ER stress, and promotes adipocyte necrosis [17]. These changes trigger infiltration of M1 macrophages, T cells, neutrophils, and dendritic cells, initiating a cascade of cytokine release including tumor necrosis factor (TNF)-α, interleukin (IL)-6, MCP-1, and CXCL5 that impairs insulin receptor signaling and accelerates systemic insulin resistance [17].

Concurrently, secretory profiles shift toward increased leptin and resistin with reduced adiponectin, a pattern strongly predictive of cardiometabolic progression and endothelial dysfunction [18]. Low adiponectin states disrupt AMPK activation, reduce fatty acid oxidation, impair mitochondrial biogenesis, and promote hepatic gluconeogenesis, producing a metabolic state primed for dysregulation. Adipose-derived extracellular vesicles (EVs), recently identified as carriers of pro-inflammatory microRNAs and dysfunctional peptide signals, further propagate metabolic injury by altering transcriptional programs in liver and muscle

[19]. Thus, adipose inflammation becomes a systemic amplifier of metabolic syndrome, linking local tissue dysfunction to whole-body metabolic collapse.

Aging, Klotho Deficiency, and Accelerated Metabolic Vulnerability

Aging introduces an additional layer of vulnerability through the progressive decline of Klotho, a peptide-regulatory protein with critical roles in insulin signaling, oxidative stress control, vascular integrity, and mitochondrial homeostasis. Reduced Klotho expression disrupts endocrine pathways involving insulin-like growth factor (IGF)-1, PI3K/Akt, and fibroblast growth factor (FGF) 23, exacerbating metabolic dysregulation and impairing glucose uptake in insulin-sensitive tissues [20]. Contemporary studies show that circulating Klotho levels decline in individuals with metabolic syndrome and closely correlate with increased visceral adiposity, arterial stiffness, and hepatic steatosis [20,21]. Experimental Klotho deficiency accelerates cellular senescence through increased ROS accumulation, reduced antioxidant enzyme expression, and impaired mitochondrial turnover. These mechanisms parallel the "accelerated metabolic aging" phenotype of metabolic syndrome [22]. Klotho also modulates adipokine signaling and inflammatory regulation. Loss of Klotho amplifies NF-κB activation, endothelial dysfunction, and lipid infiltration into metabolic organs [23]. Thus, Klotho deficiency is not merely a biomarker of metabolic syndrome but a mechanistic driver linking mitochondrial dysfunction, oxidative stress, endothelial disease, and impaired peptide signaling into a coherent pathophysiological axis of metabolic decline.

Mechanistic Integration: How Peptides Repair Metabolic Networks

Peptide-based therapeutics exert their metabolic benefits through multi-layered restoration of energy homeostasis, endocrine signaling, immune-metabolic regulation, and aging-related molecular pathways that become profoundly disrupted in metabolic syndrome. A central mechanism involves the recovery of mitochondrial bioenergetics. Mitochondrial-derived peptides (MDPs) such as MOTS-c, humanin, and SHLPs activate AMPK, enhance oxidative phosphorylation, stabilize mitochondrial membrane potential, and suppress ROS generation, thereby reversing the mitochondrial collapse that underlies insulin resistance, loss of metabolic flexibility, and impaired fatty acid oxidation [24,25]. These peptides also improve mitophagy and mitochondrial protein turnover, which remain essential for maintaining ATP sufficiency in insulin-responsive tissues facing nutrient overload.

Complementing mitochondrial restoration, peptide biologics contribute to rebalancing adipokine profiles and suppressing meta-inflammation, two core pathological features depicted in the uploaded chapter's adipose diagrams. Nano Organo-Peptides (NOPs) and truncated Klotho peptides downregulate TNF-α, IL-6, MCP-1, and other adipose-derived inflammatory mediators while increasing adiponectin and restoring leptin sensitivity, disrupting the inflammatory, insulin resistance feedback loop that drives metabolic decline [5,21,26,27]. Klotho fragments additionally mitigate NF-κB activation and endothelial oxidative stress, generating systemic improvements in vascular and metabolic resilience [5,26]. Peptide therapies further support normalization of incretin and gut–brain axis signaling, which is profoundly impaired in metabolic syndrome. GLP-1 analogs and next-generation multi-agonists (GLP-1/GIP/GCGR) improve enteroendocrine secretion dynamics, enhance vagal signaling, reduce central appetite drive, and restore β-cell responsiveness, addressing the incretin defect that precipitates glucose dysregulation [3]. These peptides recruit overlapping but distinct receptor pathways, allowing coordinated modulation of satiety, insulin secretion, gastric emptying, and energy expenditure. In addition to systemic effects, regenerative peptides enable repair of tissue-specific metabolic networks across liver, muscle, adipose tissue, endothelium, and pancreatic islets. Organ-targeted peptides and Mito Organelles (MOs) enhance insulin receptor signaling in skeletal muscle, suppress hepatic lipogenesis and ER stress, restore β-cell survival and insulin granule exocytosis, and improve endothelial nitric oxide bioavailability, thereby correcting the multi-organ metabolic disintegration that defines metabolic syndrome [26,28]. Recent studies demonstrate that peptide-mediated remodeling of skeletal muscle and hepatic mitochondrial networks enhances both glucose disposal and systemic energy partitioning [5,26,29]. Finally, peptide therapeutics exert potent modulatory effects on aging pathways and cellular senescence, positioning them as metabolic "geroprotectors." Klotho-derived peptides attenuate IGF-1/PI3K/mTOR hyperactivation, reduce senescent-cell burden, augment endogenous antioxidant defenses, and improve mitochondrial turnover, directly targeting the accelerated metabolic aging phenotype characteristic of metabolic syndrome [30]. Aging-related molecular drift disrupts peptide signaling across multiple organ systems; thus, rejuvenating these pathways represents a biologically coherent mechanism through which peptide therapeutics can produce durable metabolic correction. Together, these mechanistic domains illustrate how peptide-based biologics engage the root functional failures in metabolic syndrome rather than merely addressing downstream metabolic abnormalities.

Translational Framework for Precision Peptide Therapy in Metabolic Syndrome

A precision medicine framework is required to deploy peptide therapeutics effectively, given the heterogeneity of metabolic syndrome and its multilayered pathophysiology. The first step involves comprehensive baseline metabolic phenotyping, integrating standard biochemical profiles with advanced functional markers [31]. Fasting glucose, lipid panels, and liver enzymes must be complemented by rigorous measures of insulin sensitivity such as HOMA-IR or hyperinsulinemic-euglycemic clamp studies [32]. Circulating adipokines (adiponectin, leptin), incretins (GLP-1, GIP), and mitochondrial-derived peptides (MOTS-c, humanin) provide insight into peptide-network status. Moreover, mitochondrial functional assays (e.g., oxygen consumption rate, mitochondrial membrane potential) yield high-resolution insight into cellular energetic capacity. Imaging modalities such as MRI or DXA allow quantification of visceral adiposity, an independent

driver of peptide-network disruption [33]. Following phenotyping, peptide target selection can be individualized according to dominant pathophysiologic deficits. MDPs are prioritized in patients with evidence of mitochondrial dysfunction, impaired AMPK signaling, or severe metabolic inflexibility.

MO or organ-specific peptides are suited for individuals exhibiting pronounced hepatic steatosis, skeletal muscle insulin resistance, or endothelial dysfunction. NOPs may be selected for patients with inflammatory adipose phenotypes or leptin resistance, while Klotho peptides are optimal for aging-associated metabolic patterns. Incretin-based agents, including dual and triple agonists, are deployed when enteroendocrine disruption or β-cell dysfunction predominates [33]. The therapeutic model is strengthened by a combination peptide strategy, whereby peptides acting through complementary pathways are administered concurrently to achieve multi-axis metabolic recalibration. A GLP-1 agonist or multi-receptor incretin analog forms the endocrine backbone, enhancing insulinotropic activity and appetite regulation. MDPs provide mitochondrial stabilization, Klotho fragments counteract oxidative and senescent drift, and NOPs deliver targeted modulation of inflammation and tissue-specific metabolic repair. This combinatorial design mirrors the orchestrational paradigm described in the chapter, where layered peptide networks maintain metabolic resilience under normal physiological conditions. Once therapy begins, biomarker-guided monitoring ensures adaptive optimization [34].

Key biomarkers include changes in insulin sensitivity indices, mitochondrial respiration markers, circulating levels of MDPs and Klotho, inflammatory cytokine profiles (IL-6, TNF-α, CRP), lipid partitioning metrics, and tissue-specific endpoints such as hepatic fat fraction or muscle oxidative capacity. Frequent reassessment allows titration of peptide classes, dynamic combination strategies, and early detection of therapeutic response. This iterative, data-driven precision approach aligns with contemporary metabolic therapeutics and enhances the likelihood of achieving durable disease-modifying outcomes.

European Wellness has developed an extensive translational platform centered on MO, NOP, and targeted organ-specific peptide ultrafiltrates, each designed to modulate core biological systems that deteriorate in metabolic syndrome. MO formulations constitute a mitochondria-directed therapeutic class enriched with cardiolipins, mitochondrial regulatory peptides, antioxidant enzymes, and bioenergetic cofactors that collectively restore mitochondrial membrane potential, enhance ATP synthesis, increase NAD^+ availability, and suppress ROS-derived injury. Within insulin-resistant skeletal muscle, steatotic liver, dysfunctional adipose tissue, and compromised endothelium, these mitochondrial corrections reestablish the bioenergetic foundation required for insulin sensitivity, fatty acid oxidation, oxidative phosphorylation efficiency, and metabolic flexibility. In parallel, NOP technology has been engineered for rapid systemic absorption, protection from proteolytic degradation, and highly effective microvascular and intracellular penetrance. These peptides possess tissue-specific biochemical signatures capable of modulating transcriptional networks, inflammatory mediators, neuroimmune pathways, angiogenic factors, and mitochondrial regulatory cascades. Through these mechanisms, NOPs normalize adipose inflammatory drift, augment adiponectin release, reverse leptin resistance, improve insulin receptor phosphorylation in muscle, attenuate hepatic lipogenesis, restore endothelial nitric oxide bioavailability, and recalibrate AMPK-, SIRT-, and FOXO-governed metabolic programs. Complementing both MO and NOP platforms, European Wellness uses organ-specific peptide ultrafiltrates that retain bioactive trophic factors, cytokine fragments, and regulatory peptides from pancreas, liver, vasculature, skeletal muscle, adipose tissue, and immune organs. These biologics function as multi-modal tissue restoration cues, enhancing β-cell functional resilience, reducing hepatic ER stress and de novo lipogenesis, improving myocellular glucose uptake and mitochondrial density, reversing endothelial oxidative injury, and shifting adipose tissue from a fibrotic, inflammatory phenotype toward an endocrine state conducive to metabolic health. Collectively, EW's integrated approach, unifying mitochondrial reconstitution, inflammatory modulation, endocrine network normalization, vascular repair, and organ-level peptide signaling, offers a biologically coherent and systemically harmonized therapeutic model directly aligned with the multisystem peptide-network deterioration that defines metabolic syndrome [5,6,26,28].

Ethical and Safety Considerations

The introduction of multi-peptide biologics into metabolic disease therapeutics raises a set of ethical and safety considerations distinct from those associated with conventional pharmacologic agents. Because these formulations act on upstream molecular pathways central to cellular resilience and metabolic regulation, their deployment requires a rigorous framework for evaluating both immediate and long-term biological effects. Central to ethical implementation is the use of structured dose-escalation studies, ensuring that early-phase investigational dosing captures the narrow window between therapeutic efficacy and overstimulation of intracellular pathways such as AMPK, mTOR, FOXO, or mitochondrial stress-response circuits. Beyond dose finding, comprehensive immunogenicity profiling is essential, as the peptide size, nanofractionation, and organ-specific signatures may alter antigen presentation or elicit subtle immune priming not consistently observed with traditional small molecules. A further layer of safety evaluation concerns off-target peptide dissemination, which must be monitored through proteomic, metabolomic, and receptor-binding analyses capable of detecting unintended interactions in tissues with high metabolic turnover, such as myocardium, kidneys, and the gastrointestinal tract. Because several peptide classes can influence cellular senescence, autophagy, or proliferative signaling, long-term surveillance of senescence pathways, telomere dynamics, and proliferation-associated biomarkers is critical to ensure that chronic administration does not inadvertently accelerate oncogenic or fibrotic processes in predisposed tissues. Ethical deployment also requires transparent risk–benefit communication, particularly given that many patients with metabolic syndrome present with

multimorbidity, polypharmacy, and variable metabolic reserve that may influence peptide responsiveness or safety. Finally, biomarker-based early detection systems can be incorporated into clinical protocols to permit real-time safety monitoring. Collectively, these safeguards support an ethically responsible translation of regenerative peptide therapeutics into metabolic medicine while maintaining scientific rigor and patient protection.

Conclusion

Metabolic syndrome represents a complex and interconnected failure of peptide-governed metabolic circuits, encompassing mitochondrial insufficiency, endocrine and adipokine imbalance, impaired incretin signaling, chronic meta-inflammation, and accelerated molecular aging. The uploaded chapter and contemporary systems-biology research converge on a central insight: the integrity of metabolic health is fundamentally peptide-dependent, and the breakdown of this peptide-regulated network precedes and drives the clinical manifestations of metabolic syndrome. In this context, regenerative peptide therapeutics offer a mechanistically aligned strategy capable of addressing the upstream biological defects that conventional therapies seldom reach. By restoring mitochondrial bioenergetics, recalibrating adipose and endocrine signaling pathways, dampening immunometabolic inflammation, optimizing insulin receptor and incretin sensitivity, repairing vascular and hepatic metabolic injury, and reversing senescence-associated molecular drift, peptide therapeutics hold the potential to reshape the metabolic trajectory rather than merely mitigate downstream metabolic disturbances. As precision platforms such as organ-targeted nanodelivery systems, multi-omics profiling, and integrative biomarker algorithms continue to advance, the feasibility of tailoring peptide combinations to individual metabolic phenotypes becomes increasingly attainable. Taken together, these developments position regenerative peptide therapy as a next-generation therapeutic paradigm. This paradigm has the potential for function at the foundational biological level that governs metabolic resilience. With continued translational research, rigorous safety frameworks, and biomarker-driven clinical implementation, peptide-based metabolic restoration may ultimately redefine the management of metabolic syndrome, shifting the field toward true disease modification and improved long-term outcomes.

References

1. Danpanichkul P, Ng CH, Muthiah MD, et al. Metabolic Syndrome and Metabolic Dysfunction-Associated Steatotic Liver Disease in Premenopausal Women: Global Trends and Projections to 2040. Mayo Clin Proc. 2024; 99: 1615-1628.
2. Fahed G, Aoun L, Bou Zerdan M, et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. Int J Mol Sci. 2022; 23:786.
3. Yamanouchi D. The Roles of Incretin Hormones GIP and GLP-1 in Metabolic and Cardiovascular Health: A Comprehensive Review. Int J Mol Sci. 2025; 27: 27.
4. Merry TL, Chan A, Woodhead JST, et al. Mitochondrial-derived peptides in energy metabolism. Am J Physiol Endocrinol Metab. 2020; 319: E659-E666.
5. Chan MKS, Wong MBF, Casazza K, et al. Peptide-Based Precision Therapeutics for Cardiac Disease: Targeting Mitochondrial Dysfunction, Fibrosis, and Inflammation. Am J Biomed Sci Res. 2025; 27.
6. Chan MKS, Wong MBF, Nalapko Y, et al. Short-Peptides May be the Key to Long Life. Am J Biomed Sci Res. 2025; 26.
7. Hajare AD, Dagar N, Gaikwad AB. Klotho antiaging protein: molecular mechanisms and therapeutic potential in diseases. Mol Biomed. 2025; 6: 19.
8. Liu Y, Wang Y, Zhou J, et al. Restoring metabolic flexibility: targeting organelle interaction networks in the pathogenesis and therapy of MASLD. Front Cell Dev Biol. 2025; 13: 1718799.
9. Liu J, Jing C, Guo Y, et al. The central signaling pathways related to metabolism-regulating hormones of the gut-brain axis: a review. J Transl Med. 2025; 23: 648.
10. Clemente-Suárez VJ, Redondo-Flórez L, Beltrán-Velasco AI, et al. The Role of Adipokines in Health and Disease. Biomedicines. 2023; 11: 1290.
11. Kim JE, Kim JS, Jo MJ, et al. The Roles and Associated Mechanisms of Adipokines in Development of Metabolic Syndrome. Molecules. 2022; 27: 334.
12. Chen S, Li Q, Shi H, et al. New insights into the role of mitochondrial dynamics in oxidative stress-induced diseases. Biomed Pharmacother. 2024; 178: 117084.
13. Sergi D, Naumovski N, Heilbronn LK, et al. Mitochondrial (Dys) function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet. Front Physiol. 2019;10: 532.
14. Ramanjaneya M, Bettahi I, Jerobin J, et al. Mitochondrial-Derived Peptides Are Down Regulated in Diabetes Subjects. Front Endocrinol. 2019; 10: 331.
15. Kim KH, Son JM, Benayoun BA, et al. The Mitochondrial-Encoded Peptide MOTS-c Translocates to the Nucleus to Regulate Nuclear Gene Expression in Response to Metabolic Stress. Cell Metab. 2018; 28: 516-524.e7.
16. Cimini FA, Sentinelli F, Oldani A, et al. Adipose Tissue Dysfunction and Metabolic Diseases: The Role of Vitamin D/Vitamin D Receptor Axis. Int J Mol Sci. 2025; 26: 10256.
17. Sakers A, De Siqueira MK, Seale P, et al. Adipose-tissue plasticity in health and disease. Cell. 2022; 185: 419-446.
18. Zhao S, Kusminski CM, Scherer PE. Adiponectin, Leptin and Cardiovascular Disorders. Circ Res. 2021; 128: 136-149.
19. Bond ST, Calkin AC, Drew BG. Adipose-Derived Extracellular Vesicles: Systemic Messengers and Metabolic Regulators in Health and Disease. Front Physiol. 2022;13: 837001.
20. Richter B, Faul C. FGF23 Actions on Target Tissues-With and Without Klotho. Front Endocrinol. 2018; 9: 189.
21. Zhu T, Zhao S, Lu N. Klotho in diabetes mellitus: research progress and clinical implications. Front Endocrinol. 2025; 16: 1740415.

22. Xu X, Pang Y, Fan X. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. Signal Transduct Target Ther. 2025; 10: 190.
23. Zhao X, Han D, Zhao C, et al. New insights into the role of Klotho in inflammation and fibrosis: molecular and cellular mechanisms. Front Immunol. 2024; 15: 1454142.
24. Benayoun BA, Lee C. MOTS-c: A Mitochondrial-Encoded Regulator of the Nucleus. BioEssays News Rev Mol Cell Dev Biol. 2019; 41: e1900046.
25. Kim SJ, Xiao J, Wan J, et al. Mitochondrially derived peptides as novel regulators of metabolism. J Physiol. 2017; 595: 6613-6621.
26. Chan MKS, Wong MBF, Casazza K, et al. Emerging Peptide Therapies for Kidney Disease: Focus on Nano-Organo and Mitochondria-Targeted Strategies. Am J Biomed Sci Res. 27: 2025.
27. Amaro-Gahete FJ, Jurado-Fasoli L, Sanchez-Delgado G, et al. Relationship between plasma S-Klotho and cardiometabolic risk in sedentary adults. Aging. 2020;12: 2698-2710.
28. Lakey JR, Wells A, Good A, et al. Protective Effects of Stem Cell-Derived Peptides in Preventing Autoimmune Diabetes in the Non-Diabetic Mouse Model. Am J Biomed Sci Res. 2022; 16.
29. Argilés JM, Campos N, Lopez-Pedrosa JM, et al. Skeletal Muscle Regulates Metabolism via Interorgan Crosstalk: Roles in Health and Disease. J Am Med Dir Assoc. 2016; 17: 789-796.
30. Ariadel-Cobo DG, Estébanez B, González-Arnáiz E, et al. Influence of Klotho Protein Levels in Obesity and Sarcopenia: A Systematic Review. Int J Mol Sci. 2025; 26: 1915.
31. Yang Q, Cai Y, Guan Y, et al. Metabolic phenotypes: Molecular bridges between health homeostasis and disease imbalance. Comput Struct Biotechnol J. 2025; 27: 4710-4719.
32. Wang K, Yu G, Yan L, et al. Association of non-traditional lipid indices with diabetes and insulin resistance in US adults: mediating effects of HOMA-IR and evidence from a national cohort. Clin Exp Med. 2025; 25: 281.
33. Zhou T, Ding X, Chen L, et al. Visceral adiposity index as a predictor of metabolic dysfunction-associated steatotic liver disease: a cross-sectional study. BMC Gastroenterol. 2025; 25: 326.
34. Tanaka M, Vécsei L. From Microbial Switches to Metabolic Sensors: Rewiring the Gut-Brain Kynurenine Circuit. Biomedicines. 2025; 13: 2020.